Energetics of muscular exercise

FERRETTI, Guido

FERRETTI, Guido. *Energetics of muscular exercise*. Heidelberg : Springer, 2015, 180 p.

DOI : 10.1007/978-3-319-05636-4

Guido Ferretti

Energetics of Muscular Exercise

Springer

Energetics of Muscular Exercise

Guido Ferretti

Energetics of Muscular Exercise

Springer

Guido Ferretti
Dipartimento di Scienze Cliniche e
Sperimentali Health&Wealth@unibs
Università di Brescia
Brescia
Italy

and

Départements de Anesthésiologie,
Pharmacologie et Soins Intensifs et de
Neurosciences Fondamentales
Université de Genève
Geneva
Switzerland

ISBN 978-3-319-05635-7 ISBN 978-3-319-05636-4 (eBook)
DOI 10.1007/978-3-319-05636-4

Library of Congress Control Number: 2015933155

Springer Cham Heidelberg New York Dordrecht London

Printed on acid-free paper

Springer International Publishing AG Switzerland is part of Springer Science+Business Media (www.springer.com)

This book is dedicated to my four great loves: my wife Silvia and my children Lavinia, Livio and Lapo

Foreword

Pietro di Prampero's review of 1981 is the landmark that set the state of the art of our knowledge in the field of the energetics of muscular exercise in those times. It resumed what can now be considered as classical studies under the perspective of the general theory of the energetics of muscular exercise developed within the School of Milano created by Rodolfo Margaria, which di Prampero is an eminent member of. The study of the energetics of muscular exercise dives back in history much more than we may imagine at a first sight, owing a lot to classical chemistry, morphology and biochemistry. Yet the first key concepts of it were essentially outlined by Margaria in 1933, and progressively refined, first by Margaria himself, then by his pupils, as long as the experimental evidence grew. That era was finally framed by di Prampero in 1981. The general theory of the energetics of muscular exercise has been the cultural reference of this book.

Other physiological schools played crucial roles in that story as well. In particular, I would like to mention the Scandinavian school, whose most eminent representatives in those times had been Erich Höhwu Christensen in the 1930s, Erling Asmussen in the 1950s and Per-Olaf Åstrand in the 1960s. That school, however, was mainly characterised by an empirical approach to science: those physiologists generated huge, fundamental amounts of original experimental data, but were scarcely attracted by theoretical thinking, which conversely was the most important treat of Margaria and co-workers. Great theoretical advances were obtained in Rochester and Buffalo within the school led by Wallace Fenn and Hermann Rahn, and in Göttingen by Johannes Piiper: those advances, however, were mostly in the field of gas exchange rather than in that of exercise energetics, although the heirs of Margaria owe a lot of their way of thinking also to Buffalo and Göttingen, especially Paolo Cerretelli and Pietro Enrico di Prampero.

Similar exchanges can be perceived also between the general theory of the energetics of muscular exercise and the cross-bridge theory of muscle contraction, the link being represented by the role of ATP as main energy source for muscular contraction. The former concerns the way chemical energy is generated and stored in ATP, the latter has to do with the way the chemical energy stored in ATP is transformed into mechanical energy in the cross-bridge cycle. These exchanges,

however, were less direct, as long as there had been no collaboration between Margaria and Andrew Huxley. When Margaria spent some time with Archibald Vivian Hill and John Barcroft, Huxley was a child.

Thirty-four years of further work and thinking, summarized in the six chapters of this book, have elapsed since the publication of di Prampero's review. The questions now are: How did the general theory of the energetics of muscular exercise resist the deterioration of time and the impact of new knowledge? What is its state of health? What are the most important advances of the last 30 years?

Concerning the last question, I would say that several new concepts were created and took shape since 1981. I do not include in this list George Brooks' lactate shuttle, a concept which di Prampero was already aware of in 1981, although it received theoretical systematisation within the general theory only more recently: di Prampero's concepts of hyperaerobic and hypoaerobic muscle fibres make use of the lactate shuttle, which is therefore included in the general theory. Most important novel contributions appear, to my eyes, the multifactorial models of maximal oxygen uptake limitation, the critical power models, the identification of the slow component (although its occurrence had already been suggested in 1981), although its theoretical systematisation is still to be perfected, and the double exponential model of oxygen uptake kinetics. All the above-listed concepts challenged the general theory seriously; most of them could be conveniently accommodated in it; some required refinements of the general theory. Yet I would conclude that overall the general theory has resisted pretty well and is still in good health, despite the modifications that had to be introduced.

In my vision, the most important threat to the general theory came from the two-site model of the kinetics of oxygen uptake upon exercise onset, which undermined the automatic link between oxygen deficit and energy delivery. Significant changes in the general theory with respect to di Prampero's review had to be introduced for this reason. Thanks essentially to the excellent work carried out by the British school led by Brian Whipp, it is generally accepted nowadays, even by those within the school of Milano who were opposed to that vision in the past, that the first exponential of the two-site model (phase I) is unrelated to an energetic mechanism. The need for tightly coupling oxygen delivery and oxygen consumption implied the emergence of other mechanisms, related to cardio-respiratory control, in the regulation of oxygen delivery. The concept that what is measured at the mouth reflects what occurs from the energetic viewpoint in contracting muscles has weakened. The current formulation of the general theory admits different regulation of oxygen delivery and of oxygen consumption. The former includes specific features (phase I) related to cardio-respiratory control and has a primary component whose time constant increases with the exercise intensity. The latter is dictated by the kinetics of activation of glycolysis and is characterised by a time constant which is invariant and independent of exercise intensity. Therefore, as long as the former time constant is faster than the latter, oxygen delivery copes with oxygen demand, and the time constant of oxygen consumption corresponds to that of muscle phosphocreatine hydrolysis and of the primary components of pulmonary oxygen uptake: in sum, to that of glycolysis activation. Conversely, when the time constant

of the primary component of oxygen delivery becomes slower than that of glycolysis activation, oxygen delivery becomes inadequate and the kinetics of oxygen consumption slows down. As a consequence, early lactate is accumulated, as much as is necessary to cover the missing energy, compatibly with an energy equivalent of blood lactate accumulation of 3 ml $mmol^{-1}$ kg^{-1}.

Another important point concerns the slow component, for which the situation appears more ambiguous. The appearance of the slow component implies a non-linear relationship between oxygen uptake and power and the lack of a clearly visible steady state for oxygen uptake during intense exercise. This induced several scientists to reject the concept of maximal aerobic power as the power requiring an oxygen uptake equivalent to the maximum. I kindly disagree with this view, as long as we have no demonstration that the extra-oxygen consumption pertaining to the slow component is necessary to replace the chemical energy that is converted into mechanical work in the cross-bridge cycle. To my mind, the classical relationship between oxygen uptake and power concerns the steady state attained by the primary component (phase 2 in the double exponential model) of the oxygen uptake kinetics, on the assumption that the slow component reflects other phenomena than energy transformation in the cross-bridge cycle. However, the mechanistic understanding of the slow component is still poor, and some evidence suggests that it may be related to phenomena occurring within the active muscle mass. Thus I cannot exclude that in the near future our view of the slow component may still change, with consequences on the formulation of the general theory.

The critical power has become crucial concept in exercise physiology. Although the concept still existed in 1981, it was considered minor and was not even mentioned in di Prampero's review. Its importance grew in more recent years, thanks to the experimental work of the British school, especially David Poole and Andy Jones. Yet we owe the theoretical systematisation of the critical power concept to Hugh Morton, who developed the two-parameter and the three-parameter models of critical power and formulated the theory applying the critical power concept to ramp exercise. His theoretical work, of greatest importance in the field, fits well in the general theory as long as we admit a univocal relation, with precisely known values of mechanical efficiency, between mechanical energy (work) and metabolic energy.

Last but not least, the multifactorial models of maximal oxygen uptake limitation revolutionised our understanding of this issue. The resumption, by Ewald Weibel and Dick Taylor, of the oxygen conductance equation led di Prampero to create the concept, to the formulation of which I also contributed. In parallel, Peter Wagner elaborated a nice analysis of the interaction between cardiovascular oxygen delivery and muscle oxygen diffusion, which designed a novel integrative perspective of the subject. It is curious to note that the two multifactorial models were considered in competition for long. Only very recently the demonstration came, that the two models say the same things in a different language, and lead to the same conclusions. Starting from this notion, I expect a generalisation of the multifactorial models to include quantitatively the entire respiratory system in all experimental conditions: this however requires a sound theoretical, rather than empirical, mathematical solution of the oxygen equilibrium curve.

The panorama of activity in the field has remarkably changed in the last 40 years, getting open to a larger variety of contributions, whether theoretical or experimental, which represent a remarkable intellectual enrichment with respect to the past. Several individuals, I think especially of Peter Wagner and Brian Whipp, developed new major schools of exercise physiology, which generated important thinking, produced remarkable experimental results, and disseminated a large number of important scientists, above all, for his strong acquaintance with both schools, David Poole. The Scandinavian school has not disappeared; it rather further developed, under the forceful example of Bengt Saltin, who imposed himself as actual school leader. Under his example, the Scandinavian school expanded its interests to new experimental contexts and much information acquired in those contexts provided useful pieces of evidence completing empty slots of the general theory, think as an example of the lactate-proton co-transporter. Yet that school continued to generate essentially huge amounts of experimental data, poorly contributing to theoretical thinking. The school of Milano is still in good shape, with new generations of scientists continuing its tradition. The technical developments have dramatically enlarged the possibility of obtaining and treating complex physiological data. Several individuals, outside those schools, have produced original contributions, also in theoretical analysis (Hugh Morton above all). Exercise therapy and exercise physiopathology are opening new perspectives in the field. The picture generates an optimistic view of the future, although the field of exercise physiology is not as central as it was 50 years ago in the consideration of funding agencies.

What should we expect next? I do not know, I do not dare to say. Multifactorial models, slow component, critical power are concepts that are well present in the current debate of the energetics of muscular exercise, although they could not be predicted when di Prampero wrote his review. It is preposterous to indicate the way research should take. What will come next depends on the freedom, fantasy and originality in thinking that scientists in the field will show in next years. I nevertheless put forward two predictions: that the general theory will survive, after several readjustments under the pressure of new experimental evidence, and that new people will continue the task of elaborating new concepts and ideas. In this book, I have re-elaborated the current knowledge of the energetics of muscular exercise under the perspective of the general theory and from the viewpoint of the school of Milano, where my way of thinking was forged. I will not be surprised, if I will have the chance of getting old, to learn that somebody of a new generation will have done the same job within 30 years from now, re-analysing the general theory and adapting it to the new concepts that will have been created and the new findings that will have been obtained meanwhile. The picture of the general theory of the energetics of muscular exercise, which will then be reported, will be significantly different form the one emerging from this book, pretty much the same way this book reports a significantly different picture from that outlined by di Prampero in 1981.

Acknowledgments

I would like to express my gratitude to all those who trained me and forged my way of thinking, above all Paolo Cerretelli and Pietro Enrico di Prampero, whom I had the longest acquaintance and the most intense exchanges with, but also Dave Pendergast, Don Rennie, and Arsenio Veicsteinas. A special thanks goes to my friends and colleagues Carlo Capelli, Fabio Esposito, Hans Hoppeler, and Dag Linnarsson, as well as to all those who happened to collaborate with me at different times, for the pleasure and enrichment that the fruitful discussions which we had so many times provided to me. A special thanks goes to Giovanni Vinetti for careful re-reading of the entire text.

Contents

Abbreviations and Symbols

A	Area
a	Moles of ATP resynthesized per mole of phosphocreatine hydrolysed
A_1	Amplitude of a physiological variable increase during phase I of the exercise transient
A_2	Amplitude of a physiological variable increase during phase II of the exercise transient
ADP	Adenosine diphosphate
a_g	Gravity acceleration
A_p	Projection area on the frontal plane
ATP	Adenosine triphosphate
$\overleftarrow{A\dot{T}P}$	Rate of ATP hydrolysis
$\overrightarrow{A\dot{T}P}$	Rate of ATP resynthesis
b	Moles of ATP resynthesized per mole of lactate accumulated
BTPS	Body temperature and pressure, saturated with water vapour
C	Energy cost of locomotion
c	Moles of ATP resynthesized per mole of oxygen consumed
$Ca\mathrm{CO}_2$	Carbon dioxide concentration in arterial blood
$Ca\mathrm{O}_2$	Oxygen concentration in arterial blood
C_D	Fraction of energy cost of locomotion to overcome drag
C_f	Fraction of energy cost of locomotion to overcome frictional forces
Cr	Creatine
C_r	Energy cost of running
$C\bar{v}\mathrm{CO}_2$	Carbon dioxide concentration in mixed venous blood
$C\bar{v}\mathrm{O}_2$	Oxygen concentration in mixed venous blood
C_x	Drag coefficient
D	Drag
d	Gas diffusion constant
D_L	Lung diffusing capacity
$D\,\mathrm{O}_{2\mathrm{AL}}$	Alactic oxygen deficit
$D\,\mathrm{O}_{2\mathrm{LA}}$	Lactic oxygen deficit

$D\,O_{2M}$	Muscular oxygen deficit
Dt	Tissue diffusing capacity
DtO_2	Tissue diffusing capacity for oxygen
E	Energy
E_{PC}	Anaerobic alactic component of the metabolic energy expenditure
$\dot{E}$	Metabolic power
$\dot{E}_0$	Y-intercept of the linear relationship between $\dot{E}$ and $\dot{w}$
$\dot{E}_D$	Metabolic power to overcome drag
$\dot{E}_E$	Metabolic power to overcome external mechanical power
$\dot{E}_e$	Metabolic power during exercise time in an intermittent exercise
$\dot{E}_f$	Metabolic power to overcome frictional force
$\dot{E}_I$	Metabolic power to overcome internal mechanical power
E_{La}	Anaerobic lactic component of the metabolic energy expenditure
$Emax$	Maximal capacity
$\dot{E}max$	Maximal metabolic power
$\dot{E}_{NET}$	Net metabolic power
$\dot{E}_R$	Resting metabolic power
$\dot{E}_r$	Metabolic power during recovery time in an intermittent exercise
F_ACO_2	Carbon dioxide fraction in alveolar air
F_AO_2	Oxygen fraction in alveolar air
F_Eco_2	Carbon dioxide fraction in expired air
F_Eo_2	Oxygen fraction in expired air
F_f	Frictional force
f_H	Heart rate
$f_{H,r}$	Heart rate at rest
F_i	Fraction of oxygen flow limitation imposed by the ith resistance to oxygen flow
F_Io_2	Oxygen fraction in inspired air
F_L	Pulmonary fraction of oxygen flow limitation
F_m	Mitochondrial fraction of oxygen flow limitation
F_p	Peripheral fraction of oxygen flow limitation
f_p	Pedalling frequency
F_Q	Cardiovascular fraction of oxygen flow limitation
f_s	Stroke frequency
F_t	Tissue fraction of oxygen flow limitation
F_V	Ventilatory fraction of oxygen flow limitation
G	Gibbs free energy
G_0	Gibbs free energy in a standard condition (1 M at 25 °C and 760 mmHg)
G_L	Pulmonary conductance of oxygen flow
Gly	Glycogen
G_m	Mitochondrial conductance of oxygen flow
G_p	Peripheral conductance of oxygen flow

G_Q	Cardiovascular conductance of oxygen flow
G_t	Tissue conductance of oxygen flow
G_V	Ventilatory conductance of oxygen flow
H	Enthalpy
H	Heaviside function
H_0	Enthalpy in a standard condition (1 M at 25 °C and 760 mmHg)
Hb	Haemoglobin
k	Velocity constant of an exponential equation (subscripts 1 or 2 further indicate pertinence to phase I or phase II of an exercise transient)
k'	Proportionality constant between energy cost against drag and square of speed
k_d	Proportionality constant between drag and square of speed
K_p	Dimensionless constant relating mixed venous and mean capillary oxygen partial pressure
k_t	X-axis asymptote for the three-parameter critical power model
K_W	Wagner's constant
L	Length
$[La]_b$	Blood lactate concentration
$\dot{L}a$	Rate of blood lactate accumulation in blood
M_L	Mass of the legs
n	Number of moles of a chemical compound
NMR	Nuclear magnetic resonance
O_{2def}	Oxygen deficit
P	Pressure
P_ACO_2	Alveolar carbon dioxide partial pressure
P_aCO_2	Arterial carbon dioxide partial pressure
P_AN_2	Alveolar nitrogen partial pressure
P_AO_2	Alveolar oxygen partial pressure
P_aO_2	Arterial oxygen partial pressure
P_B	Barometric pressure
PC	Phosphocreatine
P_c	Capillary partial pressure
P_cO_2	Capillary oxygen partial pressure
$P_{\bar{c}}O_2$	Mean capillary oxygen partial pressure
$P_{c'}O_2$	End-capillary oxygen partial pressure
PCO_2	Carbon dioxide partial pressure (generic)
P_d	Dynamic pressure exerted on a moving body
PFK	Phospho-fructo-kinase
Pi	Inorganic phosphate
P_IN_2	Inspired nitrogen partial pressure
P_IO_2	Inspired oxygen partial pressure (generic)
P_mO_2	Mitochondrial oxygen partial pressure
PO_2	Oxygen partial pressure
Pto_2	Tissue oxygen partial pressure

P_vO_2	Venous oxygen partial pressure
$P_{\bar{v}}CO_2$	Mixed venous carbon dioxide partial pressure
$P_{\bar{v}}O_2$	Mixed venous oxygen partial pressure
Py	Pyruvate
$\dot{P}C$	Rate of phosphocreatine decrease in muscle
q_c	Lung capillary blood volume
Q_s	Stroke volume
$Q_{s,r}$	Stroke volume at rest
$\dot{Q}$	Cardiac output
$\dot{Q}\,ao_2$	Systemic oxygen delivery
$\dot{Q}\,ao_{2max}$	Maximal systemic oxygen delivery
$\dot{Q}_{max}$	Maximal cardiac output
$\dot{Q}_r$	Cardiac output at rest
$\dot{Q}\bar{v}o_2$	Oxygen flow in the mixed venous blood
R	Universal gas constant (in Chap. 1)
R	Resistance
R_i	ith resistance to oxygen flow
R_L	Lung resistance to oxygen flow
R_m	Mitochondrial resistance to oxygen flow
R_p	Peripheral resistance to oxygen flow (in Chap. 4)
R_p	Total peripheral resistance to blood flow
R_Q	Cardiovascular resistance to oxygen flow
RQ_B	Respiratory quotient for blood
RQ_L	Gas exchange ratio
RQ_M	Metabolic respiratory quotient
R_T	Total resistance to oxygen flow
R_t	Tissue resistance to oxygen flow
R_V	Ventilatory resistance to oxygen flow
S	Entropy
S	Slope of a ramp test
S_0	Entropy in a standard condition (1 M at 25 °C and 760 mmHg)
s	Gas solubility constant
Sao_2	Arterial oxygen saturation
STPD	Standard temperature and pressure, dry
T	Temperature
T	Time to exhaustion in a ramp test (in Chap. 5, Fig. 5.3)
t	Time
T_0	Gas temperature at which $E = 0$ J
t_c	Contact time
T_d	Time delay
t_e	Time of exercise during intermittent exercise
t_{lim}	Maximal time that can be sustained at a work rate above critical power
t_r	Time of recovery during intermittent exercise
T_S	Step duration of a discrete ramp test

V	Volume
v	Speed or velocity
$V\mathrm{m}$	Mitochondrial volume
$V\mathrm{o}_2$	Oxygen volume
$V\mathrm{o}_{2\mathrm{M}}$	Oxygen volume extracted by contracting muscles
V_v	Venous blood volume
$V_v\mathrm{O}_2$	Venous blood oxygen store
$\dot{V}$	Gas flow
$\dot{V}_A$	Alveolar ventilation
$\dot{V}_E$	Expiratory ventilation
$\dot{V}_I$	Inspiratory ventilation
$\dot{V}\,\mathrm{co}_2$	Carbon dioxide output
$\dot{V}\,\mathrm{o}_2$	Oxygen consumption/lung oxygen uptake
$\dot{V}\,\mathrm{o}_{2cr}$	Oxygen consumption at critical power/critical oxygen consumption
$\dot{V}\,\mathrm{o}_{2\mathrm{max}}$	Maximal oxygen consumption
$\dot{V}\,\mathrm{o}_2^s$	Oxygen consumption at steady state above resting
$\dot{V}\,\mathrm{o}_2^t$	Oxygen consumption at a given time
W	Work
W'	Work that can be performed above critical power/energy store component
$\dot{w}$	Mechanical power
$\dot{w}_0$	Maximal instantaneous power
$\dot{w}_{\mathrm{cr}}$	Critical power
$\dot{w}_e$	Mechanical power during exercise time in an intermittent exercise
$\dot{w}_r$	Mechanical power during recovery time in an intermittent exercise
$\dot{w}_{\mathrm{max}}$	Maximal mechanical aerobic power
$\dot{w}_{\mathrm{peak}}$	Peak mechanical power of a ramp test
β	Gas transport coefficient
β_b	Oxygen transport coefficient for blood
βc	Carbon dioxide transport coefficient for blood
β_g	Oxygen transport coefficient for air
δ	Distance
Δ	Before a variable, designates a change in the value of that variable
ε	Proportionality constant between internal power and the weight of the legs
ζ	Angular coefficient of the linear relationship between $\dot{E}$ and $\dot{w}$, the reciprocal of which "delta-efficiency of exercise"
η	Mechanical efficiency
Θ	Heat
λ	Proportionality constant between time constant and lactate accumulation in exercise transients
ρ	Air density
τ	Time constant of an exponential equation

τ_1	Time constant of a physiological variable during phase I of the exercise transient
τ_2	Time constant of a physiological variable during phase II of the exercise transient
ϕ	Proportionality constant between internal power and the square of the pedalling frequency times the weight of the legs

Chapter 1
Introductory and Historical Remarks

Abstract This chapter contains a short summary of the historical developments that led to the contemporary vision of the energetics of muscular exercise, from the perspective of the School of Milano created by Rodolfo Margaria. Special attention is given to the history of respiratory gases and to the biochemical developments that led to the conception of intermediate metabolism (glycolysis, Krebs cycle, oxidative phosphorylation) and of the Lohmann's reaction. The developments that led to the cross-bridge theory of muscular contraction are mentioned. The development of the concept of respiratory system and the creation of the oxygen equilibrium curve are also treated. The historical developments concerning key concepts such as maximal oxygen consumption and oxygen deficit are presented. The confutation of Hill and Meyerhof theory of exercise energetics by Margaria is discussed. This confutation led to the formulation of the general equation of the energetics of muscular exercise. The general equation was analytically discussed by di Prampero in 1981. That review was the last systematic overview of the energetics of muscular exercise. Several important reviews came afterwards, but only on specific, selected aspects of the energetics of muscular exercise (e.g. maximal oxygen consumption or exercise transients). This book has the ambition of bridging the temporal gap between di Prampero's review and current knowledge. It is an attempt at providing a critical answer to the following question: How did the general theory of the energetics of muscular exercise resist 30 years of further developments? What could be accommodated into it, what was a challenge to it? Under which respects was it consolidated, and under which respects was it falsified, by the continuously growing knowledge in the field? Answering these questions is a complex, perhaps somewhat presumptuous task, which requires revisiting the concepts discussed by di Prampero in 1981 in the perspective of nowadays knowledge, and introducing and discussing some new concepts, which had been meanwhile created, in the context of the general theory.

G. Ferretti, *Energetics of Muscular Exercise*,
DOI 10.1007/978-3-319-05636-4_1

Contents

Introduction

The mechanical energy (work) of a moving body on Earth, where it is subject to the action of gravity acceleration, is given by the sum of kinetic and potential energy. The kinetic energy is directly proportional to the body mass and the square of speed along the direction of movement, whereas potential energy is directly proportional to the body mass, the acceleration of gravity and the height from the ground. If the path along which the body moves is flat, there is no net vertical movement of the body centre of mass, and potential energy is nil: all the mechanical energy is used to move horizontally along the path, as kinetic exercise. However, when a body moves on Earth, it must also overcome air and frictional resistances. Thus, maintaining a given speed invariant requires also the continuous generation of the amount of mechanical energy (work) that is dissipated to overcome these resistances. The continuous introduction of a new amount of mechanical energy implies energy transformation, in order to comply with the first law of thermodynamics. This energy generally comes from the conversion of chemical energy into mechanical energy. In non-living bodies, chemical energy transformation is due to fuel oxidation in an applied engine, as is the case in cars. In an engine, however, only a fraction of chemical energy can be transformed into mechanical energy, the remainder being transformed into heat: that fraction corresponds to the **mechanical efficiency** of the engine. The **maximal power** of the engine is the maximal rate at which the chemical energy transformation occurs, whereas the **maximal capacity** is the maximal quantity of chemical energy that can be made available to the engine for transformation in mechanical energy. In an ordinary gasoline car, this corresponds to the volume of the fuel tank.

Man is a mammal, and, as an animal, his main characteristic is motion. In animals, motion is sustained by muscular contraction: mechanical energy is generated by the transformation of chemical energy within contracting muscles. Thus, from the physical viewpoint, muscles behave like engines. Ever since it was thought that the chemical energy sustaining muscle contraction in an exercising animal was

derived from aliments. In complex and sufficiently big animals such as mammals, breathing and the heartbeat were also considered essential components of the energy transformation. The inability to understand the chemistry and the physiology of a living body led to several metaphysical theories, which included the action of a vital spirit or of a soul. In the last four centuries, thanks to the change in the psychological approach to science that took place since the sixteenth century, there have been dramatic developments of our chemical and physiological knowledge. The final result, in the present context, was that today it is commonly admitted that mechanical energy for animal motion derives from the **hydrolysis of adenosine triphosphate (ATP) by the ATP-ase activity of myosin** during the cross-bridge cycle in the muscle contraction process. ATP is continuously resynthesized by phosphorylation processes in the biochemical pathways of intermediate metabolism. Nevertheless, muscles are very special engines. Whereas the human-made engines that move cars rely on one source of energy only (gasoline, electricity, alcohol or whatever), muscles rely on three substrates (glycogen, free fatty acids and phosphocreatine) intermingled in **three concomitant energetic pathways (aerobic metabolism, anaerobic lactic metabolism and anaerobic alactic metabolism)**. As a consequence, animals can cover a wide spectrum of locomotion conditions. The two extremes can be exemplified, on one side by Usain Bolt running the 100-m dash in 9.58 s and on the other side by Dennis Kimetto running the marathon in 122 min and 57 s.

In this chapter, I will follow some of the historical developments that led to set the current knowledge in the field of exercise physiology, with special reference to the energetics of muscular exercise. Of course, the pathway was complex, tortuous and filled with accelerations and pauses, parallel tracks and crossings and even oblivions, as splendidly pointed out by Huxley (1978). Here, the aim was not to trace a general history of exercise physiology. My aim is much more limited: I just evidence and list some significant milestones that marked the process that led to set the current view of the energetics of muscular exercise. This simplified approach may give the false impression of a linear, progressive development of scientific knowledge, which I am far from endorsing, but has the advantage, to my eyes, to carry us directly to the starting point of the story that I will tell in this book. This chapter is also my tribute of recognition to the giants, on the shoulders of whom contemporary physiologists have the privilege to sit and look from a widespread and deep perspective at the ever fascinating world of a human at exercise, in an attempt to better and better understand how it works.

A Short History of Respiratory Gases

The understanding of the energetics of muscular exercise proceeded in parallel with the basic developments in chemistry and physiology. The construction of the chemistry of gases was one of the main scientific adventures of the seventeenth and eighteenth centuries. The concept of gas was well presented in previous times,

and pre-scientific wise men were aware of the existence of air, although it was thought that air consisted of a single, pure gas. This concept was present also in the mind of Robert Boyle (1627–1691), when he described the inverse relationship between pressure and volume in a given quantity of gas. This relationship indicated that the amount of energy contained in that very amount of gas was a constant.

The concept of **temperature** was created in the same epoch. The scientific revolution of those times, introducing the notion of quantitative experimental science, imposed the need of finding an objective manner of measuring heat—no more the terms hot and cold sufficed, in the new context. The result was the invention of temperature, and the thermometer was the instruments associated with its measurement. Of the many temperature scales invented in those times, one was particularly successful, the centigrade scale that was proposed by Anders Celsius (1701–1744) in 1742. The subsequent demonstration that Boyle's constant—the product of pressure and volume of a given gas quantity—varied linearly with temperature led Emile Clapeyron (1799–1864) to the definition in 1834 of what is now known as the **equation of state of perfect gases** (Fig. 1.1), whose algebraic formulation is as follows:

$$E = PV = nR(T - T_0) \tag{1.1}$$

where E, P, V and T stand for energy, pressure, volume and temperature (expressed in °C), n represents the amount of gas, currently expressed in moles, and R indicates the amount of energy introduced into 1 mol of gas by a unit increase in temperature, corresponding to the slope of the linear relationship for $n = 1$ in Fig. 1.1. Constant T_0, which appears in Fig. 1.1 as the x-axis intercept on which all isopleths for n converge, is the temperature at which $E = 0$ J. It corresponds to −273.14 °C and

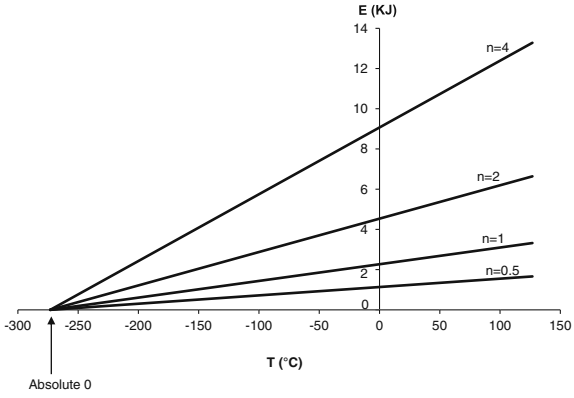


Fig. 1.1 Relationship between energy (E, in kJ), i.e. the product of pressure times volume, and temperature (T, in °C) for given quantities of gas. Straight lines for the four indicated molar amounts of gas (n) are reported. The slope of the line for $n = 1$ yields what was called the universal constant of perfect gases (R). The x-axis intercept indicates the temperature at which $E = 0$ kJ, which was defined as the absolute zero. Taken from Ferretti and Capelli (2008)

was called the absolute zero. When Lord William Kelvin (1824–1907) set this temperature equal to zero—in practice, in Fig. 1.1, he shifted the *x*-axis intercept rightwards to have it coinciding with the origin of the axes— he gave origin to the absolute temperature scale, named in his honour. This very simple operation implies that, if in Eq. (1.1) we express temperature in absolute scale (Kelvin degrees, °K) instead than in centigrade scale, we obtain the following:

$$E = PV = nRT \tag{1.1a}$$

In fact, Eq. (1.1a) sets a relation of direct proportionality between energy and temperature, which allowed reintroducing **heat** in the game as a form of energy. More than a century later, since for any given quantity of gas:

$$PVT^{-1} = nR \tag{1.1b}$$

which is a constant, Eqs. (1.1a) and (1.1b) provided the physical basis for the criteria of quantitative standardization for gas volumes and flows, which were established by the American Physiological Society. Two standard conditions for volume measurement comparisons were defined, one called **BTPS**—body temperature (37 °C or 310 °K) and pressure (barometric pressure of the day), saturated with water vapour (47 mmHg at 37 °C)—the other called **STPD**—standard temperature (0 °C or 273 °K) and pressure (760 mmHg), dry. Conventionally, the former is used for standardizing volumes and flows of overall gas mixtures such as air, so that pulmonary ventilation or lung volumes are expressed in BTPS condition and the latter is employed for flows or volumes of a single pure gas (American Physiological Society 1950). This convention is respected in this book.

Despite the fact that about a century earlier John Mayhow (1643–1679) had already perceived that muscle work involved some kind of "nitro-aerial" component of air, the processes of respiration and metabolism started to be seen in a little bit clearer way only after Joseph Black (1728–1799) had "discovered" **carbon dioxide** in 1764, which he called "fixed air", and which he realized to be liberated by respiration, and Joseph Priestley (1733–1804) had "discovered" **oxygen** in 1774, which he called "dephlogisticated air", which means air free from phlogiston (see below). Shortly afterwards, Antoine Lavoisier (1743–1794), who coined the name oxygen, realized that this gas was not only essential to human life, for humans consume oxygen, but was essential also to human locomotion and exercise, for he demonstrated that oxygen consumption ($\dot{V}O_2$) increased when a man exercised. Moreover, together with Armand Séguin (1767–1835), he showed that exercise was associated also with an increased elimination of carbon dioxide and an increased production of heat. These observations implied that the chemical energy transformation supporting the production of mechanical energy in muscle contraction was a process of **combustion**, in which oxygen played the role of oxidizer, and carbon dioxide was the end product.

This conclusion had two conceptual consequences: (1) the process of chemical energy transformation requires oxidation of an organic fuel, and (2) a tight match

between oxygen consumption and fuel degradation must be in place. But no idea existed about the chemical transformations at stake and the way this matching could take place. In fact, Lavoisier was convinced that combustion took place in the lungs and that the heat produced during combustion was taken away by means of blood circulation. Adair Crawford (1748–1795), a pupil of Joseph Black, put forward another curious theory of animal heat, which in modern terms can be summarized as follows: the oxygen contained in ambient air gives up its heat as it is converted into carbon dioxide in the lungs; the heat liberated by oxygen transformation does not lead to an increase in lung temperature, because of differences in the specific heat of arterial and venous blood, such that the blood in the pulmonary vein undergoes an increase in specific heat as a consequence of heat exchange from the lung. To explain these "events", Crawford resurrected the phlogistic theory, created by Georg Ernst Stahl (1660–1734), according to which combustibles consisted of ash combined with a fire principle, the "phlogiston", which was liberated during burning: fire could not be maintained in closed spaces because air became saturated with phlogiston. Crawford believed that the action of phlogiston prompted the alleged heat exchange between lungs and arterial blood, despite Lavoisier had already falsified the phlogiston theory by means of his demonstration that combustion was the result of a combination of a fuel with oxygen. A nice example indeed of how difficult is to discard by means of experimental falsification a theory that has become a belief.

The identification of oxygen and carbon dioxide had a huge impact also in another sense, since it provided a demonstration that air is not a "pure" gas, but a mixture of different gases, some of which were essential for life. Priestley had already shown that oxygen was one of the chemical components of air. Yet, and surprisingly enough in those times, the most abundant gas in air was neither oxygen nor carbon dioxide, but **nitrogen**, whose identification is generally attributed to Daniel Rutherford (1749–1819), although its existence had already been perceived by Priestley, Scheele and Cavendish, and although Rutherford did not realize it was a pure gas, but thought it was air saturated with phlogiston. It was once more Lavoisier, perhaps the greatest genius of the classical epopee of gas chemistry, who first recognized nitrogen to be a pure gas and realized that air was a mixture of at least an "active" gas (oxygen), sustaining combustion and respiration, and an "inactive" gas, nitrogen, fully inert with respect to respiration. Subsequently, the study of gas mixtures led John Dalton (1766–1844) to define the independent behaviour of single gases in a mixture, whose quantitative description is called Dalton's law, and to create the concepts of **partial pressure** of a gas and of gas fraction. With time, several other inert components of air were identified and quantitated. What is currently considered the normal composition of dry atmospheric air is reported in Table 1.1. In respiratory and exercise physiology, in view of their very small fraction in air composition, inert gases other than nitrogen are normally neglected.

The partial pressure of a given gas in air, when air is exposed to a liquid, is the force that pushes that gas to dissolve into the liquid. The amount of gas entering the liquid is exactly the one that is necessary to counterbalance the action of external

Table 1.1 Fractional composition of dry air, and the corresponding partial pressures, at the indicated altitudes above or depths below sea level

	O_2	CO_2	N_2	Other gases	Atmosphere	Atmosphere
Gas fraction	0.2094	0.0003	0.78	0.0103	1	1
Gas pressure	PO_2 (mmHg)	PCO_2 (mmHg)	PN_2 (mmHg)	P_{gas} (mmHg)	P (mmHg)	P (Atm)
Top of Mount Everest (8848 m)	53.0	0.08	197	2.6	253	0.3
Top of Mont Blanc (4810 m)	90.0	0.13	335	4.4	430	0.6
La Paz, Bolivia (3600 m)	104.7	0.15	390	5.1	500	0.7
Mexico City (2200 m)	121.5	0.17	452	6.0	580	0.8
Sea level	159.1	0.23	593	7.8	760	1.0
Depth—10 m	318.3	0.46	1186	15.7	1520	2.0
Depth—20 m	477.4	0.68	1778	23.5	2280	3.0
Depth—50 m	954.9	1.37	3557	47.0	4560	6.0
Depth—100 m	1750.6	2.51	6521	86.1	8360	11.0
Depth—300 m	4933.5	7.07	18,377	242.7	23,560	31.0

It is noteworthy that inspired air attained the alveoli saturated with water pressure at body temperature (37 °C): as a consequence, at sea level, $P_IO_2 = 0.2094\ (P - PH_2O) = 0.2094\ (760 - 47) = 150$ mmHg. Under other gases, the greatest fraction is that of argon (0.0093). Carbon dioxide is present with 394 ppm, neon with 18 ppm, helium with 5 ppm, methane with 2 ppm, krypton with 1 ppm, hydrogen with 0.6 ppm and nitrous oxide with 0.3 ppm. Other gases such as carbon monoxide, xenon, ozone and nitrogen dioxide are also present with smaller fractions

partial pressure. This led William Henry (1774–1836) to establish the relation of direct proportionality between gas pressure and gas concentration in a liquid. On this basis, the partial pressure of a gas in a liquid (e.g. blood) was defined as the pressure that is necessary to keep a given gas concentration in that very liquid. The law of Henry sets the physical context for otherwise bizarre expressions such as "oxygen partial pressure in arterial blood", as long as there is no column of oxygen above arterial blood and actually compressing it directly.

Of Energy and Work

At the beginning of the nineteenth century, the identification of heat as a form of energy led to the creation of a new branch of chemistry, now called thermodynamics. In this context, the law of energy conservation states that in a close thermodynamic system, the overall amount of energy is a constant. The internal energy

of a part of the system can thus vary only if there is energy transfer in or out that part of the system. Spontaneously, any thermodynamic system tends to a condition of equilibrium. This equilibrium, however, is not necessarily attained at the state where the system possesses the minimum amount of energy. Two tendencies coexist, one moving towards a state of minimal energy and the other moving towards a state of maximal disorder. The former tendency is reflected by the variations of **enthalpy** (H, in J). In a reaction occurring at constant pressure and volume, the variations of enthalpy correspond to the heat (Θ) that is liberated (negative sign, spontaneous exergonic reaction) or absorbed (positive sign, endergonic reaction) by the system. The latter tendency is reflected by the variations of **entropy** (S, in J K^{-1}), which is the constant characterizing the relationship between heat and temperature. Entropy is qualitatively defined as the tendency of a system to evolve towards a state of greater "disorder". The equilibrium between these two tendencies is defined by their combination in the following form:

$$G = H - T \cdot S = \Theta + P \cdot V - T \cdot S \tag{1.2}$$

where G is the overall energy possessed by a given part of the system and is termed **Gibbs free energy**, in honour of Willard Gibbs (1839–1903), who created the concept of entropy and defined the equilibrium between enthalpy and entropy in 1874–1878. A consequence of Eq. (1.2) is that any chemical reaction proceeds spontaneously as long as the tendency is towards the attainment of minimal G. G cannot be measured in absolute terms, but we can measure its variations in the course of a chemical reaction. The variations are generally measured in a standard condition (1 M at 25 °C and 760 mmHg), designated with suffix 0:

$$\Delta G_0 = \Delta H_0 - T \cdot \Delta S_0 \tag{1.2a}$$

In 1847, Hermann Ludwig von Helmholtz (1821–1894) demonstrated that the law of energy conservation applies also to living organisms, including man (Atwater 1904). This implied that Eq. (1.2) applies to all chemical reactions occurring in humans. Keeping a human alive requires increasing his amount of G, while death implies a decrease in G. This explains why life requires continuous introduction of energy from outside into the living system. Moreover, all reactions characterised by an increase in G necessitate external energy supporting them.

Meanwhile, the development of the first techniques of motion pictures, anticipating the birth of the cinematograph, allowed Etienne-Jules Marey (1830–1904) and Georges Demény (1850–1917) to carry out the first mechanical analyses of human locomotion. These authors established the principles on which Wallace Fenn (1893–1971) constructed the laws of human motion, which are still applied nowadays in the study of human locomotion, and created the concepts of external and internal work (Fenn 1930).

The advancements in optical microscopy led also to the first structural descriptions of muscle fibres. Already in 1781, Felice Fontana (1730–1805) realized that muscle fibres consisted of fascicles of many cylinders disposed in series, with regular indentations that conferred an aspect of striation. William Bowman (1816–1892) demonstrated that these cylinders consisted of compact bundles of parallel fibrils, enclosed by a thin membrane that he called sarcolemma (Frixione 2006). From fibrils, in 1864, Wilhelm Kühne (1836–1900) extracted a protein, which he called **myosin**. The ATP-ase activity of myosin was demonstrated only (Engelhardt and Lyubimova 1939) after Kurt Lohmann (1898–1978) had identified, in 1928, a new type of high-energy organic phosphate called **adenosine-tri-phosphate (ATP)**, and had demonstrated, in 1934, that this was the essential energy provider for muscular contraction. Louis-Antoine Ranvier (1835–1922) recognized, in 1873, two different types of muscle fibres, "white" and "red", with different structural and functional characteristics, the latter being rich with mitochondria and filled with a pigment called myoglobin and contracting at slow speed. **Actin** entered the game in 1943, thanks to the work of Albert Szent-György (1893–1986) and Bruno Ferenc Straub (1914–1996). The former was awarded the Nobel Prize for Physiology and Medicine in 1937 for his contributions to the understanding of the metabolism of ascorbic acid (C vitamin). By 1945, all bricks were in place to allow the conclusion, undisputed ever since, that **the energy transfer during muscular contraction was to come from ATP hydrolysis** with the liberation of one mole of inorganic phosphate per mole of ATP split. On a somewhat longer time scale, reversal of this reaction implied phosphorylation of adenosine diphosphate (ADP) by the transfer of inorganic phosphate from phosphocreatine (Lohmann's reaction). The concentration of phosphocreatine was then maintained or restored by the organic phosphates generated in glycolysis and oxidative metabolism. The mechanisms of work generation were underpinned a few years later, after the developments in electron microscopy. Beside confirming several histological observations of the nineteenth century meanwhile forgotten (Huxley 1978), the use of electron microscopy allowed the identification of the sliding process of intermingled thick and thin filaments in the sarcomere (Hanson and Huxley 1953; Huxley 1953; Huxley and Niedergerke 1954; Huxley and Hanson 1954). These structural observations led Sir Andrew Huxley (1918–2013), who was awarded the Nobel Prize for Physiology or Medicine in 1963 for his contribution to our understanding of action potential generation and transmission in nerve axons, to formulate the **sliding filament theory, or cross-bridge theory, of muscular contraction** (Gordon et al. 1966; Huxley 1957, 1974). A nice history of the events that led to the sliding filament theory was published by Huxley himself (Huxley 1978). ATP hydrolysis is integrated in the theory as the chemical reaction yielding, through the cross-bridge cycle, the energy allowing the shortening of the sarcomere during contraction. For details on the mechanisms of muscle contraction, a reader can refer to several fine reviews (Goldman 1987; Gordon et al. 2000; Huxley 2000).

Oxidative and Anaerobic Metabolism

The question of what could be the fuel supporting the combustion process that generates mechanical energy for locomotion and movement started to receive an answer after the chemical experiments on aliments of the first half of the nineteenth century, when carbohydrates and fatty acids were identified by Justus von Liebig (1803–1873) and Michel Eugène Chevreul (1786–1889). The evolution of chemical knowledge afterwards progressively led to the definition of the main biochemical pathways of intermediate metabolism, and particularly **glycolysis** [by Otto Fritz Meyerhof (1884–1951), Nobel Prize winner for Physiology or Medicine in 1922] (Meyerhof 1921, 1924), the **Krebs cycle** [by Hans Krebs (1900–1981), Nobel Prize winner for Physiology or Medicine in 1953, and Hans Kornberg] (Krebs and Kornberg 1957), the **beta oxidation of fatty acids** and the **oxidative phosphorylation** in the electron transport chain.

The definition of these fundamental pathways was not the result of a discovery made by a genius. Meyerhof and Krebs made the final synthesis out of a process lasting tenths of years and implying the work of several scientists from numerous laboratories who defined the single steps and described the various chemical components of each pathway. Concerning beta oxidation, this work of synthesis was carried out mainly by Beinert (1963); for oxidative phosphorylation, we are indebted mainly to Peter Mitchell, Nobel Prize winner for Physiology or Medicine in 1978, and to David Keilin (Mitchell 1979). The ensemble of these pathways constitutes the biochemical basis of what is nowadays known as **oxidative metabolism**. Oxidative metabolism explains exhaustively the links between substrates (fuel) and oxygen (oxidiser) and the tight coupling between oxygen consumption and carbon dioxide production, since carbon dioxide is a major side product of the combustion process. Those who are interested in the historical details of this epopee can refer to various reviews on the subject (Ghisla 2004; Kornberg 2000; Krebs 1970; Mitchell 2004, 2011; Racker 1983).

Glycolysis was the first biochemical pathway of intermediate metabolism to be fully described. The process of formation of lactate as a results of glycolysis, through the reduction of pyruvate, which can be looked at as the end point of the glycolytic pathway, was already inserted in a coherent picture by 1927, although several details were still to be identified (Meyerhof and Lohmann 1927). Six years later, the overall glycolytic pathway was elucidated (Embden et al. 1933). The growing knowledge on glycolysis had a great impact on the early development of exercise physiology and specifically of the energetics of muscular exercise. After Fletcher and Hopkins (1907) demonstrated that **lactic acid**, an end product of glycolysis, accumulates in contracting muscles, Archibald Vivian Hill (1886–1977), who shared with Otto Meyerhof the 1922 Nobel Prize for Physiology or Medicine, formulated in 1924 the first systematic theory of the energetics of muscular contraction (Hill 1924). According to this theory, the main energy source for muscle contraction is the oxidation of glycogen to lactic acid through glycolysis: oxygen consumption intervenes at a later stage, during recovery, to ensure the

complete oxidation of a fraction of the accumulated lactic acid, allowing for the resynthesis of glycogen from the remainder of lactic acid. In this context, Hill created the term **oxygen debt** to define the volume of oxygen consumed to this aim.

When Hill formulated his theory of the energetics of muscular exercise, lactic acid was well known since long. It was originally identified by Carl Wilhelm Scheele (1742–1786), who isolated it from sour milk as impure brown syrup. It was soon recognized as an important chemical component of living organisms. In 1808, Jöns Jacob Berzelius (1779–1848) demonstrated that lactic acid is produced in muscles during contraction. He also identified **pyruvic acid** in 1835. The structure was established by Johannes Wislicenus (1835–1902) in 1873. The structure of the enzyme catalysing the reduction of pyruvate to form lactate, then called **lactate dehydrogenase**, was fully described in 1933 (Andersson 1933).

The reversible reduction of pyruvate into lactate was the chemical keystone of Hill's theory. The biochemical foundation of the theory implied glycogen oxidation to pyruvate that, during muscle contraction, is converted into lactate. At the end of exercise, pyruvate synthesis falls and the equilibrium of the reaction is inverted to the oxidation of lactate—accumulated in excess—into pyruvate. Of this, part is further oxidized by the Krebs cycle in order to generate the energy sustaining the endergonic process of glycogen resynthesis.

Hill's theory of the energetics of muscular exercise did not establish a clear distinction between aerobic and anaerobic metabolism. Whereas the energy balance during muscle contraction was seen as an essentially anaerobic process, centred on lactate synthesis and accumulation, the energy balance during recovery was seen as an aerobic process, for oxygen consumption was thought to be necessary to glycogen resynthesis. The cycle was closed by the combination of the two processes. Moreover, a crucial step was missing that related to the transformation of chemical energy into mechanical work. The further evolution of biochemical knowledge bridged this gap and undermined Hill's theory. A new actor was entering the scene: **phosphate**.

Already in 1922, Embden and Lawaczek observed that the concentration of inorganic phosphate increases during muscle contraction, suggesting the hypothesis that some phosphate-containing compound, called "phosphagen", might play a key role in the conversion of chemical energy into mechanical energy. Soon, the concept of phosphagen was related to a new substance that had been identified in muscle: **phosphocreatine** (Eggleton and Eggleton 1927). The fall of phosphocreatine concentration in muscle following contraction (Nachmanson 1928) was soon associated with the increase in inorganic phosphate. Was phosphocreatine the phosphagen? The observation by Lundsgaard (1930) that a muscle poisoned with mono-iodo-acetic acid can contract without lactic acid accumulation seemed to give a positive answer to this question, by excluding lactate as a necessary chemical intermediate of muscle contraction. But this was not so. Kurt Lohmann (1898–1978), who in 1928 had identified a new type of high-energy organic phosphate called **adenosine-tri-phosphate (ATP)** (Lohmann 1928), demonstrated in 1934 that this was the essential energy provider for muscular contraction (Lohmann 1934). The demonstration of the

ATP-ase activity of myosin (Engelhardt and Lyubimova 1939) provided a potential direct mechanism for the conversion of chemical energy stored in ATP into mechanical work.

Hill understood that the appearance of phosphagen, or more in general phosphates, on the scene could undermine his vision. He was a real scientist and accepted the risk of refutation. In 1932, he wrote a marvellous review (Hill 1932), in which, from a "loser" perspective, he announced a "revolution" in muscle physiology and tried to defend his theory by integrating the new ideas in it—pretty much as Necker, prime minister of King Louis XVI, tried to do at the onset of the French revolution in 1789. This is a text that every physiologist should read to take a lesson of humility and intellectual honesty. However, it was not phosphate that killed Hill's theory. Phosphate could in principle be accommodated in Hill's theory by considering it as the link between the chemical pathway and the contractile unit in muscle fibres.

Refutation of Hill's theory was provided by Rodolfo Margaria (1901–1983) and David Bruce Dill (1891–1986) (see Fig. 1.2) on a totally different basis, before the understanding of the role of ATP in muscular contraction. Hill's theory predicted that during recovery after exercise, if oxygen is consumed to remove the lactate accumulated during muscle contractions, there must be parallelism between lactate

Fig. 1.2 Portrait of Rodolfo Margaria (*left*) with David Bruce Dill. They were co-authors of the celebrated 1933 paper in which refutation of Hill's theory of the energetics of muscular exercise was provided. The paternity of the idea was recognized to Margaria by Dill himself

disappearance from blood and oxygen consumption. Margaria et al. (1933), in a classical paper that set basis for most of the subsequent developments in the field, demonstrated that the kinetics of $\dot{V}O_2$ during recovery after exercise differs from that of lactate removal, the former being much faster than the latter (half time of ~40 s vs. ~15 min, respectively), thus being acquitted from the charge of responsibility in lactate removal. Moreover, the demonstration that during light exercise there is an increase in $\dot{V}O_2$ in the absence of lactate accumulation provided the final dissociation of the two and led to the recognition of oxygen consumption as a direct energy source for muscular exercise.

Margaria was the first to talk of different, yet concomitant metabolisms during exercise, namely **aerobic metabolism**, sustaining light exercise for long periods of time, and **anaerobic metabolism**, sustaining explosive exercise but for short periods of time. He later corrected his view by including phosphagen and the resynthesis of ATP from the Lohmann's reaction in the picture and splitting the concept of anaerobic metabolism in two: **anaerobic lactic metabolism**, implying lactate accumulation in blood, and **anaerobic alactic metabolism**, centred on the ATP resynthesis from phosphocreatine without lactate accumulation. The latter accounts for explosive efforts of few seconds duration. In his view, each metabolism was characterized by a **maximal capacity**—maximal amount of energy that it can provide—and by a **maximal power**. Maximal oxygen consumption was identified as the maximal power attained by aerobic metabolism. He defined the maximal lactic power as the power yielding the maximal rate of blood lactate accumulation (he said production, Margaria et al. 1964). This definition implied the concept of an **energy equivalent of blood lactate accumulation** (Margaria et al. 1963). More generally speaking, Margaria was convinced, and rightly enough in my opinion, that there must be a relationship of direct proportionality between the variables characterizing each metabolism—steady state $\dot{V}O_2$ for aerobic metabolism, rate of increase in blood lactate concentration for anaerobic lactic metabolism, rate of decrease in muscle phosphocreatine concentration for anaerobic alactic metabolism—and the rate of energy delivery (metabolic power) of each metabolism. The maximal powers and capacities and the corresponding energy equivalents, as reported by di Prampero (1981), are shown in Table 1.2.

The subsequent complete description of the reaction chains involved in intermediate metabolism—Krebs cycle and oxidative phosphorylation—the demonstration that in a contracting muscle phosphocreatine concentration decreases

Table 1.2 Maximal capacity (*Emax*), maximal power ($\dot{E}max$) and time (*t*) at $\dot{E}max$ for the three energetic metabolisms, calculated for an ordinary human at 25 years of age

	Emax (mmol kg^{-1})	$\dot{E}max$ (μmol kg^{-1} s^{-1})	*t* at $\dot{E}max$ (s)
Anaerobic alactic	1.65 − 0.022 $\dot{V}O_2^s$	120 − 1.6 $\dot{V}O_2^s$	7.5
Anaerobic lactic	2.5	56	44
Aerobic	126 t − 0.132 t^2	37	56,400 – 1200 $\dot{V}O_2^s$

$\dot{V}O_2^s$ is the steady-state oxygen uptake. Modified after di Prampero (1981)

proportionally to the increase in $\dot{V}O_2$, the analysis of blood lactate accumulation in supramaximal exercise, defined as an exercise requiring a $\dot{V}O_2$ higher than the maximum, the creation of the concept of oxygen deficit and the energetic analysis of rest-to-exercise transients, have led to the formulation of a **general theory of the energetics of muscular exercise**, which we mostly owe to the physiological school that Rodolfo Margaria established in Milano after World War II. This theory was shaped in a fundamental paper published in 1968 (di Prampero and Margaria 1968) and received its systematic representation in a celebrated critical review by di Prampero (1981) a few years later. Although with some refinements, and with the addition of some further bricks—think for instance of the concepts of maximal instantaneous muscular power and of multifactorial $\dot{V}O_{2\,max}$ limitation of maximal oxygen consumption— the general theory of the energetics of muscular exercise still represents the essence of the contemporary conception of exercise physiology. It definitely is the keystone sustaining the development of thinking in this book.

The Respiratory System

Providing oxygen to sustain oxidative metabolism is nonetheless an enormous problem due to body size, since oxygen must be taken from ambient air to be utilized in cell mitochondria. Moving oxygen from ambient air to mitochondria requires a complex, huge, finely tuned oxygen transfer system (Weibel 1984). This is called the **respiratory system**, which includes several components in series. The first component consists of the lung–thorax apparatus, which is responsible for the transfer of oxygen from ambient to the lung alveoli, where it can diffuse to lung capillaries to join arterial blood. The second component includes the heart and the circulation of blood, which is responsible for oxygen transfer from lung capillaries to peripheral capillaries (at exercise, mostly muscle capillaries). The third is very vast, consisting of the entire network of body cells, within which oxygen diffuses from peripheral capillaries to mitochondria: at exercise, since blood is destined essentially to working muscles, predominant becomes the diffusion of oxygen across muscle fibres. This holistic vision of the respiratory system gave rise to a number of quantitative analyses that are resumed in the algebraic concept of **oxygen cascade**, created on the analogy with the electric resistance model. The oxygen cascade (Fig. 1.3) relies on the concept that oxygen flow (the analogous of current) occurs sustained by a pressure gradient (potential) against several resistances in series. We owe the first exhaustive algebraic formulation of the oxygen cascade concept (oxygen conductance equation) to Shephard (1969). The same respiratory system sustains also the transfer of carbon dioxide produced by the oxidative metabolism, flowing however in the opposite sense with respect to oxygen. But this is not all. The respiratory system must sustain and ensure adequate oxygen delivery to working muscles at all submaximal powers, since oxygen consumption during exercise is directly proportional to mechanical power. Finally, the activity of the

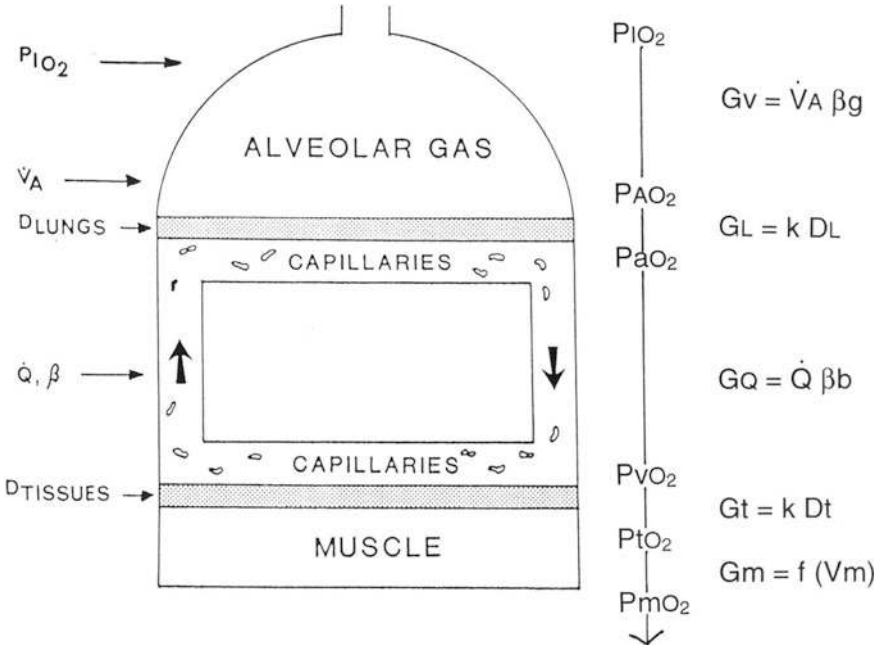


Fig. 1.3 A sketch of the oxygen cascade from ambient air to cells. The assumption is that oxygen flows from ambient air to the mitochondria driven by oxygen pressure gradients against in series resistances. The following partial pressures for oxygen are indicated, from proximal to distal: inspired air (P_IO_2), alveolar air (P_AO_2), arterial blood (P_aO_2), venous blood ($P_{\bar{v}}O_2$), tissue cytoplasm (P_tO_2) and mitochondria (P_mO_2). The corresponding conductances are the ventilatory (G_V), lung (G_L), cardiovascular (G_Q), tissue (G_t) and mitochondrial (G_m) conductance. Of these, only G_V and G_Q are identified by measurable physiological variables, whereas G_L, G_t and G_m are made proportional to a lumped variable. $\dot{V}_A$, aleveolar ventilation; β_g, oxygen transport coefficient in air; $\dot{Q}$, cardiac output; β_b, oxygen transport coefficient in blood; D_L, lung diffusing capacity; D_t, tissue diffusing capacity; and V_m, mitochondrial volume. From Taylor and Weibel (1981)

respiratory system must be coupled with that of fuel flow, to converge to the end point of oxidative metabolism, namely the synthesis of ATP in the electron transport chain.

The holistic vision of the respiratory system is widely accepted nowadays, to be even integrated in the scopes of a major scientific journal in the field (Respiration Physiology and Neurobiology). Yet this is a relative novel approach. For centuries, respiration was considered to be the function of the lungs, blood convection the function of the heart and of the circulatory system, and muscle contraction and oxygen consumption the function, at least at exercise, of muscles. Historically, each of these systems was taken as an autonomous system, whose function was independent from, though, for homoeostatic reasons, somehow connected with, that of the other systems.

Going through the history of respiration in detail is impossible in this book. Several excellent texts on this subject are available in the literature, think for instance of the magnificent historical chapter of the first edition of the Handbook of Physiology (Perkins 1964). What counts here is to stress how, at a given time, focus was moved from an organistic vision to a holistic vision of the respiratory system. This epochal change occurred approximately around World War II, and I think it is essentially a consequence of the deep evolution of knowledge in respiration that took place in those times, especially in the field of gas exchange. The construction of the body of knowledge that set the fundaments of all subsequent developments in gas exchange physiology led to the algebraic definition of the **three-compartment model of gas exchange** (Riley and Cournand 1949) and to the analytical construction of the **O_2-CO_2 diagram** (Rahn and Fenn 1955). The missing rings in this chain were the quantitative analysis of the diffusion–perfusion interaction at alveolar and peripheral levels. These rings were forged in Göttingen some 30 years later, when the **diffusion–perfusion interaction equations** were developed (Piiper and Scheid 1981; Piiper et al. 1984).

These concepts contain a well-defined notion of the oxygen cascade principle, to which they gave full physiological meaning. Its first formulation, however, well preceded those studies, for it can be traced back to Paul Bert (1833–1883) and Claude Bernard (1813–1878) and to the definition of homoeostasis by the latter (Bert 1870; Bernard 1879). Yet their pioneering vision was concealed by the predominant organistic approach to physiological research. This approach was so strongly rooted that, despite the epochal developments in gas exchange physiology prompted in the USA under the pressure of the war effort, it is still present under several respects in contemporary physiological research. This is another example of what Andrew Huxley called "negative progress" in scientific knowledge (Huxley 1978).

A corollary of the above developments was the redefinition of the **steady-state concept**, according to which the flow of oxygen along the entire pathway from ambient air to peripheral cells is at steady state if and only if this flow is (i) invariant in time and (ii) equal at each point along the pathway. The same is the case for carbon dioxide flow, on the opposite direction. The mirror concept is that of unsteady state, which refers to all situations in which the two points above are not fulfilled. As a consequence, there occurred a split of the respiratory quotient concept in two: (i) the metabolic respiratory quotient (RQ_M) that refers to the ratio of CO_2 production to O_2 consumption in cellular intermediate metabolism, whose value depends on the substrate mixture that is being oxidized; and (ii) the gas exchange ratio (RQ_L) that concerns the ratio of CO_2 output ($\dot{V}\,CO_2$) to O_2 uptake ($\dot{V}\,O_2$) in the lungs. At steady state, the respiratory quotient is the same along the entire oxygen pathway, so that RQ_M and RQ_L must coincide. In unsteady states, however, RQ_M and RQ_L must be dissociated, taking different values due to the mobilization of body CO_2 stores. The novelty here is the term "must", since it implies the logical necessity of a theoretical analysis. Of course, the respiratory quotient was measured from respiratory gas flows also before this definition of steady state, but the relation of a respiratory quotient measured at the mouth to the

fractional utilization of substrates in oxidative metabolism in the cells was assumed on a practical basis, and it was not a necessary consequence of a systematic theory or respiration including the concepts of unsteady states.

The steady-state concept was nevertheless challenged in recent times during intense exercise, after the introduction of two other pertinent concept, which I will try to integrate in the general theory, namely that of critical power (Monod and Scherrer 1965) and of slow component (Poole et al. 1994).

Maximal Oxygen Consumption

Another pillar in the construction of exercise physiology was the creation of the concept of **maximal oxygen consumption** ($\dot{V}\,O_{2\,max}$), which is exemplified in Fig. 1.4. It was obvious that the increase in oxygen consumption with power could not proceed indefinitely. Yet the concept of $\dot{V}\,O_{2\,max}$ was created, when it was observed that the linear relationship between oxygen consumption and mechanical power attains a plateau which cannot be overcome (Verzar 1912; Hill and Lupton 1923; Herbst 1928). This concept set an upper limit to the power developed by oxidative metabolism. Such a limit must be imposed somewhere along the oxygen pathway. The quest for the factor that limits $\dot{V}\,O_{2\,max}$ has not ceased ever since. At first, also under the pressure of the organistic vision, physiologists focused on the search of the single factor limiting $\dot{V}\,O_{2\,max}$. An impressive body of knowledge led to

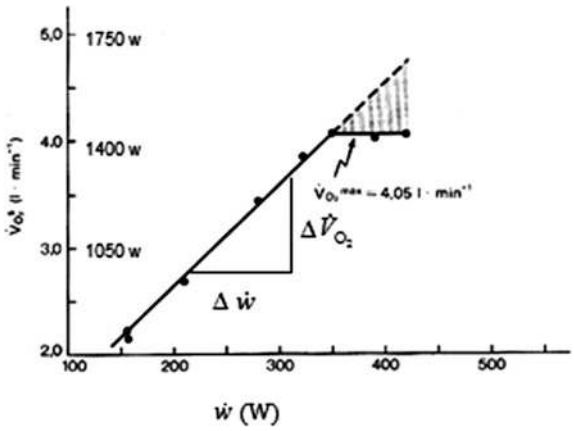


Fig. 1.4 Classical graphical representation of the relationship between oxygen uptake at steady state ($\dot{V}\,O_2$) and mechanical power on the cycle ergometer ($\dot{w}$) up to the maximal oxygen consumption ($\dot{V}\,O_{2\,max}$). The attainment of $\dot{V}\,O_{2\,max}$ is demonstrated by the plateau in the relationship above a given power. Expressing $\dot{V}\,O_2$ in W, the slope of the line ($\Delta\dot{V}\,O_2/\Delta\dot{w}$) is equal to the reciprocal of the mechanical efficiency of exercise. Modified from di Prampero (1985b)

the conclusion that $\dot{V}O_{2\,max}$ is limited by the cardiovascular system (Åstrand 1952; Ekblom 1969; Saltin 1973; Scheuer and Tipton 1977), a concept—surprisingly enough—still heavily hinged in most recent physiological thinking (Levine 2008).

In contrast with this, on the basis of apparently contradictory evidence with the above principles, obtained especially in altitude studies or in studies on exercise with small muscle masses, other authors concluded that muscle oxidative capacity, rather than cardiovascular oxygen transport, limits $\dot{V}O_{2\,max}$ (Cerretelli 1980; Saltin 1977). The search for the factor that limits $\dot{V}O_{2\,max}$ in humans had brought to such a diversity in viewpoints, that a long-lasting, stirred and essentially unresolved debate developed for several decades, so that still in 1992, Saltin and Strange could state that no consensus exists on what limits the $\dot{V}O_{2\,max}$.

Nevertheless, under the positive pressure of the holistic view of the respiratory system, something slowly changed in the perception of $\dot{V}O_{2\,max}$ limitation. Prompted by the holistic definition of steady state, and by the creation of the oxygen conductance equation and of the diffusion–perfusion interaction equations, new multifactorial models of $\dot{V}O_{2\,max}$ limitation were developed. The starting axiom was that several factors acting at different levels along the respiratory system, each providing a measurable fraction of the overall limitation, could limit $\dot{V}O_{2\,max}$, rather than a single factor, generally corresponding to an organ—system (the lung, the heart the blood circulation and the muscles). The track along this way was traced by Taylor and Weibel (1981) in a context of comparative physiology. Shortly afterwards, they were followed by di Prampero (1985a), who formulated the first algebraic version of a multifactorial model. Then came Wagner (1992), who proposed an apparently alternative approach to a multifactorial model, played on the interaction between perfusion and diffusion. These models represent the basis for the discussion of $\dot{V}O_{2\,max}$ limitation in this book (see Chap. 4).

The Oxygen Equilibrium Curve

The multifactorial models of $\dot{V}O_{2\,max}$ limitation include some characteristics of the **oxygen equilibrium curve**, which provides a quantitative description of oxygen binding to haemoglobin with respect to dissolved oxygen, expressed in terms of partial pressure. Bert (1878) was the first to construct a plot with blood oxygen concentration on the *y*-axis against air oxygen partial pressure on the *x*-axis, demonstrating how the former decreased as a function of the latter (Fig. 1.5). The most surprising aspect of Bert's graph was that the oxygen decrease in blood was not proportional to the oxygen drop in air, since that decrease was steep at low partial pressures, almost flat at high partial pressures. Some 10 years earlier, Felix Hoppe-Seyler (1825–1895) had purified the blood pigment, that he called **haemoglobin**, and had demonstrated that it could bind oxygen. The link between haemoglobin and Bert's plot was established in 1885 by Christian Bohr (1855–1911), who exposed 4 % solutions of haemoglobin to varying partial pressures of

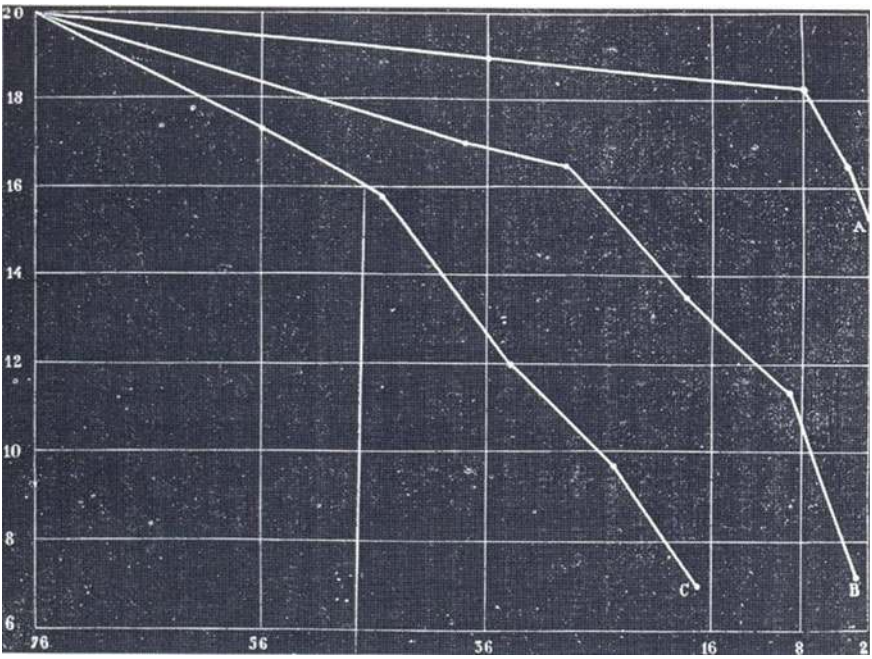


Fig. 1.5 Reproduction of the first oxygen dissociation curve of haemoglobin that Paul Bert published in his book entitled *La Pression Barométrique*. In this representation, blood oxygen concentration is on the *y*-axis and air oxygen partial pressure is on the *x*-axis. Reproduced from Astrup and Severinghaus (1986)

oxygen, and obtained for the first time what we now call the oxygen dissociation curve for haemoglobin or **oxygen equilibrium curve**, to which he gave at first a hyperbolic solution (Bohr 1885). It was again Bohr who, in 1903, after the perfection of blood pumps, demonstrated the sigmoid shape of the oxygen dissociation curve of haemoglobin for whole blood, which resembled the primitive curve of Bert (Bohr 1903).

The question of the meaning of the sigmoid shape of the oxygen dissociation curve was obviously put forward as a consequence. This question, in those times, was less experimental than theoretical. In 1910, before the molecular structure and the number of iron atoms of haemoglobin were known, Hill (1910) proposed that the oxygen equilibrium curve could reflect the equilibrium of a chemical reaction between haemoglobin and oxygen of the following form:

$$\mathrm{Hb} + n\mathrm{O_2} \leftrightarrow \mathrm{Hb(O_2)}n \tag{1.3}$$

where n is the stoichiometric ratio of the reaction, for which Hill conjectured $n > 1$. This led to the formulation of what is now called Hill's model of the oxygen equilibrium curve. The genial aspect of Hill's conjecture was that constant n would

correspond to the number of oxygen molecules that one molecule of haemoglobin can bind. Hill obtained $n = 1$ for myoglobin and $n = 2.8$ for haemoglobin, and he took these values as the stoichiometric ratios for either pigment. The identification of the quaternary structure of haemoglobin by Max Perutz (1914–2002) led to the refutation of Hill's conjecture and to the experimental demonstration that $n = 4$ instead of 2.8, despite simultaneous confirmation of $n = 1$ for myoglobin (Perutz 1970). This value means that each oxygen molecule is bound to myoglobin independent from the others, whereas the former value indicates that haemoglobin binds oxygen in cooperative manner. The impact on the theory of $\dot{V}\,O_{2\,max}$ limitation is related to the effect that cooperativity has on the resistance to oxygen flow by the cardiovascular system. An interested reader can find a nice detailed account of the history of the oxygen equilibrium curve elsewhere (Astrup and Severinghaus 1986).

Exercise Transients

The classical paper by Margaria et al. (1933) introduced also the concept that an **oxygen deficit** (they actually called it oxygen debt) is contracted at the onset of exercise, before the attainment of a $\dot{V}\,O_2$ steady state, and is paid (with interests, as Margaria put it) during recovery after exercise. The contraction of the oxygen deficit justified the delay between exercise start and attainment of the $\dot{V}\,O_2$ steady state (some 3 min, according to Margaria) and led to the first attempts at investigating the kinetics of $\dot{V}\,O_2$ at the start of square wave exercise (Henry 1951; Henry and de Moor 1956; Margaria et al. 1965). Behind these investigations, there were two implicit axiomatic statements, derived from the original paper of Margaria et al. (1933), namely that (i) increasing $\dot{V}\,O_2$ from resting level to steady-state exercise level is tantamount to charging a capacitance, and (ii) the energy that aerobic metabolism is unable to provide during the rest–exercise transition must come from some other energy source. As a consequence, the kinetics of net (i.e. above resting) $\dot{V}\,O_2$ during a rest-to-exercise transition could be described by a single exponential equation of the following form:

$$\dot{V}\,O_2{}^s - \dot{V}\,O_2{}^t = \dot{V}\,O_2{}^s \cdot e^{-kt} \tag{1.4}$$

where superscripts s indicates the steady-state value above resting, t is time and k the velocity constant. The solution for $\dot{V}\,O_2{}^t$ of Eq. (1.4) is as follows:

$$\dot{V}\,O_2{}^t = \dot{V}\,O_2{}^s(1 - e^{-kt}) \tag{1.4a}$$

In this context, the oxygen deficit (O_{2def}) is equal to the time integral of Eq. (1.4) with respect to time:

$$O_{2def} = \int_0^{\infty} \dot{V}O_2{}^s \cdot e^{-kt}\, dt = \dot{V}O_2{}^s \cdot k^{-1} \tag{1.5}$$

The value of O_{2def} yields the amount of energy, expressed in oxygen equivalents, that during a rest-to-exercise transient is generated from sources other than aerobic metabolism. The subsequent energetic analysis of O_{2def}, in compliance with the theory exposed by di Prampero and Margaria (1968), led to the conclusion that most—if not all, at light exercise—of the energy constituting the O_{2def} was delivered by anaerobic alactic energy sources (di Prampero 1981). However, at least at powers higher than the so-called lactate threshold, a further component of the O_{2def} was identified, related to anaerobic lactic metabolism: this generated the concept of **early lactate**, which identifies the lactate accumulated in blood during an exercise transient (Cerretelli et al. 1979).

The energetic interpretation of the O_{2def} was challenged by the British school of exercise physiology, led by Brian Whipp (1937–2011). The technical developments in single breath $\dot{V}O_2$ analysis allowed the identification in the earliest phase of exercise of a rapid component of the $\dot{V}O_2$ response (Wasserman et al. 1974). This rapid component was associated with a rapid increase in cardiac output as exercise started (Weissman et al. 1982), eventually, I add, as a consequence of the equally rapid increase in heart rate following suppression of resting vagal stimulation of heart rhythm (Fagraeus and Linnarsson 1976). These results, in the view of the British school, restricted the energetic interpretation of the O_{2def} to what they called the phase II response, or primary component of the $\dot{V}O_2$ kinetics, whereas the rapid component, which they called phase I, was unrelated to energetic mechanisms. For the first time, a concrete challenge to the general theory of the energetics of muscular exercise was launched. A stirred debate followed, not fully composed yet, nonetheless very useful to stimulate new theoretical thinking. As often is the case in science, the subsequent formulation of the double capacitance model of gas exchange kinetics in exercise transients (Barstow and Molé 1987) was at the origin of further developments and of an attempt at including the "cardiodynamic" hypothesis of Brian Whipp in the general theory of the energetics of muscular exercise. But this concerns contemporary times more than history.

The Perspective of This Book

The review article by di Prampero (1981) was the last attempt at giving a systematic, coherent and comprehensive representation of the energetics of muscular exercise, centred on the general theory developed by the school of Margaria. Many

review articles were published ever since on specific subjects such as $\dot{V}O_{2\,max}$ (see e.g. Ferretti 2014; Levine 2008; Saltin and Strange 1992; Taylor 1987; Wagner 1996), the exercise transients (Grassi 2000; Jones and Poole 2005; Whipp and Ward 1990), the effects of training (Fluck 2006; Maughan et al. 1997), anaerobic metabolisms (di Prampero and Ferretti 1999), the energetics of human locomotion (di Prampero 2000; Zamparo et al. 2011) or the cardiovascular responses to exercise (Fadel 2008; Joyner 2006; Laughlin 1999; Rowell and O'Leary 1990). New aspects were investigated, such as the effects of extreme environments or of ageing. Further theoretical advances took place in several domains, consider, e.g. the multifactorial models of $\dot{V}O_{2\,max}$ limitation or the double capacitance model of pulmonary gas exchange kinetics at exercise onset. A better understanding of the cardiovascular responses to exercise was made possible by the obtention of beat-by-beat recordings of arterial blood pressure and cardiac output. New concepts were created, such as that of phase III or slow component of the $\dot{V}O_2$ response to exercise (Gaesser and Poole 1996) or of oxygen flow in mixed venous blood (Ferretti et al. 1992). The technical developments in single fibre muscle physiology, and in molecular biology, led to deeply investigate the molecular functional characteristics of muscle diversity (Bottinelli 2001; Cerretelli and Gelfi 2011; Schiaffino and Reggiani 2011). More than 30 years have not elapsed in vain.

In spite of this, the only systematic analysis of exercise physiology, apart from the new editions of the classical *summa* of exercise physiology, the Åstrand-Rodahl textbook, the last version of which was published 12 years ago (Åstrand et al. 2003), was carried out by the American Physiological Society with the 1997 volume of the Handbook of Physiology. That was the classical analytical report of empirical knowledge, an impressive, very exhaustive compilation of excellent data. Analysis, not synthesis, was its leading principle. Several important scientists wrote meritorious chapters on single subjects, sometimes with clear expression of established ideas, but without the unifying vision characterizing the 1981 review by di Prampero. Paolo Cerretelli's textbook of exercise physiology (unfortunately unpublished in English) had the great merit, to my eyes, of being more compact around a coherent vision emanating from the school of Margaria, which he is another eminent figure of (Cerretelli 2001). However, that vision was in part diluted in a wider context related to the unavoidable need of completeness that accompanies the writing of a textbook. Cerretelli's task was different, he had to fulfil another aim.

This book has the ambition of bridging the temporal gap between the appearance of di Prampero's review, a never-ending stimulus to thinking for any exercise physiologist, and current times. It is an attempt at providing a critical answer to the following question: How did the general theory of the energetics of muscular exercise resist 30 years of further developments? What could be accommodated into it, what was a challenge to it? Under which respects was it consolidated, and under which respects was it falsified, by the continuously growing knowledge in the field? Answering these questions is a complex, perhaps somewhat presumptuous task,

which requires revisiting the concepts discussed by di Prampero in 1981 in the perspective of nowadays knowledge, and introducing and discussing some new concepts, which had been meanwhile created, in the context of the general theory. I will let a reader judge whether the answers that I have provided are convincing or not, and thus, whether I fulfilled my task or not.

Such a strongly focused approach implies a cultural bias, which I apologise for, for it is the main source of incompleteness of this book: some readers may indeed take this as a limit. In fact, for the epideictic reasons expressed above, this book could not become a comprehensive textbook of exercise physiology. It rather is a representation, in the light of today's knowledge, of the energetics of muscular exercise, guided by the cultural imprinting of the school I come from, which was instilled by and cultivated through the never-ending interaction with my masters, especially Paolo Cerretelli and Pietro Enrico di Prampero. I derived from these interactions the deep conviction that the mechanisms governing the energetics of muscular exercise act under the constraint of the physical world, compatibly with the laws of energy transformation, as dictated by the first principle of thermodynamics. This can be taken as the axiomatic statement at the basis of the general theory of the energetics of muscular exercise and thus at the basis of this book. Exercise is a matter of work and power, and whenever work is done, energy must be transformed and eventually introduced in the system from outside. Chemical energy transformation can well be described in the physiological terms of rate of oxygen consumption, rate of lactate accumulation or rate of phosphocreatine splitting, yet at one condition, that these rates correspond precisely to energy flow rates through proportionality constants of known values. Whether this occurs at steady state or in dynamic conditions, at cellular or at whole body level, whenever we generate work, we consume chemical energy with a given mechanical efficiency, and the functioning of the underlying machinery cannot escape the quantitative constraints that this imposes.

I am aware that such a starting point, with such a strong declaration of partisanry, may generate allegations of dogmatism. Although I understand them, I reject these allegations with force, for this does not mean to express an ideological vision of science. Science is a combination of theory and experiment, where the latter prevails on the former as long as it is the experimental result that leads to reject a theory (the slaying of a beautiful hypothesis by an ugly fact). I recognize great value to all schools that have produced original theoretical thinking and generated after it remarkable experimental work. Their work is acknowledged, criticized and inserted in the perspective of this book, as is the work emanating from the school of Margaria. This work is more frequently referred to, not only because it represents my personal background, but mostly because it is more closely related to the general theory of the energetics of muscular exercise. Theoretical analysis and experimental work must be inserted in a perspective: I cannot conceal that the general theory is the comet driving this book and that the aforementioned bias is a consequence of it. This is a book on a thesis, not a general treaty.

References

American Physiological Society (1950) Standardization of definitions and symbols in respiratory physiology. Fed Proc 9:602–605

Andersson B (1933) Über Co-Zymaseaktivierung einiger Dehydrogenasen. Z Physiol Chem 217:186–190

Åstrand PO (1952) Experimental studies of physical working capacities in relation to sex and age. Munksgaard, Copenhagen

Åstrand PO, Rodahl K, Dahl HA, Strømme SB (2003) Textbook of work physiology. Physiological bases of exercise, 4th edn. Human Kinetics, Champaign, IL, USA

Astrup P, Severinghaus JW (1986) The history of blood gases, acids and bases. Munksgaard, Copenhagen

Atwater WO (1904) Neue Versuche über Stoff- und Kraftwechsel im menschlichen Körper. Ergeb Physiol 3:497–622

Barstow TJ, Molé PA (1987) Simulation of pulmonary O_2 uptake during exercise transients in humans. J Appl Physiol 63:2253–2261

Beinert H (1963) Acyl coenzyme a dehydrogenases. In: Boyer PD, Lardy H, Myrbäck K (eds) The enzymes, chapter 17, vol VII. Academic Press Inc., New York, pp 447–476

Bernard C (1879) Leçons sur les Phénomènes de la Vie Communs aux Animaux et aux Végétaux, vol II. Baillière, Paris

Bert P (1870) Leçons sur la Physiologie Comparée de la Respiration. Baillière, Paris

Bert P (1878) La pression barométrique. Masson, Paris

Bohr C (1885) Experimentale Untersuchungen über die Sauerstoffaufnahme des Blutfarbstoffes. OC Olsen & Co Buchdruckerei, Copenhagen

Bohr C (1903) Theoretische Behandlung der quantitativen Verhältnisse bei der Sauerstoffaufnahme der Hemoglobins. Zentralbl Physiol 17:682–691

Bottinelli R (2001) Functional heterogeneity of mammalian single muscle fibres: do myosin isoforms tell the whole story? Pflügers Arch 443:6–17

Cerretelli P (1980) Gas exchange at high altitude. In: West JB (ed) Pulmonary gas exchange, vol II. Academic Press, New York, pp 97–147

Cerretelli P (2001) Fisiologia dell'Esercizio. Società Editrice Universo, Roma

Cerretelli P, Gelfi C (2011) Energy metabolism in hypoxia: reinterpreting some features of muscle physiology on molecular grounds. Eur J Appl Physiol 111:421–432

Cerretelli P, Pendergast DR, Paganelli WC, Rennie DW (1979) Effects of specific muscle training on VO2-on response and early blood lactate. J Appl Physiol 47:761–769

di Prampero PE (1981) Energetics of muscular exercise. Rev Physiol Biochem Pharmacol 89:143–222

di Prampero PE (1985a) Metabolic and circulatory limitations to $\dot{V}O_{2\,max}$ at the whole animal level. J Exp Biol 115:319–331

di Prampero PE (1985b) La locomozione umana su terra, in acqua, in aria: fatti e teorie. Edi Ermes, Milano

di Prampero PE (2000) Cycling on Earth, in space, on the Moon. Eur J Appl Physiol 82:345–360

di Prampero PE, Ferretti G (1999) The energetics of anaerobic muscle metabolism: a reappraisal of older and recent concepts. Respir Physiol 118:103–115

di Prampero PE, Margaria R (1968) Relationship between O_2 consumption, high energy phosphates and the kinetics of O_2 debt in exercise. Pflügers Arch 304:11–19

Eggleton P, Eggleton GP (1927) The inorganic phosphate and a labile form of organic phosphate in the gastrocnemius of the dog. Biochem J 21:190–195

Ekblom B (1969) The effect of physical training on oxygen transport system in man. Acta Physiol Scand Suppl 328:1–45

Embden G, Deuticke HJ, Kraft G (1933) Über die intermediären Vorgänge bei der Glykolyse in der Muskulatur. Klin Wochenschr 12:213–215

Embden G, Lawaczeck H (1922) Über die Bildung anorganischer Phosphorsäure bei der Kontraktion des Froschmuskels. Biochem Z 127:181–199

Engelhardt VA, Lyubimova MN (1939) Myosin and adenosine-triphosphatase. Nature 144:668–669
Fadel PJ (2008) Arterial baroreflex control of the peripheral vasculature in humans: rest and exercise. Med Sci Sports Exerc 40:2055–2062
Fagraeus L, Linnarsson D (1976) Autonomic origin of heart rate fluctuations at the onset of muscular exercise. J Appl Physiol 40:679–682
Fenn WO (1930) Work against gravity and work due to velocity changes in running. Am J Physiol 93:433–462
Ferretti G (2014) Maximal oxygen consumption in healthy humans: theories and facts. Eur J Appl Physiol 114:2007–2036
Ferretti G, Capelli C (2008) Dagli abissi allo spazio. Edi Ermes, Milano
Ferretti G, Kayser B, Schena F, Turner DL, Hoppeler H (1992) Regulation of perfusive O_2 transport during exercise in humans: effects of changes in haemoglobin concentration. J Physiol Lond 455:679–688
Fletcher WM, Hopkins FG (1907) Lactic acid in amphibian muscle. J Physiol Lond 35:247–309
Fluck M (2006) Functional, structural and molecular plasticity of mammalian skeletal muscle in response to exercise stimuli. J Exp Biol 209:2239–2248
Frixione E (2006) Muscle microanatomy and its changes during contraction: the legacy of William Bowman (1816–1892). J Muscle Res Cell Motil 27:9–20
Gaesser GA, Poole DC (1996) The slow component of oxygen uptake kinetics in humans. Exerc Sport Sci Rev 24:35–71
Ghisla S (2004) Beta-oxidation of fatty acids. Eur J Biochem 271:459–461
Goldman YE (1987) Kinetics of the actomyosin ATPase in muscle fibers. Annu Rev Physiol 49:637–654
Gordon AM, Homsher E, Regnier M (2000) Regulation of contraction in striated muscle. Physiol Rev 80:853–924
Gordon AM, Huxley AF, Julian FJ (1966) The variation in isometric tension with sarcomere length in vertebrate muscle fibres. J Physiol Lond 184:170–192
Grassi B (2000) Skeletal muscle $\dot{V}O_2$ on-kinetics: set by O_2 delivery or by O_2 utilization? New insights into an old issue. Med Sci Sports Exerc 32:108–116
Hanson J, Huxley HE (1953) Structural basis of the cross-striation in muscle. Nature 172:530–532
Henry FM (1951) Aerobic oxygen consumption and alactic debt in muscular work. J Appl Physiol 3:427–438
Henry FM, de Moor J (1956) Lactic and alactic oxygen consumption in moderate exercise of graded intensity. J Appl Physiol 8:608–614
Herbst R (1928) Der Gasstoffwechsel als Mass der körperlichen Leistungsfähigkeit. I. Mitteilung: die Bestimmung des Sauerstoffaufnahmevermögens bein Gesunden. Deut Arch Klin Med 162:33–50
Hill AV (1910) The possible effects of the aggregation of the molecules of haemoglobin on its dissociation curves. J Physiol Lond 40:iv–vii
Hill AV (1924) Muscular activity and carbohydrate metabolism. Science 60:505–514
Hill AV (1932) The revolution in muscle physiology. Physiol Rev 12:56–67
Hill AV, Lupton H (1923) Muscular exercise, lactic acid, and the supply and utilization of oxygen. Q J Med 16:135–171
Huxley AF (1957) Muscle structure and theories of contraction. Prog Biophys Biophys Chem 7:255–318
Huxley AF (1974) Muscular contraction. J Physiol Lond 243:1–43
Huxley AF (1978) Reflections on muscle contraction. Princeton University Press, Princeton
Huxley AF (2000) Cross-bridge action: present views, prospects, and unknowns. J Biomech 33:1189–1195
Huxley AF, Niedergerke R (1954) Interference microscopy of living muscle fibres. Nature 173:971–973
Huxley HE (1953) Electron microscope studies of the organisation of the filaments in striated muscles. Biochim Biophys Acta 12:387–394

Huxley HE, Hanson J (1954) Changes in the cross-striation of muscle during contraction and stretch and their structural interpretation. Nature 173:973–976
Jones AM, Poole DC (eds) (2005) Oxygen uptake kinetics in sport, exercise and medicine. Routledge, London
Joyner MJ (2006) Baroreceptor function during exercise: resetting the record. Exp Physiol 91:27–36
Kornberg H (2000) Krebs and his trinity of cycles. Nat Rev Mol Cell Biol 1:225–228
Krebs HA (1970) The history of the tricarboxylic acid cycle. Perspect Biol Med 14:154–170
Krebs HA, Kornberg H (1957) Energy transformation in living matter. Springer, Berlin
Laughlin MH (1999) Cardiovascular response to exercise. Am J Physiol 277:S244–S259
Levine BD (2008) $\dot{V}O_{2\,max}$: what do we know, and what do we still need to know? J Physiol Lond 586:25–34
Lohmann K (1928) Über die Isolierung verschiedener natürlicher Phosphorsäureverbindungen und die Frage ihrer Einheitlichkeit. Biochem Z 194:306–327
Lohmann K (1934) Über die enzymatische Aufspaltung der Kreatin-phosphorsäure, zugleich ein Beitrag zur Muskelkontraktion. Biochem Z 271:264–277
Lundsgaard E (1930) Untersuchungen über Muskelkontraktionen ohne Milchsäurebildung. Biochem Z 217:162–177
Margaria R, Edwards HT, Dill DB (1933) The possible mechanism of contracting and paying the oxygen debt and the role of lactic acid in muscular contraction. Am J Physiol 106:689–714
Margaria R, Cerretelli P, di Prampero PE, Massari C, Torelli G (1963) Kinetics and mechanism of oxygen debt contraction in man. J Appl Physiol 18:371–377
Margaria R, Cerretelli P, Mangili F (1964) Balance and kinetics of anaerobic energy release during strenous exercise in man. J Appl Physiol 19:623–628
Margaria R, Mangili F, Cuttica F, Cerretelli P (1965) The kinetics of the oxygen consumption at the onset of muscular exercise in man. Ergonomic 8:49–54
Maughan R, Gleeson M, Greenhaff PL (1997) Biochemistry of exercise and training. Oxford University Press, Oxford
Meyerhof O (1921) Milchsäurebildung und mechanische Arbeit. Pflügers Arch 191:128–183
Meyerhof O (1924) Chemical dynamics of life phenomena. JB Lippincott, London
Meyerhof O, Lohmann K (1927) Über die enzymatische Milchsäurebildung im Muskelextrakt. IV. Mitteilung: die Spaltung der Hexosemonophosphorsäuren. Biochem Z 185:113–164
Mitchell PD (1979) The ninth Sir Hans Krebs lecture. Compartmentation and communication in living systems. Ligand conduction: a general catalytic principle in chemical, osmotic and chemiosmotic reaction systems. Eur J Biochem 95:1–20
Mitchell PD (2004) Foundations of vectorial metabolism and osmochemistry. Biosci Rep 24:386–434
Mitchell P (2011) Chemiosmotic coupling in oxidative and photosynthetic phosphorylation. Biochim Biophys Acta 1807:1507–1538
Monod H, Scherrer J (1965) The work capacity of a synergic muscular group. Ergonomics 8:329–338
Nachmanson D (1928) Über den Zerfall der Kreatinphosphorsäure in Zusammenhang mit der Tätigkeit des Muskels. Biochem Z 196:73–97
Perkins JF jr (1964) Historical development of respiratory physiology. In: Fenn WO, Rahn H (eds) Handbook of physiology. Respiration, Section 3, vol I. American Physiological Society, Washington, DC, pp 1–62
Perutz MF (1970) Stereochemistry of cooperative effects in haemoglobin. Nature 228:726–733
Piiper J, Meyer M, Scheid P (1984) Dual role of diffusion in tissue gas exchange: blood-tissue equilibration and diffusion shunt. Respir Physiol 56:131–144
Piiper J, Scheid P (1981) Model for capillary-alveolar equilibration with special reference to O_2 uptake in hypoxia. Respir Physiol 46:193–208
Poole DC, Barstow TJ, Gaesser GA, Willis WT, Whipp BJ (1994) $\dot{V}O_2$ slow component: physiological and functional significance. Med Sci Sports Exerc 26:1354–1358
Racker E (1983) Resolution and reconstitution of biological pathways from 1919 to 1984. Fed Proc 42:2899–2909

Rahn H, Fenn WO (1955) A graphical analysis of the respiratory gas exchange. American Physiological Society, Washington DC
Riley RL, Cournand A (1949) "Ideal" alveolar air and the analysis of ventilation—perfusion relationships in the lungs. J Appl Physiol 1:825–847
Rowell LB, O'Leary DS (1990) Reflex control of the circulation during exercise: chemoreflexes and mechanoreflexes. J Appl Physiol 69:407–418
Saltin B (1973) Oxygen transport by the circulatory system during exercise in man. In: Keul J (ed) Limiting factors of physical performance. Thieme, Stuttgart, pp 235–252
Saltin B (1977) The interplay between peripheral and central factors in the adaptive response to exercise and training. Ann N Y Acad Sci 301:224–231
Saltin B, Strange S (1992) Maximal oxygen uptake: "old" and "new" arguments for a cardiovascular limitation. Med Sci Sports Exerc 24:30–37
Scheuer J, Tipton CM (1977) Cardiovascular adaptations to physical training. Annu Rev Physiol 39:221–251
Schiaffino S, Reggiani C (2011) Fiber types in mammalian skeletal muscles. Physiol Rev 91:1447–1531
Shephard RJ (1969) A non-linear solution of the oxygen conductance equation: applications to performance at sea level and at an altitude of 7350 ft. Int Z angew Physiol 27:212–225
Taylor CR (1987) Structural and functional limits to oxidative metabolism: insights from scaling. Annu Rev Physiol 49:135–146
Taylor CR, Weibel ER (1981) Design of the mammalian respiratory system. I. Problem and strategy. Respir Physiol 44:1–10
Verzar F (1912) The gaseous metabolism of striated muscle in warm-blooded animals. J Physiol 44:243–258
Wagner PD (1992) Gas exchange and peripheral diffusion limitation. Med Sci Sports Exerc 24:54–58
Wagner PD (1996) Determinants of maximal oxygen transport and utilization. Annu Rev Physiol 58:21–50
Wasserman K, Whipp BJ, Castagna J (1974) Cardiodynamic hyperpnea: hyperpnea secondary to cardiac output increase. J Appl Physiol 36:457–464
Weibel ER (1984) The pathway for oxygen. Harvard University Press, Cambridge MA
Weissman ML, Jones PW, Oren A, Lamarra N, Whipp BJ, Wasserman K (1982) Cardiac output increase and gas exchange at start of exercise. J Appl Physiol 52:236–244
Whipp BJ, Ward SA (1990) Physiological determinants of pulmonary gas exchange kinetics during exercise. Med Sci Sports Exerc 22:62–71
Zamparo P, Capelli C, Pendergast D (2011) Energetics of swimming: a historical perspective. Eur J Appl Physiol 111:367–378

Chapter 2
Aerobic Metabolism and the Steady-State Concept

Abstract This chapter contains an analysis of the steady-state concept, as it is applied during light exercise. In this case, oxygen consumption increases upon exercise onset to attain a steady level, which can be maintained for a long period of time. The steady-state oxygen consumption is proportional to the exerted mechanical power. Under these circumstances, there is neither accumulation of lactate in blood nor changes in muscle phosphocreatine concentration: aerobic metabolism sustains the entire energy requirement of the exercising body. Once the steady state has been attained, the flow of oxygen is the same at all levels along the respiratory system. The quantitative relations determining the flow of oxygen across the alveoli and in blood are discussed. Special attention is given to the effects of ventilation—perfusion inequality and to the diffusion—perfusion interaction equations. The cardiovascular responses at exercise steady state are analysed in the context of the equilibrium between systemic oxygen delivery and systemic oxygen return. The relationship between oxygen consumption and power is discussed, along with the distinction between external and internal work during cycling. The concepts of mechanical efficiency of exercise and energy cost of locomotion are analysed. Concerning the latter, the distinction between aerodynamic work and frictional work is introduced. The roles of the cross-sectional surface area on the frontal plane and of air density in aerodynamic work are discussed. To end with, an equation linking ventilation, circulation and metabolism at exercise in a tight manner is developed, around the notion that the homeostasis of the respiratory system at exercise is maintained around given values of the constant oxygen return. This equation tells that, as long as we are during steady-state exercise in normoxia, any increase in the exercise metabolic rate requires an increase in ventilation that is proportional to that in oxygen consumption only if the pulmonary respiratory quotient stays invariant does not change, and an increase in cardiac output that is not proportional to the corresponding increase in oxygen consumption. At intense exercise, when lactate accumulation also occurs and hyperventilation superimposes, a new steady state would be attained only at P_ACO_2 values lower than 40 mmHg: the homeostasis of the respiratory system would be modified. This new steady state, however, is never attained in fact, for reasons that are discussed in Chap. 3.

G. Ferretti, *Energetics of Muscular Exercise*,
DOI 10.1007/978-3-319-05636-4_2

Contents

Introduction

The general theory of the energetics of muscular exercise looks at muscle as a biological engine, in which chemical energy—or metabolic energy—is transformed in mechanical work and heat. The ultimate step of this energy transformation is provided by ATP hydrolysis in the cross-bridge cycle. The low ATP concentration in muscle (on average 5 mmol per kg of wet muscle) requires continuous ATP resynthesis, which we owe to the ensemble of reactions comprised in the concept of intermediate metabolism. The detailed description of these reactions can be found in biochemistry textbooks, and the historical developments that led to them are summarized in Chap. 1. The general theory summarizes these reactions in three basic physiological concepts: aerobic metabolism, anaerobic lactic metabolism and anaerobic alactic metabolism. **Aerobic metabolism** includes the oxidation of glycogen and fatty acids to pyruvate and acetate, respectively, and their introduction into the Krebs cycle which feeds oxidative phosphorylation. It uses oxygen as oxidizer and has carbon dioxide as end product. **Anaerobic lactic metabolism** concerns the degradation of glycogen to pyruvate, with subsequent transformation in lactate. It occurs when the rate of energy transformation in the glycolytic pathway exceeds that of further oxidation of pyruvate in the Krebs cycle. **Anaerobic alactic metabolism** consists of the Lohmann's reaction. A qualitative representation of these concepts is shown in Fig. 2.1. A practical consequence of this picture of metabolism is that the rate at which metabolic energy is transformed by aerobic metabolism can be determined by a simple measure of oxygen consumption ($\dot{V}O_2$). Similarly, the rate of lactate accumulation in blood ($\dot{La}$) is a measure of the rate of anaerobic lactic metabolism, and the rate at which phosphocreatine concentration varies in muscle ($\dot{PC}$) defines the rate of anaerobic alactic metabolism.

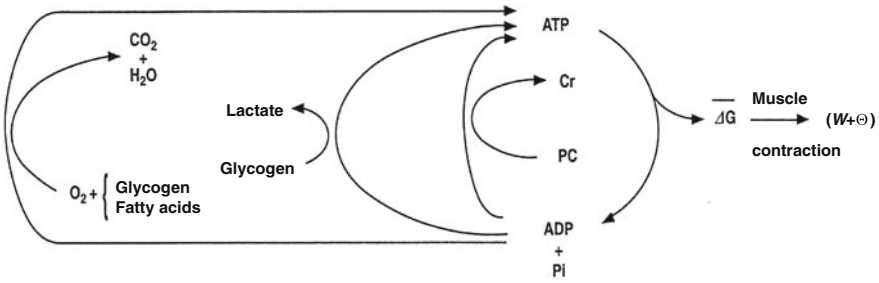


Fig. 2.1 Schematic representation of the energetics of muscular exercise. ATP hydrolysis liberates the free energy (ΔG) that contractile proteins use to generate work (W) and heat (Θ). ATP resynthesis takes place through the indicated pathways. *ADP* adenosine di-phosphate; *Pi* inorganic phosphate; *PC* phosphocreatine; *Cr* creatine. Modified after di Prampero (1985)

The quantitative representation of the same concepts takes the following algebraic form:

$$\dot{E} \propto \overleftarrow{\dot{ATP}} = \overrightarrow{\dot{ATP}} = c\,\dot{V}\,O_2 + b\,\dot{La} + a\,\dot{PC} \tag{2.1}$$

where $\overleftarrow{\dot{ATP}}$ and $\overrightarrow{\dot{ATP}}$ are the rates of ATP hydrolysis and resynthesis, respectively. Equation (2.1) can be defined as the **general equation of the energetics of muscular exercise**. In this equation, $\dot{E}$ is the overall rate of metabolic energy liberation, whereas the three constants *a, b* and *c* are proportionality constants indicating the moles of ATP resynthesized, respectively, by a mole of phosphocreatine hydrolysed, a mole of lactate accumulated, and a mole of oxygen consumed. The Lohmann's reaction tells that *a* is equal to 1; *c* (otherwise P/O_2 ratio) takes a mean value of 6.17 for glycogen oxidation into glycolysis. For constant *b,* the situation is a bit more complex than this (di Prampero 1981; di Prampero and Ferretti 1999) and will be discussed in Chap. 6.

In humans at rest and during light exercise, $\dot{V}\,O_2$ attains a steady level which can be maintained for a long period of time. Under these steady-state conditions, there is neither accumulation of lactate in blood nor changes in muscle phosphocreatine concentration. Thus, Eq. (2.1) reduces to the following:

$$\dot{E} \propto \overleftarrow{\dot{ATP}} = \overrightarrow{\dot{ATP}} = c\,\dot{V}\,O_2 \tag{2.2}$$

Equation (2.2) indicates that all energy-sustaining body functions at rest plus the mechanical work of exercise derives from aerobic energy sources. This represents a particularly favourable condition for exercise physiologists, because a simple measure of $\dot{V}\,O_2$ at the mouth informs on the overall metabolic power, which remains invariant in time.

In this chapter, I will discuss the steady-state concept and describe the quantitative relationships that characterize it. Making use of the steady-state concept,

I will then introduce the concepts of energy cost of locomotion and of mechanical efficiency of exercise. Finally, I will present and discuss the cardiopulmonary responses to exercise at steady state, and I will propose a synthesis of the interrelated phenomena along the respiratory system by which a steady $\dot{V}O_2$ is maintained throughout the exercise.

The Steady-State Concept

The steady-state concept was clearly defined for the first time by Bock et al. (1928). According to them, a steady state implies an invariant $\dot{V}O_2$, a steady rate of elimination of carbon dioxide ($\dot{V}CO_2$) produced by metabolism only, steady heart rate (f_h) and an essentially stable internal environment. If this is so, then (i) the $\dot{V}O_2$ measured at the mouth corresponds to the rate of oxygen consumption by the mitochondria; (ii) both $\dot{V}O_2$ and $\dot{V}CO_2$ are characterized by equal values at any level along the respiratory system; (iii) as a consequence, the respiratory quotient determined at the lungs (RQ_L)—or gas exchange ratio, defined as the ratio between $\dot{V}CO_2$ and $\dot{V}O_2$—is equal at any level along the respiratory system, so that it corresponds exactly to the metabolic respiratory quotient (RQ_M), that is, the ratio between the moles of carbon dioxide produced and the moles of oxygen consumed in the cellular aerobic energy transformation processes. Starting from these bases, taken as axioms, several developments in the analysis of the quantitative relationships describing gas flows in the respiratory system at rest and exercise were pursued.

Before entering into these details, however, it is necessary to point out that the steady-state concept is a mental creation of some bright physiologists, which represents an oversimplification of what actually occurs in a living organism. In fact, even at steady state, the respiratory system is characterized by oxygen flow discontinuities, heterogeneities and spontaneous variations, depending on the macroscopic and microscopic organization of the system itself. From the macroscopic viewpoint, note that ventilation occurs in a dead-end pathway, so that inhalation and exhalation occur necessarily in alternate manner. Moreover, the heart alternates systoles and diastoles, with associated opening and closing of heart valves. Both mechanisms are sources of discontinuities, the former in air, the latter in blood flow, both in oxygen flow. Moreover, there is a spontaneous variability of respiratory and cardiac rhythms, related to mechanical and neural control mechanisms (Cottin et al. 2008; Perini and Veicsteinas 2003). This being the case, the $\dot{V}O_2$ at steady state is not a continuous invariant flow: it rather corresponds to an invariant integral mean of a flow that is highly variable in time, at several levels even discontinuous.

From the microscopic viewpoint, blood flow is pulsatile in lung capillaries, because of their heterogeneous recruitment, and of interferences from the rhythmic activity of the heart and the lungs (Baumgartner et al. 2003; Clark et al. 2011; Tanabe et al. 1998). This heterogeneity may be reduced during exercise due to

simultaneous recruitment of a larger number of lung capillaries. Similar heterogeneities have been demonstrated also in contracting skeletal muscles, both in space and in time (Armstrong et al. 1987; Ellis et al. 1994; Heinonen et al. 2007; Marconi et al. 1988; Piiper et al. 1985). Heterogeneous muscle blood flow was reported also in non-contracting muscles of exercising humans (Heinonen et al. 2012). Contracting muscle fibres are likely unperfused, because they generate pressure, which compresses and closes muscle capillaries from outside. If this is so, perfusion occurs only in relaxing muscle fibres, so that muscle fibre oxygenation takes place during relaxation, not during contraction. In this case, the alternate recruitment of neighbouring motor units becomes a functional necessity, the inevitable consequence of which is heterogeneity of muscle blood flow distribution during muscular work.

Quantitative Relationships at Steady State

The first relationships to be established in time concern the net amount of gas exchanged in the lungs and in blood, calculated as difference between a flow in and a flow out for the gas at stake. Concerning blood, this gave origin to what is nowadays called the **Fick principle**, whose algebraic expression is as follows (Fick 1870):

$$\dot{V}\,\mathrm{O}_2 = \dot{Q}\,Ca\mathrm{O}_2 - \dot{Q}\,C\bar{v}\mathrm{O}_2 = \dot{Q}\,(Ca\mathrm{O}_2 - C\bar{v}\mathrm{O}_2) \tag{2.3}$$

where $\dot{Q}$ is total blood flow—or more commonly **cardiac output**—and $Ca\mathrm{O}_2$ and $C\bar{v}\mathrm{O}_2$ are the oxygen concentrations in arterial and mixed venous blood, respectively. This expression in fact defines the amount of oxygen that leaves the blood in peripheral capillaries to be consumed in cells in a unit of time. By analogy, Geppert and Zuntz (1888) defined $\dot{V}\,\mathrm{O}_2$ as the difference between inspired and expired oxygen flows, as follows:

$$\dot{V}\,\mathrm{O}_2 = \dot{V}_I\,F_I\mathrm{O}_2 - \dot{V}_E\,F_E\mathrm{O}_2 \tag{2.4}$$

where $\dot{V}_I$ is the total inspired air flow—or more commonly inspiratory ventilation; $\dot{V}_E$ is the total expired air flow—or more commonly expiratory ventilation; and $F_I\mathrm{O}_2$ and $F_E\mathrm{O}_2$ are the oxygen fractions in inspired and expired air, respectively. By definition, at steady state, Eqs. (2.3) and (2.4) have equal solutions.

Similar equations can be written to define $\dot{V}\,\mathrm{CO}_2$, by replacing its concentrations in blood—or its fractions in air—for the corresponding concentrations or fractions of oxygen. It is noteworthy, however, that the carbon dioxide concentration is higher in alveolar than in inspired air, and in mixed venous than in arterial blood, so that $\dot{V}\,\mathrm{CO}_2$ turns out negative. This being so, we have in blood:

$$\dot{V}\,\mathrm{CO_2} = \dot{Q}\,Ca\mathrm{CO_2} - \dot{Q}\,C\bar{v}\mathrm{CO_2} = \dot{Q}\,(Ca\mathrm{CO_2} - C\bar{v}\mathrm{CO_2}) \tag{2.5}$$

where $Ca\mathrm{CO_2}$ and $C\bar{v}\mathrm{CO_2}$ are the carbon dioxide concentrations, respectively, in arterial and mixed venous blood. It is of note that, in spite of its negative values, it soon became customary to express $\dot{V}\,\mathrm{CO_2}$ as absolute value, making abstraction of the sign.

Considering alveolar air, since in respiration physiology the carbon dioxide fraction in inspired air is considered nil, $\dot{V}\,\mathrm{CO_2}$ computation turns out simplified, as follows:

$$\dot{V}\,\mathrm{CO_2} = -\dot{V}_E\,F_E\mathrm{CO_2} = -\dot{V}_A\,F_A\mathrm{CO_2} = -\dot{V}_A\,\frac{P_A\mathrm{CO_2}}{P_B} \tag{2.6}$$

where $\dot{V}_A$ is alveolar ventilation, $F_A\mathrm{CO_2}$ and $P_A\mathrm{CO_2}$ are the fraction and partial pressure, respectively, of carbon dioxide in alveolar air, and P_B is the barometric pressure. Equation (2.6) demonstrates that at any given P_B and $\dot{V}\,\mathrm{CO_2}$, $\dot{V}_A$ is inversely proportional to $P_A\mathrm{CO_2}$, whereas at any given $P_A\mathrm{CO_2}$, it is directly proportional to $\dot{V}\,\mathrm{CO_2}$. The former relationship is reported in Fig. 2.2a. The latter relationship, which appears in Fig. 2.2b, is stable on a precise $P_A\mathrm{CO_2}$ isopleth (that for $P_A\mathrm{CO_2} = 40$ mmHg) as long as a "true" steady state is maintained. This is so if there is no accumulation of lactate in blood. On ordinary non-athletic individuals, blood lactate accumulation starts having an impact on pH regulation at powers corresponding to some two-thirds of the maximal aerobic power. Although the exercise is still submaximal, above this power pH is not sufficiently buffered, hyperventilation superimposes and the $\dot{V}_A$ versus $\dot{V}\,\mathrm{CO_2}$ relationship bends upwards—higher $\dot{V}_A/\dot{V}\,\mathrm{CO_2}$ ratio and lower $P_A\mathrm{CO_2}$: the steady-state condition is broken. The origin of lactate in steady-state submaximal exercise is discussed in Chap. 3. It is nonetheless noteworthy already at this stage that the buffering of lactic acidosis in these circumstances has nothing to do with the concept, unfortunately deeply rooted in sport science, of shifting from aerobic to anaerobic metabolism.

If we express Eq. (2.4) in terms of partial pressures of alveolar gases, and we combine Eqs. (2.4) and (2.6) in the definition of RQ_L, we obtain

$$RQ_L = \frac{-P_A\mathrm{CO_2}}{(P_I\mathrm{O_2} - P_A\mathrm{O_2})} \tag{2.7}$$

where $P_L\mathrm{O_2}$ is the oxygen partial pressure in inspired air. The solution of Eq. (2.7) for $P_A\mathrm{O_2}$ and $P_A\mathrm{CO_2}$ is

$$P_A\mathrm{O_2} = P_I\mathrm{O_2} - \frac{P_A\mathrm{CO_2}}{-RQ_L} \tag{2.8a}$$

$$P_A\mathrm{CO_2} = RQ_L(P_A\mathrm{O_2} - P_I\mathrm{O_2}) \tag{2.8b}$$

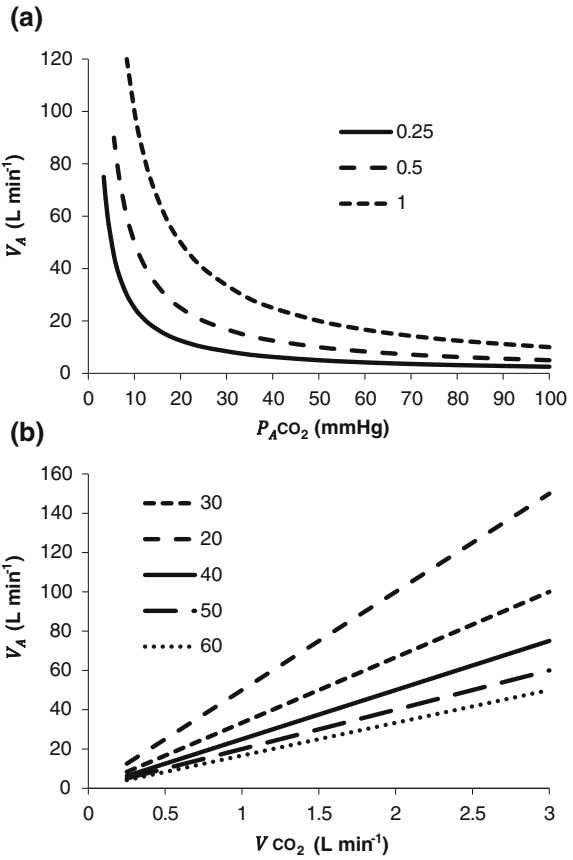


Fig. 2.2 *Panel a* Inverse relationship between alveolar ventilation ($\dot{V}_A$) and alveolar partial pressure of carbon dioxide (P_ACO_2) at the three indicated levels of steady-state carbon dioxide flow ($\dot{V}\,CO_2$, in L min^{-1}). *Panel b* Direct relationship between $\dot{V}_A$ and $\dot{V}\,CO_2$ at the indicated levels of P_ACO_2 (in mmHg)

These equations are algebraic expressions of what is generally called the **alveolar air equation.** Its graphical representation is the **O_2–CO_2 diagram for alveolar gases** (Rahn and Fenn 1955, see Fig. 2.3a), wherein we plot P_ACO_2 on the *y*-axis and P_AO_2 on the *x*-axis. Equation (2.8b) tells that there is a linear relationship between these two variables, with negative slope equal to $-RQ_L$ and *x*-axis intercept corresponding to the inspired air composition, with $P_ACO_2 = 0$ mmHg and $P_AO_2 = P_IO_2$. A family of isopleths for RQ_L, all converging on a given inspired air composition (e.g. $P_IO_2 = 150$ mmHg at sea level), can be constructed. At steady state, the only possible combinations of P_ACO_2 and P_AO_2 are those that lie on the RQ_L isopleth corresponding to the actual RQ_M. For any metabolic level below the critical power (see Chap. 5), the $\dot{V}_A/\dot{V}\,CO_2$ ratio is about 20 and the P_ACO_2 is about 40 mmHg, whereas the steady-state P_AO_2 would vary depending on RQ_L. Of course, P_IO_2 decreases in hypoxia and increases in hyperoxia, so that the inspired air point is accordingly shifted leftwards and rightwards, respectively, and so is the entire family of RQ_L isopleths converging on it. In spite of this, as long as the metabolic rate stays below the critical power or the anaerobic threshold and there is no hyperventilation

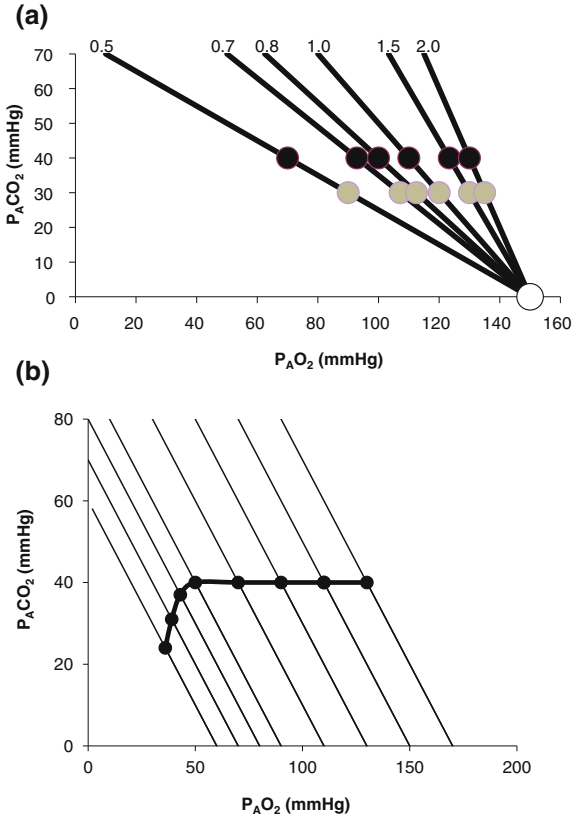


Fig. 2.3 *Panel a* An O_2–CO_2 diagram for alveolar air on which six isopleths of pulmonary respiratory quotient are indicated, all converging on the inspired air point corresponding to sea level (barometric pressure of 760 mmHg, *white dot*). On each isopleth, the points corresponding to alveolar air composition (*black dots*) and expired air composition (*grey dots*) are also shown. *Panel b* An O_2–CO_2 diagram for alveolar air, on which eight parallel isopleths (*thin lines*), corresponding to a pulmonary respiratory quotient of 1.0, are indicated, converging on different inspired air points. The lower is the inspired partial pressure of oxygen, the more the isopleth is displaced to the left. The corresponding alveolar air compositions are also shown (*black dots*) and connected by the alveolar air curve (*thick black curve*)

consequent to hypoxaemic stimulation of peripheral chemoreceptors, the $\dot{V}_A/\dot{V}\,CO_2$ ratio remains about 20, and the steady-state P_ACO_2 remains equal to 40 mmHg. Conversely, as hyperventilation appears, e.g., due to ventilatory response to hypoxaemia, the $\dot{V}_A/\dot{V}\,CO_2$ ratio increases and, since it is inversely proportional to P_ACO_2, this decreases, moving downwards and rightwards along the corresponding RQ_L isopleth, in the direction of the inspired air point. If at all P_IO_2 values we connect all the points representing the steady-state alveolar air composition, we obtain a curve like that reported in Fig. 2.3b, which is generally called the **normal mean alveolar air curve**.

Equation (2.7) is a particular case in which nitrogen balance is nil, which is the case only when $RQ_L = -1$. A resting human at steady state takes up 300 ml of oxygen per minute and gives out 250 ml of carbon dioxide per minute, on average, so that his RQ_L is equal to −0.83. This means that inspired ventilation, or the air flow inside the alveoli, is higher than expired ventilation, because there is less carbon dioxide that is added to alveolar air than oxygen that is subtracted. Since pressure must equilibrate, this implies that inert gases, namely nitrogen, compensate for pressure differences. Thus, when $RQ_L \neq -1$, Eq. (2.7) becomes

$$RQ_L = \frac{-P_A\mathrm{CO}_2}{\left(P_I\mathrm{O}_2 \cdot \frac{P_A\mathrm{N}_2}{P_I\mathrm{N}_2} - P_A\mathrm{O}_2\right)} \tag{2.9}$$

The two theoretical extremes for possible variations of RQ_L are represented by $RQ_L = 0$ and $RQ_L = -\infty$. The former is the case when $\dot{V}\,\mathrm{CO}_2$ is nil, the latter when $\dot{V}\,\mathrm{O}_2$ is nil. In the former case, since there is no carbon dioxide addition to the alveoli, $P_A\mathrm{CO}_2 = 0\,\mathrm{mmHg}$: the corresponding isopleth for RQ_L coincides with the *x*-axis. In the latter case, we have carbon dioxide addition to the alveoli in the absence of oxygen uptake: in this condition, there is a progressive dilution of oxygen and nitrogen in carbon dioxide, which goes on until carbon dioxide becomes the only alveolar gas. In this case, $F_A\mathrm{CO}_2 = 1$ and $P_A\mathrm{CO}_2 = 713\,\mathrm{mmHg}$ at sea level. As a consequence, the corresponding isopleth for RQ_L does not coincide with the *y*-axis, but connects the point on the *x*-axis corresponding to inspired air composition to the point on the *y*-axis representing $P_A\mathrm{CO}_2 = 713\,\mathrm{mmHg}$.

The Effects of Ventilation—Perfusion Heterogeneity

Although the O_2–CO_2 diagram was established for alveolar air, a similar diagram can be constructed for blood, starting from the computation of the respiratory quotient for blood (RQ_B) after Eqs. (2.3) and (2.5):

$$RQ_B = \frac{(\mathrm{CaCO}_2 - C\bar{v}\mathrm{CO}_2)}{(Ca\mathrm{O}_2 - C\bar{v}\mathrm{O}_2)} \tag{2.10}$$

from which we obtain the following solution for CaCO_2:

$$\mathrm{CaCO}_2 = C\bar{v}\mathrm{CO}_2 - RQ_B(Ca\mathrm{O}_2 - C\bar{v}\mathrm{O}_2) \tag{2.11}$$

Equation (2.11), which is called the **arterial blood equation**, tells that, if we plot CaCO_2 as a function of $Ca\mathrm{O}_2$, we obtain a family of straight lines, with negative slopes equal to RQ_B, which converge on a point, whose coordinates define the respiratory gas composition of mixed venous blood (Fig. 2.4). This means that,

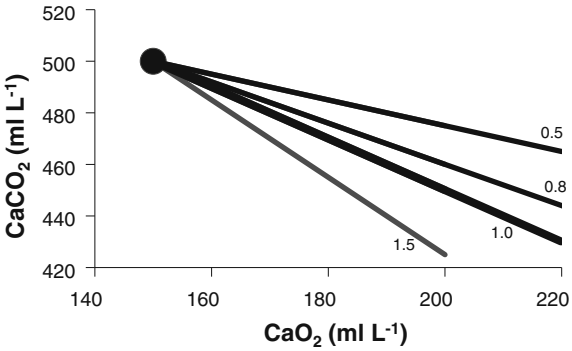


Fig. 2.4 Carbon dioxide concentration in arterial blood ($Caco_2$) as a function of oxygen concentration of arterial blood (Cao_2). The large dot refers to the concentrations incurring in mixed venous blood, where the isopleths for blood respiratory quotient (four of them are reported on the Figure, for the indicated values of respiratory quotient) converge

if no gas exchange occurs in the lungs, arterial blood would have the same oxygen and carbon dioxide concentrations as mixed venous blood.

Respiratory gases move across the alveolar–capillary barrier by diffusion, driven by differences in partial pressure, not in concentration, which is dictated by the binding characteristics of respiratory gases to haemoglobin. So, it would have some interest expressing Eq. (2.11) in terms of partial pressures:

$$\beta c\, P_a\mathrm{CO}_2 = \beta c\, P_{\bar{v}}\mathrm{CO}_2 - RQ_B\beta_b(P_a\mathrm{O}_2 - P_{\bar{v}}\mathrm{O}_2) \tag{2.12}$$

where constants β_c and β_b are the blood transport coefficients of carbon dioxide and oxygen, respectively, i.e. the slopes of the respective equilibrium curves with haemoglobin. The segment of the carbon dioxide equilibrium curve corresponding to the physiological range is practically linear, so that β_c can be taken as invariant. In contrast, this is not so for β_b: due to the shape of the oxygen equilibrium curve, β_b is lower the higher is the $P\mathrm{O}_2$. An analytical solution of Eq. (2.12) thus requires an *a priori* solution of the oxygen equilibrium curve.

All models describing the oxygen equilibrium curve are empirical, except Hill's logarithmic model (Hill 1910; Ferretti 2012), whose theoretical basis, however, was confuted by the demonstration of the stereochemistry of haemoglobin (Perutz 1970). Although more precise descriptions of the oxygen equilibrium curve were published afterwards, Hill's model has the great advantage of simplicity, while remaining accurate enough for the purpose of constructing an analytical solution of Eq. (2.12). This solution is presented in Fig. 2.5, which is generally called the **O_2–CO_2 diagram for blood gases** (Rahn and Fenn 1955). This plot describes a family of curves, whose shape is dictated by the value that β_b takes at any $P\mathrm{O}_2$. All these curves converge on a point, whose coordinates define the respiratory gas partial pressures of mixed venous blood.

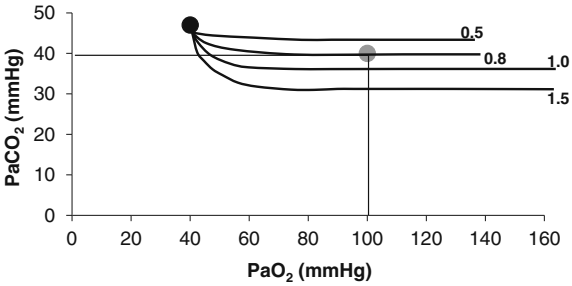


Fig. 2.5 An O_2–CO_2 diagram for blood on which four isopleths of blood respiratory quotient are indicated, all converging on the mixed venous blood point (*black dot*). The *grey dot* refers to the arterial blood gas composition of a man at rest (respiratory quotient of 0.8). *Pa*co_2 is the partial pressure of carbon dioxide in arterial blood; *Pa*co_2 is the partial pressure of oxygen in arterial blood

At steady state, $RQ_B = RQ_L$. If pulmonary gas exchange is complete, and equilibrium is attained on either side of the alveolar–capillary barrier, then arterial blood and alveolar air should have equal oxygen and carbon dioxide partial pressures. This coincidence of partial pressure values must then occur at the same respiratory quotient. Superposition on the same plot of the O_2–CO_2 diagrams for blood gases and for alveolar air (Fig. 2.6) clearly shows that this occurs at the crossing of two isopleths for a given RQ_B and RQ_L value (Farhi and Rahn 1955).

Figure 2.6 implies that (i) at any given respiratory quotient, only one combination of oxygen and carbon dioxide partial pressures is in fact possible, if we admit $P_AO_2 = P_aO_2$ (ideal air, as defined by Farhi and Rahn 1955); (ii) this combination is comprised between two extremes, one represented by $P_AO_2 = P_{\bar{v}}O_2$, the other by $P_AO_2 = P_IO_2$; and (iii) connecting all possible combinations of oxygen and carbon dioxide partial pressures at steady state leads to the construction of a curve called

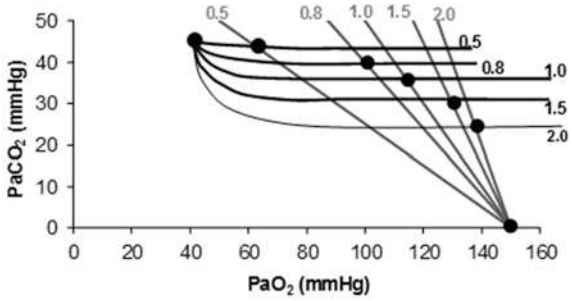


Fig. 2.6 Construction of the ideal air curve on an O_2–CO_2 diagram. The respiratory quotient isopleths for alveolar air are in *grey*, the corresponding isopleths for blood are in *black*. *Dots* are located at the crossing of each couple of isopleths and on the two extremes: the mixed venous blood composition (*upper left dot*) and the inspired air composition (*lower right dot*). The ideal air curve connects all these dots from mixed venous blood to inspired air

the **ideal air curve**. It is of note that also the ideal air curve reflects the characteristics of the oxygen equilibrium curve: at high PO_2, when we operate on the flat part of the latter curve and we hyperventilate, relatively large drops of PCO_2 are associated with small increases in PO_2; conversely, in the low PO_2 range, when we operate on the steep part of the oxygen equilibrium curve, relatively small increases of PCO_2 are associated with large drops in PO_2.

If we solve Eq. (2.6) for $\dot{V}_A$, we have

$$\dot{V}_A = -\frac{\dot{V}\,CO_2}{F_ACO_2} \tag{2.13}$$

$\dot{V}_A$ and $\dot{V}\,CO_2$ are not expressed in the same condition, since by convention the former is expressed in BTPS and the latter in STPD. Thus, if, after correcting for this inconsistency, we merge all constants and we transform F_ACO_2 in P_ACO_2 by means of Dalton's law, we obtain

$$\dot{V}_A = -\frac{(Pb - 47)\dot{V}\,CO_2}{CgP_ACO_2} \tag{2.14}$$

where Cg is the merged constant for STPD–BTPS transformation (0.863). If we replace $\dot{V}\,O_2$ for $\dot{V}\,CO_2$ in Eq. (2.14), we get

$$\dot{V}_A = -\frac{CgRQ_L\dot{V}\,O_2}{P_ACO_2} \tag{2.15}$$

whence

$$\dot{V}\,O_2 = -\frac{\dot{V}_A\,P_ACO_2}{CgRQ_L} \tag{2.16}$$

At steady state, since $\dot{V}\,O_2$ is the same at all levels along the respiratory system, Eqs. (2.16) and (2.3) must provide equivalent $\dot{V}\,O_2$ values, so that, when we take their ratio, we have

$$-\frac{\dot{V}_A\,P_ACO_2}{CgRQ_L\dot{Q}\,(CaO_2 - C\bar{v}O_2)} = 1 \tag{2.17}$$

whence, after rearrangement, we get

$$\frac{\dot{V}_A}{\dot{Q}} = -\frac{CgRQ_L(CaO_2 - C\bar{v}O_2)}{P_ACO_2} \tag{2.18}$$

which Hermann Rahn and Wallace Fenn called the **ventilation–perfusion equation** (Rahn and Fenn 1955). Equation (2.18) tells that at steady state, in any given

segment of the lungs, the $\frac{\dot{V}_A}{\dot{Q}}$ ratio is directly proportional to $-RQ_L$ and to $(Ca\mathrm{O}_2 - C\bar{v}\mathrm{O}_2)$ and inversely proportional to $P_A\mathrm{CO}_2$. As a consequence, on the ideal air curve (Fig. 2.6), each point corresponds not only to a specific RQ_L value, but also to a unique value of $\frac{\dot{V}_A}{\dot{Q}}$ ratio, which is lower the closer is RQ_L to zero. Moreover, if we look at the extremes of the ideal air curve, we note that, when $\frac{\dot{V}_A}{\dot{Q}} = 0, (Ca\mathrm{O}_2 - C\bar{v}\mathrm{O}_2) = 0$ ml L^{-1}, so that the blood that leaves alveolar capillaries in which $\frac{\dot{V}_A}{\dot{Q}} = 0$ has the same composition of mixed venous blood. On the other side, whenever $\frac{\dot{V}_A}{\dot{Q}} = \infty, P_A\mathrm{CO}_2 = 0$ mmHg, so that the composition of alveolar air becomes equal to that of inspired air.

During light exercise at steady state, as compared to rest, $\dot{V}_A$ increases in direct proportion to $-\dot{V}\,\mathrm{CO}_2$, whereas the increase of $\dot{Q}$ is less. As a consequence, the $\frac{\dot{V}_A}{\dot{Q}}$ ratio grows. Since in this case $P_A\mathrm{CO}_2$ does not move from its controlled value of 40 mmHg, most of the increase of the $\frac{\dot{V}_A}{\dot{Q}}$ ratio, apart from the changes of RQ_M due to the progressively greater fraction of aerobic energy derived from glycogen oxidation (see Chap. 1), is due to the widening of $(Ca\mathrm{O}_2 - C\bar{v}\mathrm{O}_2)$. However, as long as we operate on the flat part of the oxygen equilibrium curve, $Ca\mathrm{O}_2$ does not vary, so that an increase of $(Ca\mathrm{O}_2 - C\bar{v}\mathrm{O}_2)$ can be sustained only by a fall of $C\bar{v}\mathrm{O}_2$. This is inevitably associated with an increase in $C\bar{v}\mathrm{CO}_2$, so it moves the mixed venous point of an O_2–CO_2 diagram upwards and leftwards. Since the inspired air point is unchanged as long as we breathe air at sea level, the shape of the ideal air curve is modified at exercise with respect to rest, as represented in Fig. 2.7.

The direct proportionality between $\dot{V}_A$ and $-\dot{V}\,\mathrm{CO}_2$ implies invariance of their ratio, and thus of $P_A\mathrm{CO}_2$. The tight matching between $\dot{V}_A$ and $-\dot{V}\,\mathrm{CO}_2$ is the result of a fine regulation, mostly centred on the activity of the central chemoreceptors and the characteristics of their response. This equilibrium is broken in case of

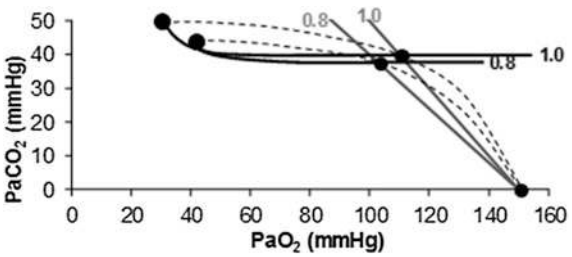


Fig. 2.7 Displacement of ideal air curve at exercise with respect to rest. The changes in the partial pressures of respiratory gases at exercise move the mixed venous point upwards and leftwards, without changes in inspired air composition. The ideal air curve is modified accordingly. Note that the ideal alveolar air composition is affected also by the change of the metabolic respiratory quotient during exercise

hyperventilation, when $\dot{V}_A$ increases in the absence of a proportional increase of metabolism, i.e. of $-\dot{V}\,CO_2$, so that their ratio goes up: in this case, the new steady state is attained at a lower value of P_ACO_2. This is so, e.g. at high altitude, due to hypoxic stimulation of peripheral chemoreceptors, or in case of pathological disturbances of $\frac{\dot{V}_A}{\dot{Q}}$ ratio heterogeneity in the lungs. The reverse takes place when hypoventilation occurs, as in case of respiratory failure or of paralysis of the respiratory centres.

Equilibration between alveolar air and arterial blood is the main assumption behind the ideal air curve. This equilibration in normoxia occurs indeed in each pulmonary capillary which is in contact with an alveolus, provided the contact time between alveolar air and capillary blood is long enough. According to Wagner and West (1972), at rest, full equilibration between the two sides of the alveolar–capillary barrier is attained when the blood has completed about one-third of the capillary length, this fraction increasing at exercise due to higher blood flow. In spite of this, $Pa O_2$ is lower than P_AO_2 in real lungs. This is a consequence of the combined effect of the heterogeneity of $\frac{\dot{V}_A}{\dot{Q}}$ distribution in the lungs and of the shape of the oxygen equilibrium curve. Alveoli perfused by capillaries in a lung segment with elevated $\frac{\dot{V}_A}{\dot{Q}}$ ratio are characterized by high P_AO_2 and end-capillary PO_2 values, in perfect equilibrium; on the other side, alveoli perfused by capillaries in a lung segment with low $\frac{\dot{V}_A}{\dot{Q}}$ ratio are characterized by low P_AO_2 and end-capillary PO_2 values, again in perfect equilibrium. One would expect that the former capillaries would compensate for the latter capillaries, when capillary blood is mixed to form arterial blood in the pulmonary vein, pretty much as air coming from different alveoli does in the trachea, where it forms the mean alveolar air that is analysed at the end of a prolonged expiration. This averaging of blood coming from different capillaries occurs indeed; however, in contrast with alveolar air, it is the binding of oxygen to haemoglobin with allosteric kinetics that dictates blood oxygen concentration at any PO_2, through an oxygen equilibrium curve that is sigmoidal. On one side, the blood draining from capillaries with low $\frac{\dot{V}_A}{\dot{Q}}$ ratio has a decreased end-capillary PO_2, close to the steep part of the oxygen equilibrium curve, so that their oxygen concentration is reduced indeed. On the other side, the blood draining from capillaries with high $\frac{\dot{V}_A}{\dot{Q}}$ ratio has an increased end-capillary PO_2, located on the flat part of the oxygen equilibrium curve, so that their oxygen concentration is not or minimally increased, which prevents them from compensating for the effect of the capillaries with low $\frac{\dot{V}_A}{\dot{Q}}$ ratio. This is the cause of the reduction of P_aO_2 with respect to P_AO_2 and of the appearance of the **alveolar–arterial pressure difference**. This state of things is illustrated in Fig. 2.8. The same is not the case for carbon dioxide, because of the steepness of a linear carbon dioxide equilibrium curve in the physiological range.

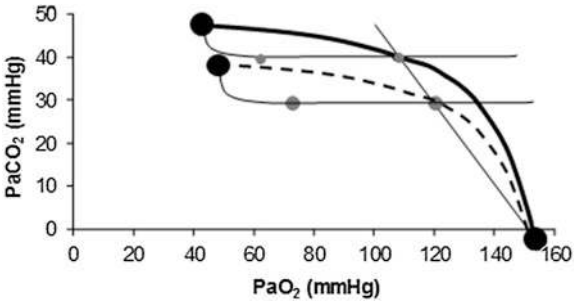


Fig. 2.8 Identification of the alveolar–arterial oxygen pressure difference on the O_2–CO_2 diagram as the horizontal distance between the two grey dots on a given respiratory quotient isopleth for blood. The effects of hyperventilation (*dashed curve*) are also shown. Note that hyperventilation does not change the alveolar–arterial oxygen pressure difference

Diffusion–Perfusion Interaction in Alveolar–Capillary Gas Transfer

Alveolar–capillary gas transfer is the result of two interrelated mechanisms: diffusion across the alveolar–capillary barrier, and lung capillary perfusion. At steady state, the flow of gas (e.g. oxygen) leaving the lungs through capillary blood must be equal to the flow of gas that crosses the alveolar–capillary barrier. This can be described with a very simple model of a meta-capillary with steady blood flow, which is in contact for its entire length with a meta-alveolus through a thin, homogeneous membrane. This is tantamount to imagine the mean pulmonary blood flow in contact with the mean alveolar air, with oxygen diffusing across a mean alveolar–capillary barrier. If this is so, the gas flow $\dot{V}$ across the membrane of given surface area A and thickness L is directly proportional to the pressure gradient across that membrane:

$$\dot{V} = \Delta P\left(\frac{d\mathrm{s}A}{L}\right) = \Delta P D_{\mathrm{L}} \tag{2.19}$$

where d and s are the diffusion and solubility constants of the gas at stake in the barrier, and D_{l} is the lumped constant called **lung diffusing capacity**. ΔP is the effective pressure gradient, i.e. the difference between $P_A\mathrm{O}_2$ and the pressure existing in the capillary at a given distance δ from the venous entrance [$P_c(\delta)$]. For the specific case of oxygen, the diffusive $\dot{V}\,\mathrm{O}_2$ across the barrier at any distance δ is thus equal to

$$d\dot{V}\,\mathrm{O}_2 = [P_A\mathrm{O}_2 - P_c\mathrm{O}_2(\delta)]D_{\mathrm{L}} \tag{2.20}$$

The infinitesimal $d\dot{V}O_2$ across the barrier progressively raises the P_cO_2 at δ from the venous to the arterial side in inverse proportion to blood flow $\dot{Q}$ and to the gas transport coefficient in blood (for oxygen, β_b)

$$d\dot{V}O_2 = \dot{Q}\,\beta_b dP_cO_2 \tag{2.21}$$

For inert gases, β is a constant that is independent of the gas pressure. For oxygen, β_b does depend on P_cO_2, because of the allosteric characteristics of oxygen binding to haemoglobin. If for simplification we assume β_b invariant, i.e. we take the average slope of the oxygen equilibrium curve as the invariant β_b value, the rate of increase of P_cO_2 along the capillary tends to an asymptote corresponding to P_AO_2 (Krogh 1922). On this basis, at steady state, combination of Eqs. (2.20) and (2.21) and subsequent integration along the capillary length yields

$$\frac{(P_AO_2 - P_{c'}O_2)}{(P_AO_2 - P_{\bar{v}}O_2)} = e^{-\frac{D_L}{\dot{Q}\beta_b}} \tag{2.22}$$

where $P_{c'}O_2$ is end-capillary PO_2. This equation has been defined as the **lung diffusion–perfusion interaction equation**. The left-end branch of Eq. (2.22) was defined as **equilibration deficit**, whose value depends only on the **equilibration coefficient**, i.e. on the exponent of the right-hand branch of the same equation, which is the ratio between the diffusive (D_L) and perfusive ($\dot{Q}\,\beta$) conductances (Piiper and Scheid 1981). When the equilibration coefficient is large (>3), the equilibration deficit tends to 0 and the gas flow is limited by perfusion; when the equilibration coefficient is small (<0.1), the equilibration deficit tends to 1 and the gas flow is limited by diffusion. For a gas like oxygen, which is mostly carried by haemoglobin, diffusion limitation occurs when we operate on the steep part of the oxygen equilibrium curve (e.g. in deep hypoxia), perfusion limitation when we operate on the flat part of the oxygen equilibrium curve (e.g. in hyperoxia). For all gases which do not bind to haemoglobin, and thus which follow the law of Henry, gas flow is limited by perfusion. The flow of carbon monoxide, which has an extremely high affinity for haemoglobin, is limited by diffusion. Generally speaking, there is diffusion limitation whenever β has a high value; conversely, when β tends to 0, there is perfusion limitation. Differences in equilibration coefficient among various gases do not depend on the geometric factors (surface area and thickness of the barrier), which in a given individual are the same for all gases. They depend only on d and s, which are included in D_L, and on β, so that the equilibration coefficient of each gas is proportional to the ratio ds/β. Thus, for any given $\dot{Q}$ value, the ratio between the equilibration coefficients of two gases is equal to the ratio between the respective ds/β.

A key aspect of the diffusion–perfusion interaction equation is the role played by the contact time (t_c), which is the time taken by a given amount of blood to move along capillary and which corresponds to the ratio of the effective lung capillary

blood volume (q_c) to $\dot{Q}$. On this basis, the equilibration coefficient (K_e) can be expressed as follows:

$$K_e = -\frac{D_L t_c}{q_c \beta_b} \tag{2.23}$$

At rest, q_c is essentially invariant and independent of $\dot{Q}$. It increases at exercise, due to the recruitment of previously closed capillaries. For any given q_c value, t_c is shorter, the higher is $\dot{Q}$. This combination lowers K_e at exercise, thus increasing the equilibration deficit, and opening the way towards diffusion limitation.

Breathing Pure Oxygen and the Correction for Nitrogen

Breathing in air concerns three main gases, two of which participate in metabolism and gas exchange, while the third, nitrogen, is inert. Conversely, when breathing pure oxygen, after nitrogen has been completely washed out, only metabolic gases are involved in respiration. In this condition, RQ_L is necessarily equal to −1, independent of the cell RQ_M, so that inspired and expired ventilations are equivalent. This is so because pressure equilibration for differences between $\dot{V}O_2$ and $\dot{V}CO_2$ is due to the displacement of an equivalent mass of oxygen instead of nitrogen. Under these conditions,

$$P_A CO_2 = P_I O_2 - P_A O_2 \tag{2.24}$$

On the O_2–CO_2 diagram, this implies that the families of RQ_L isopleths, that we have when we breathe air, reduce to the one and only possible isopleth for $RQ_L = -1$, which at sea level intercepts the x-axis at $P_A O_2 = P_I O_2 = 713$ mmHg, i.e. at a value corresponding to the barometric pressure of dry air. This situation is represented on an O_2–CO_2 diagram in Fig. 2.9. On the same figure, we find also two RQ_L isopleths for a man who breathes air at sea level, namely those for $RQ_L = -0.8$ and $RQ_L = -1$, with the corresponding alveolar gas composition.

The O_2–CO_2 diagram of Fig. 2.9 allows calculation of $P_I N_2$ and $P_A N_2$ during air breathing. $P_I N_2$ is equal to the difference between the barometric pressure of dry air and $P_I O_2$, which in Fig. 2.9 corresponds to the horizontal distance, along the x-axis, between the inspired air compositions during oxygen breathing and during air breathing. Similarly, $P_A N_2$ during air breathing is equal to the horizontal distance between the alveolar air compositions during oxygen and air breathing, for $P_A CO_2 = 40$ mmHg. When $RQ_L = -1$, the RQ_L isopleths for oxygen and air breathing are parallel and $P_A N_2 = P_I N_2$; when $RQ_L > -1$, the RQ_L isopleths for oxygen and air breathing diverge and $P_A N_2 > P_I N_2$, thus allowing pressure equilibration when $\dot{V}CO_2 < \dot{V}O_2$, as much as predicted by Eq. (2.9).

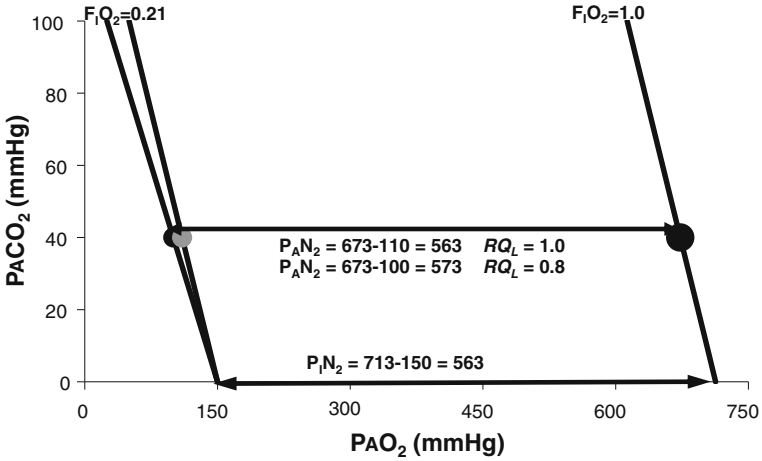


Fig. 2.9 The effects of breathing pure oxygen on alveolar gas composition. *Horizontal arrows* indicate the inspired and alveolar nitrogen partial pressures. Note that the latter varies when the lung respiratory quotient during air breathing is increased from −0.8 (*black dot*) to −1.0 (*grey dot*). P_IN_2, nitrogen partial pressure in inspired air; P_AN_2, nitrogen partial pressure in alveolar air; RQ_L, lung respiratory quotient: F_IO_2, inspired oxygen fraction

The Mechanical Efficiency of Exercise

When animals move, they perform mechanical work, i.e. they displace their body mass from a site to another covering the distance (length) between the two sites. The shorter is the time that is necessary to cover a given distance, the greater is the power (work per unit of time) that they have to develop. To do this, animals rely on muscular contraction. Muscles are biological engines, which transform the chemical energy liberated by biological substrates (mostly lipids and glycogen) in oxidative processes in mechanical work. The **mechanical efficiency** (η) of this energy transformation is given by

$$\eta = \frac{W}{E} \tag{2.25}$$

Normally, the amount of work performed is less than the chemical energy transformed, so that $\eta < 1$. During contractions implying muscle shortening—concentric contractions—$\eta = 0.25$. This means that, of the overall amount of chemical energy transformed, a quarter becomes mechanical work: the remainder is lost as heat. The rate, at which chemical energy is transformed into mechanical work and heat during exercise, is defined as the **metabolic power** of exercise [term $\dot{E}$ of Eq. (2.1)]. Of course, the metabolic power is not entirely used for exercise: a resting individual does not perform mechanical work to move his body—does not perform exercise—yet he has a positive metabolic power (resting metabolic power,

$\dot{E}_R$, some 105 W on average) sustaining resting $\dot{V}_A$ and $\dot{Q}$, smooth muscle contraction and chemicals displacement against concentration gradients, plus the isometric muscle contractions that sustain a standing or sitting body.

As already pointed out, during light dynamic exercise, the general equation of the energetics of muscular exercise reduces to Eq. (2.2). This equation indicates that all energy sustaining the development of mechanical power ($\dot{w}$) during exercise derives from aerobic energy sources, so that a simple measure of $\dot{V}O_2$ provides a complete and satisfactory measure of $\dot{E}$. If η is invariant, then the increase in $\dot{E}$ above its resting value must be proportional to the increase in $\dot{w}$, whence a linear relationship between $\dot{E}$ and $\dot{w}$ at exercise. This is indeed what happens during dynamic light exercise on a cycle ergometer, the most common type of exercise in a laboratory of integrative physiology nowadays, as shown in Fig. 2.10. This is not so, however, during walking, in which the relationship between $\dot{E}$ and $\dot{w}$ (i.e. speed) is nonlinear, indicating changes of η as a function of speed.

The linear relationship depicted in Fig. 2.10 takes the following algebraic form:

$$\dot{E} = \dot{E}_0 + \zeta \dot{w} \tag{2.26}$$

where the *y*-intercept $\dot{E}_0$ should correspond to $\dot{E}_R$—in fact $\dot{E}_0$ is slightly higher than $\dot{E}_R$, as we will see. In turn, the angular coefficient ζ is equal to

$$\zeta = \frac{d\dot{E}}{d\dot{w}} \tag{2.27}$$

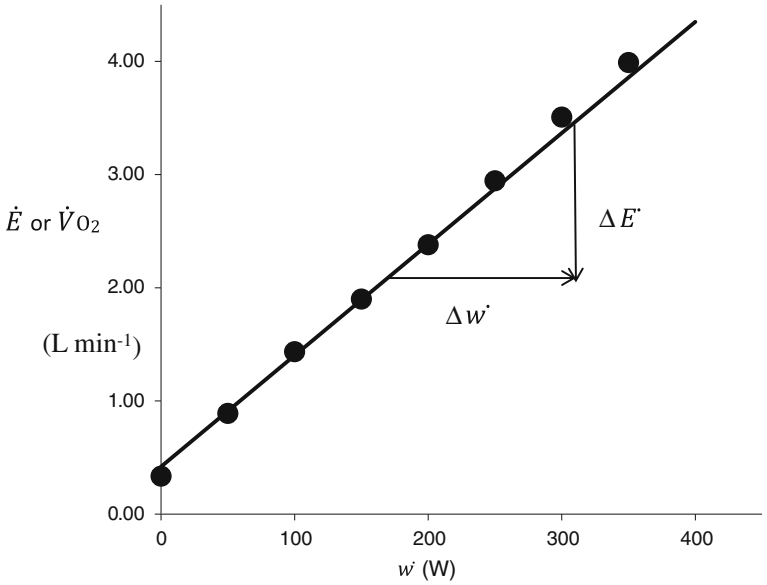


Fig. 2.10 The *dots* refer to unpublished data obtained on a top-level cyclist. The slope of the regression line is equal to the reciprocal of the mechanical efficiency of exercise

which, according to Eq. (2.25), is the reciprocal of η, for which a value between 0.23 and 0.25 is in most cases obtained. Thus, Fig. 2.10 tells that, during dynamic light exercise on a cycle ergometer, (i) η is constant indeed, as predicted; (ii) the higher is ζ (greater increase in $\dot{E}$ per unit increase in $\dot{w}$), the lower is η; and (iii) η corresponds pretty well to the mechanical efficiency of concentric muscle contractions (Gaesser and Brooks 1975). When η is calculated after Eq. (2.26), as the reciprocal of ζ, it is sometimes called the **delta-efficiency** of exercise.

The net rate of metabolic energy expenditure ($\dot{E} - \dot{E}_R$, where $\dot{E}_R < \dot{E}_0$) is equal to the sum of the rates of energy expenditure required to overcome external ($\dot{E}_E$) and internal ($\dot{E}_I$) powers. On the one side, $\dot{E}_E$ is the metabolic power actually used to overcome $\dot{w}$, whence $\dot{E}_E = \dot{E} - \dot{E}_0$; on the other side, $\dot{E}_I$ is dissipated against all other resistances than that imposed by $\dot{w}$, so that $\dot{E}_0 = \dot{E}_R + \dot{E}_I$, which explains why $\dot{E}_0 > \dot{E}_R$, as pointed out above. On this basis, Eq. (2.26) can be rewritten as follows:

$$\dot{E} - \dot{E}_R = \dot{E}_{NET} = \dot{E}_I + \dot{E}_E = \dot{E}_I + \zeta\dot{w} \tag{2.28}$$

According to this equation, $\dot{E}_I$ is independent of $\dot{w}$. It was also demonstrated that $\dot{E}_I$ is a power function of the pedalling frequency (f_p) (Francescato et al. 1995) and is a linear function of the weight of the legs, that is the product of the mass of the legs (Ml) times the gravity acceleration (a_g) (Girardis et al. 1999).

$$\dot{E}_I = \varepsilon MLa_g \tag{2.29}$$

where the constant ε, which has the dimension of a velocity, contains the length of the pedal lever and f_p. Bonjour et al. (2010) demonstrated that ε varies with the square of f_p, so that we can write

$$\dot{E}_I = \varphi f_p^2 MLa_g \tag{2.30}$$

Bonjour et al. (2010) obtained for the proportionality constant φ a value of 1.73 m s.

Studies during walking and running demonstrated that in both cases η is higher than 0.25. During walking, this is due to the fact that, since kinetic and potential energy are in opposition of phase, horizontal speed is largely sustained by continuous exchanges between these two forms of energy with an efficiency of 1, as in a pendulum. In running, the elastic strain energy that is absorbed by the tendons whenever a foot touches the ground and brakes the fall of the body is immediately returned in the subsequent bounce, again with an efficiency of 1 (Cavagna and Kaneko 1977; Cavagna et al. 1976). During uphill walking and running, at least at slopes above 20 %, all energy is expended to lift the body: the former two mechanisms are not functional anymore, and only concentric muscle contractions are carried out, with η equal to 0.25; conversely, during downhill walking and running, at least at negative slopes below −20 %, all energy is expended to brake the body fall: only eccentric muscle contractions occur, with η equal to 1.20 (Minetti et al. 2002).

Energy Cost of Locomotion

During exercise on a cycle ergometer, the pedalling individual does not move forward on a horizontal plane. The metabolic power is used to generate pedal rotational speed and overcome the resistance opposed by the brake applied on the cycle ergometer. In actual locomotion, the body does move forward in a given direction on the horizontal plane at given speeds (v_h). At steady state, the mean v_h does not vary with time. Of course, $\dot{E}$ and $\dot{w}$ increase with v_h. The slope of a relationship between $\dot{E}$ and v_h has the dimension of a force, and it represents the amount of metabolic energy that a moving animal must expend to cover a unit of distance: it is called the **energy cost** (C), so we can write

$$C = \frac{\dot{E}}{v_h} \tag{2.31}$$

The relationship between $\dot{E}$ and v_h is nonlinear for any type of locomotion: its slope gets higher the higher is v_h, implying that C increases with v_h. A positive C is needed to overcome the forces that oppose to the horizontal movement of the body. These forces are of two types: frictional forces (F_f) and aerodynamic forces—air resistance or drag (D), see e.g. di Prampero (1986). Since C includes metabolic, not mechanical, energy, we can thus write

$$C\,\eta = F_f + D \tag{2.32}$$

D is proportional to the square of speed:

$$D = k_d v_h^2 \tag{2.33}$$

where constant k_d is proportional to air density (ρ), the drag coefficient (C_x), and the projection area on the frontal plane (A):

$$k_d = 1/2\rho\, C_x A \tag{2.34}$$

ρ is some 800 times greater for water than for air, whence the much higher C in swimming than in any type of locomotion on land. In air, ρ is directly proportional to P_B and inversely proportional to temperature. C_x is a non-dimensional number depending on the surface characteristics, on the geometrical shape of the moving body, and on the characteristics of the air flow around the moving body. A corresponds to the surface area of the body that faces air on the direction of movement. If we introduce Eq. (2.34) into Eq. (2.33), and we divide by A, we obtain

$$DA^{-1} = 1/2\rho\, C_x v_h^2 = P_D \tag{2.35}$$

Fig. 2.11 A picture of Chris Boardman on his aerodynamic bicycle during his successful 1-h world record attempt at Manchester, UK, on 6 September 1996

where P_D is the dynamic pressure exerted on the moving body. *Ceteris paribus*, P_D is directly proportional to C_x, so that dynamically favourable shapes are characterized by low C_x values, as is the case for aerodynamic contemporary cars or track bicycles used for record trials (Capelli et al. 1993; di Prampero 2000) (see Fig. 2.11)

Since D is a force, in analogy with C, it can be expressed as mechanical work per unit of distance (Ferretti et al. 2011), so that

$$D = C_D \, \eta = k_d v_h^2 \tag{2.36}$$

where C_d is the fraction of C that overcomes D. As a consequence,

$$C_D = k_d \eta^{-1} v_h^2 = k' v_h^2 \tag{2.37}$$

We can also define the metabolic power against air resistance ($\dot{E}_D$) as the product of C_d times v_h. By inserting this definition of $\dot{E}_D$ into Eq. (2.37), we obtain

$$\dot{E}_D = C_d v_h = k' v_h^3 \tag{2.38}$$

which indicates that $\dot{E}_D$ is directly proportional to the cube of v_h.

Let us now consider also the metabolic power against frictional forces ($\dot{E}_f$), which corresponds to the remainder fraction of the net rate of energy expenditure $\dot{E}_n$. We then have

$$\dot{E}_n = \dot{E}_D + \dot{E}_f = k' v_h^3 + \dot{E}_f \tag{2.39}$$

A comprehensive analysis of the relationships between $\dot{E}_n$ and v_h in several types of locomotion on flat terrain in air at sea level is presented in Fig. 2.12 (di Prampero 1986; Ferretti et al. 2011). In Fig. 2.12, the bold curve is theoretical and applies for $\dot{E}_n = \dot{E}_D (\dot{E}_f = 0 \text{ W})$ Its slope corresponds to C_D. It is constructed for a k' value of 0.774 J s^2 m^{-3} (di Prampero 1985). Note that the curve is flatter and thus apparently displaced rightwards and downwards, the lower is k', as when riding aerodynamic bicycles (Capelli et al. 1993), or when cycling at altitude (di Prampero 2000); it becomes steeper when k' is increased, as when riding ancient bicycles (Minetti et al. 2001). It represents a limit that cannot be overcome on its right side. All other curves in Fig. 2.12 appear leftwards with respect to the bold curve, because of $\dot{E}_f$, whose value is higher, the more the experimental curve appears to the left of the bold curve. The vertical distance between each experimental curve and the

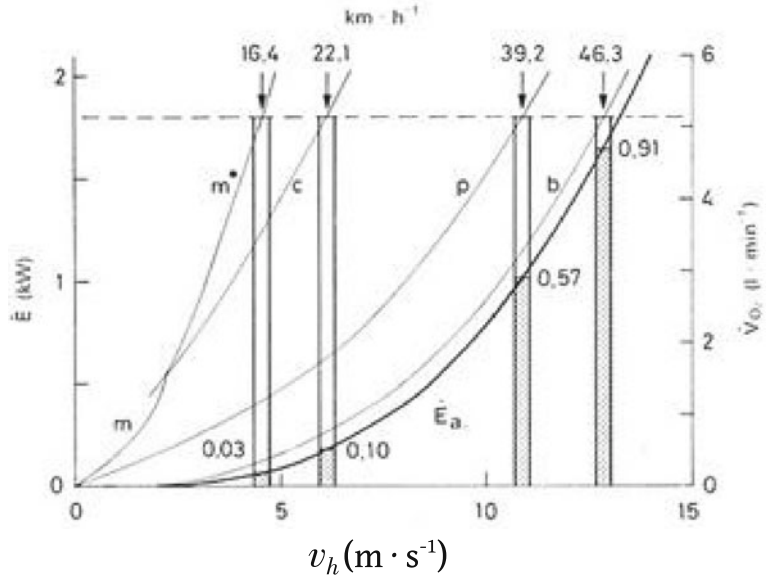


Fig. 2.12 Metabolic power ($\dot{E}$, *left ordinate*) or oxygen uptake ($\dot{V}O_2$, *right ordinate*) as a function of forward speed (v_h). The *bold curve* refers to locomotion in which only work against air resistance is carried out. This *curves* refer to actual locomotion (*b*, bicycling; *p*, skating; *c*, running; *m*, walking; *m**, competitive walking). *Histograms* indicate the fraction of metabolic power expended against aerodynamic forces. The speed on top of each histogram is the maximal aerobic speed for an athlete with a maximal oxygen consumption of 5 L min^{-1}. After di Prampero (1985)

Table 2.1 Parameters describing various types of human locomotion on land. Data taken from Ferretti et al. (2011)

Locomotion mode	k'(J s^2 m^{-3})	Cx	Cf(J m^{-1} kg^{-1})
Running	0.72	1.10	3.9*
Skating	0.79	0.50	1.0
Cycling, race	0.77	0.75	0.17
Cycling, traditional	1.14	1.00	0.27
Cycling, aerodynamics	0.58	0.65	0.15

*indicates an average value: in fact Cf varies linearly with the running speed

theoretical curve corresponds to $\dot{E}_f$. $\dot{E}_f$ is directly proportional to v_h. Thus, the energy cost against frictional forces (C_f) is a constant that is independent of v_h. In fact C_f corresponds to the y-intercept of the linear relationship between C and v_h^2, with slope equal to k', since

$$C = C_D + C_f = k' v_h^2 + C_f \tag{2.40}$$

C_f depends on the characteristics of the interaction between the terrain and the foot or the device (wheel, skates, skis). In cycling, it depends on the width and type of the tyres, on their filling pressure and on the characteristics of the terrain. It is also proportional to the overall weight of bicycle plus human (di Prampero 2000). Average values for k', C_x and C_f are reported in Table 2.1 for different types of locomotion.

Some practical consequences of Fig. 2.12 and Table 2.1 are (i) the fraction of C represented by C_d and C_f varies with the locomotion mode; (ii) k' is remarkably similar among different locomotion modes; (iii) $\dot{E}_D$ at any given is similar among locomotion modes—except walking; and (iv) differences in v_h among various locomotion modes are essentially due to differences in $\dot{E}_f$. Particularly in cycling, $\dot{E}_f$ is minimized by the rotational movement of the wheel, by the amplification effect of the gear and by the absence of work against gravity due to body stabilization by the bike, so that most of $\dot{E}$ can indeed be used to overcome air resistance. This is why cycling leads to reach the highest speeds in human locomotion.

Walking takes place in a speed range where C_d is negligible, so that, practically speaking, $\dot{E} = \dot{E}_f$. But walking, with respect to all other types of locomotion, is peculiar, because of the effects of pendulum-like mechanism and the ensuing transformation of potential energy into kinetic energy and vice versa. Concerning running, C was generally considered invariant in a given individual and thus independent of the running speed (di Prampero 1986; Ferretti et al. 2011), possibly as a consequence of the fact that most data were obtained during treadmill running, a condition in which the running human moves with respect to the treadmill's belt, but not with respect to air (Dill 1965; di Prampero et al. 1986; Hagberg and Coyle 1984; Helgerud 1994; Margaria et al. 1963; McMiken and Daniels 1976; Minetti et al. 2002; Padilla et al. 1992, to give a few examples). Yet Pugh (1970)

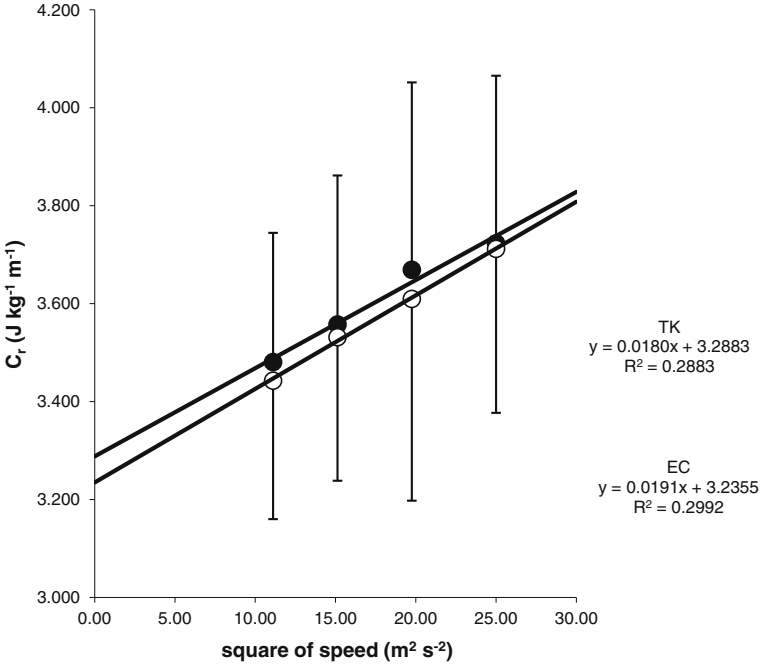


Fig. 2.13 Energy cost of running (C_r) as a function of the square of speed in top-level marathon runners from Kenya (*black dots*) and from Europe (*white dots*). From Tam et al. (2012)

demonstrated that a fraction of C varies with the square of wind velocity, although this fraction was considered small. Following his study, the concept that C could be slightly higher during track than during treadmill running, although still independent of speed, started to be admitted (di Prampero 1986; Jones and Doust 1996; Léger and Mercier 1984). I believe that the reason why it was hard to identify a clear effect of air resistance on C during running is related to the relatively low running speeds tested in most studies. In fact, the first demonstration that Eq. (2.40) applies also to running was obtained by Tam et al. (2012) on top-level marathon runners from Kenya, who were able to run in submaximal condition at speeds up to 20 km h^{-1} (Fig. 2.13): and that it was a clear effect of C_d is also demonstrated by the results of Helgerud et al. (2010), who found no differences in C as a function of v_h during treadmill running at similar speeds to those of Tam et al. (2012).

C is related also to the technical ability of the individual in a given locomotion mode: in general, the better is the technique of movement, the lower is C, so that, because of Eq. (2.31), at any given $\dot{E}$ value higher v_h can be attained. This has little importance in running, in which, although top-level runners have lower C than leisure runners or non-habitual runners (di Prampero 1986), little changes in C can be obtained with training (Morgan et al. 1989). On the contrary, in swimming, impressive decreases of C can be achieved by improving the swimming technique (Holmér 1974). Termin and Pendergast (2000) demonstrated that continuous swimming training on multiple

year basis reduces $\dot{E}$ and the stroke frequency (f_s) at any speed, thus increasing the distance covered by a stroke, with consequent drop of C. Swimming, although it follows the general rules described by Eqs. (2.31) and (2.36), is nevertheless characterized by some peculiarities related to the fact that it takes place in water, whose ρ is some 800 times greater than that of air, so that (i) buoyancy counts much more than gravity acceleration; (ii) for a given $\dot{E}$, C is much higher and v_h much lower than in any other type of locomotion on land; (iii) due to differences in buoyancy between the upper and the lower part of the body, torque tends to increase A, and thus k_d and C (Pendergast et al. 1977; Zamparo et al. 2009); (iv) due to differences in body composition, torque is less in women than in men, whence a lower C in the former than in the latter (Zamparo et al. 2008) at a given speed; (v) the effects of torque are counteracted by feet movements, so that, although all external power transmits kinetic energy to water, only a fraction of the external power is actually used to propel the body on the horizontal plane (Zamparo et al. 2011); as a consequence, (vi) the overall η of swimming is less than that of concentric muscle contractions (for a detailed discussion of η during swimming, see Zamparo et al. 2002).

The Cardiovascular Responses to Exercise

The main factor characterizing the cardiovascular responses to exercise is the increase in $\dot{Q}$, due to the simultaneous increase of its two determinants, the heart rate (f_h) and the stroke volume (Q_s) (Asmussen and Nielsen 1952; Åstrand et al. 1964; Hermansen et al. 1970; Stenberg et al. 1967). This increase is classically attributed to a remodulation of autonomic nervous system control of heart activity at exercise (Fagraeus and Linnarsson 1976; Robinson et al. 1966), although the effect of the Frank–Starling mechanism on Q_s has been considered as well (Rowell et al. 1996). At steady state, $\dot{Q}$ is a linear function of $\dot{V}\,O_2$ (Åstrand et al. 1964; Cerretelli and di Prampero 1987). The relation has a positive y-intercept, implying, as long as the exercise intensity is increased, there is a smaller growth of $\dot{Q}$ than of $\dot{V}\,O_2$, so that, according to Eq. (2.3), the $Ca O_2 - C\bar{v}O_2$ difference becomes greater. Most of the increase in $\dot{Q}$ goes into the active muscle mass, so that muscle blood flow increases remarkably, due to the stimulation of β_2-adrenergic receptors, which are found in muscles instead of α_1-adrenergic receptors, and to the action of local vasodilating mediators (Delp and Laughlin 1998; Delp and O'Leary 2004; Seals and Victor 1991). Muscle vasodilation determines a sudden drop of total peripheral resistance (R_p). Finally, systolic arterial pressure increases, whereas diastolic blood pressure, if any, tends to go down (Rowell et al. 1968).

The linear relationship between $\dot{Q}$ and $\dot{V}\,O_2$ is fairly stable. Aerobic training decreases f_H and increases Q_s, so that at any given $\dot{V}\,O_2$, $\dot{Q}$ remains unchanged (Ekblom et al. 1968; Saltin et al. 1968). The same is the case for athletes, whose maximal oxygen consumption is higher than that of non-athletic individuals: they have the same $\dot{Q}$ versus $\dot{V}\,O_2$ relationship as non-athletes, with lower f_H and higher

Q_s (Ekblom and Hermansen 1968). The superposition of arm exercise to leg exercise (Bevegård et al. 1966) and the exercise mode (Hermansen et al. 1970) have no effects on the $\dot{Q}$ versus $\dot{V}\,O_2$ relationship. Water immersion and supine posture, in spite of their acute effects on central blood volume with consequent decrease in f_H and increase in Q_s, do not alter the $\dot{Q}$ versus $\dot{V}\,O_2$ relationship (Bevegård et al. 1966; Rennie et al. 1971; Sheldahl et al. 1987). Exercise in the heat, whose effects on f_H and Q_s are opposite to those of water immersion, implies reduced $\dot{Q}$ values at any given $\dot{V}\,O_2$ only when heat is extreme and the drop of R_p for simultaneous muscular and cutaneous vasodilation is dramatic (Nadel et al. 1979; Rowell 1974). Only admitted exceptions to an essentially invariant $\dot{Q}$ versus $\dot{V}\,O_2$ relationship were the upwards shift of the $\dot{Q}$ versus $\dot{V}\,O_2$ relationship in acute hypoxia (Hartley et al. 1973; Hughes et al. 1968; Roca et al. 1989; Stenberg et al. 1966) and after moderate CO poisoning (Vogel and Gleser 1972). The concept of an invariant relationship between $\dot{Q}$ and $\dot{V}\,O_2$ was so deeply rooted in exercise physiologists, that those exceptions were explained in terms of an *error signal*, related to reduced CaO_2 influencing the control system of $\dot{Q}$ (see e.g. Cerretelli and di Prampero 1987).

Acute hypoxia and CO poisoning share a common aspect, that they both lead to a reduction of CaO_2. Conversely, when CaO_2 is increased, such as upon return to sea level after altitude acclimatization, the $\dot{Q}$ versus $\dot{V}\,O_2$ relationship is shifted downwards (Ferretti et al. 1990). On these bases, these last authors hypothesized that $\dot{Q}$ varies in inverse proportion with CaO_2 in order to maintain systemic oxygen delivery ($\dot{Q}\,aO_2$), i.e. the product of $\dot{Q}$ times CaO_2, invariant at any given $\dot{V}\,O_2$. This being the case, $\dot{Q}\,aO_2$ rather than $\dot{Q}$ would be the regulated variable at exercise steady state.

The relationship between $\dot{Q}\,aO_2$ and $\dot{w}$ was investigated by Ferretti et al. (1992) in the $\dot{w}$ range that allows attainment of a steady state for $\dot{V}\,O_2$ at exercise and was found to be linear and parallel to that between $\dot{V}\,O_2$ and power. This implies that the vertical difference between the two lines, corresponding to the oxygen flow in mixed venous blood ($\dot{Q}\,\bar{v}O_2$), is a constant, independent of $\dot{Q}$ and $\dot{V}\,O_2$, and thus of the exercise intensity. Later, $\dot{Q}\,\bar{v}O_2$ was found to depend SaO_2 (Anchisi et al. 2001) and on the activation state of the autonomic nervous system (Ferretti et al. 2005).

The $\dot{Q} - \dot{V}\,O_2$ Diagram

On the basis of what precedes, the relationship between $\dot{Q}$ and $\dot{V}\,O_2$ can be analysed under a different perspective. Since, according to Ferretti et al. (1992), $\dot{Q}\,\bar{v}O_2$ is equal to

$$\dot{Q}\,\bar{v}O_2 = K = \dot{Q}\,aO_2 - \dot{V}\,O_2 \tag{2.41}$$

If we consider that $\dot{Q}aO_2$ is the product of $\dot{Q}$ times CaO_2, Eq. (2.36) can be rewritten as follows:

$$\dot{Q}\bar{v}O_2 = \dot{Q} \cdot CaO_2 - \dot{V}O_2 \tag{2.42}$$

whose solution for $\dot{Q}$ is

$$\dot{Q} = \frac{\dot{V}O_2 + \dot{Q}\bar{v}O_2}{CaO_2} \tag{2.43}$$

Cerretelli and di Prampero (1987), in agreement with previous authors who considered $\dot{V}O_2$ to be set only by $\dot{w}$, represented $\dot{Q}$ as the dependent variable and $\dot{V}O_2$ as the independent variable. If this is so, Eq. (2.43) tells that $\dot{Q}$ is linearly related to $\dot{V}O_2$, with slope equal to CaO_2^{-1} and intercept on the *x*-axis equal to $-\dot{Q}\bar{v}O_2$. Such a relationship is constructed in Fig. 2.14a, where a family of CaO_2 isopleths is reported, all converging on the same $\dot{Q}\bar{v}O_2$ value, and validated using data obtained in normoxia, taken from different sources in the literature (Adami et al. 2014) (Fig. 2.14b), from which a mean $\dot{Q}\bar{v}O_2$ value of 1.35 L min^{-1} was computed, whereas CaO_2^{-1} (slope of the $\dot{Q}$ versus $\dot{V}O_2$ line) resulted equal to 4.93 L of blood per L of oxygen, yielding a theoretical CaO_2 of 203 ml L^{-1}. All the data shown in Fig. 2.14b are exercise data, a condition in which the parasympathetic branch of the autonomic nervous system is inactive (Fagraeus and Linnarsson 1976). At rest, in which there is predominant vagal control of heart rate (Fagraeus and Linnarsson 1976; Lador et al. 2006; Malliani et al. 1991; Perini and Veicsteinas 2003), the data lie below those obtained at exercise, compatibly with a lower $\dot{Q}\bar{v}O_2$ value. This agrees with previous observations, both during cycling (Anchisi et al. 2001; Ferretti et al. 2005) and during two-legged knee extension exercise (Koskolou et al. 1997; Roach et al. 1999). In Fig. 2.14, this implies a right shift of the CaO_2 isopleths.

The very strong dependence of $\dot{Q}$ on $\dot{V}O_2$ shown in Fig. 2.14 allows an overall theoretical view of the steady-state cardiovascular responses to exercise as a function of exercise intensity and CaO_2, based on Fig. 2.14a, which Adami et al. (2014) called **the $\dot{Q} - \dot{V}O_2$ diagram**. This figure is conceptually different from the classical $\dot{Q}$ versus $\dot{V}O_2$ relationship. The latter figure in fact, as $\dot{V}O_2$ is increased, shows a progressive shift of the $\dot{Q}$ values towards isopleths for higher arterial–venous oxygen difference, which converge on the origin of the axes (Cerretelli and di Prampero 1987). Conversely the $\dot{Q} - \dot{V}O_2$ diagram reports CaO_2 isopleths converging on a specific, negative *x*-axis intercept, corresponding to $\dot{Q}\bar{v}O_2$ (1.35 L min^{-1}, according to the regression line of Fig. 2.14b). During moderate exercise in normoxia, the regression line of Fig. 2.14b coincides with a specific CaO_2 isopleth because CaO_2 is fairly invariant. Anaemic individuals (Roach et al. 1999; Woodson et al. 1978), whose CaO_2 is reduced because of [Hb] loss in the

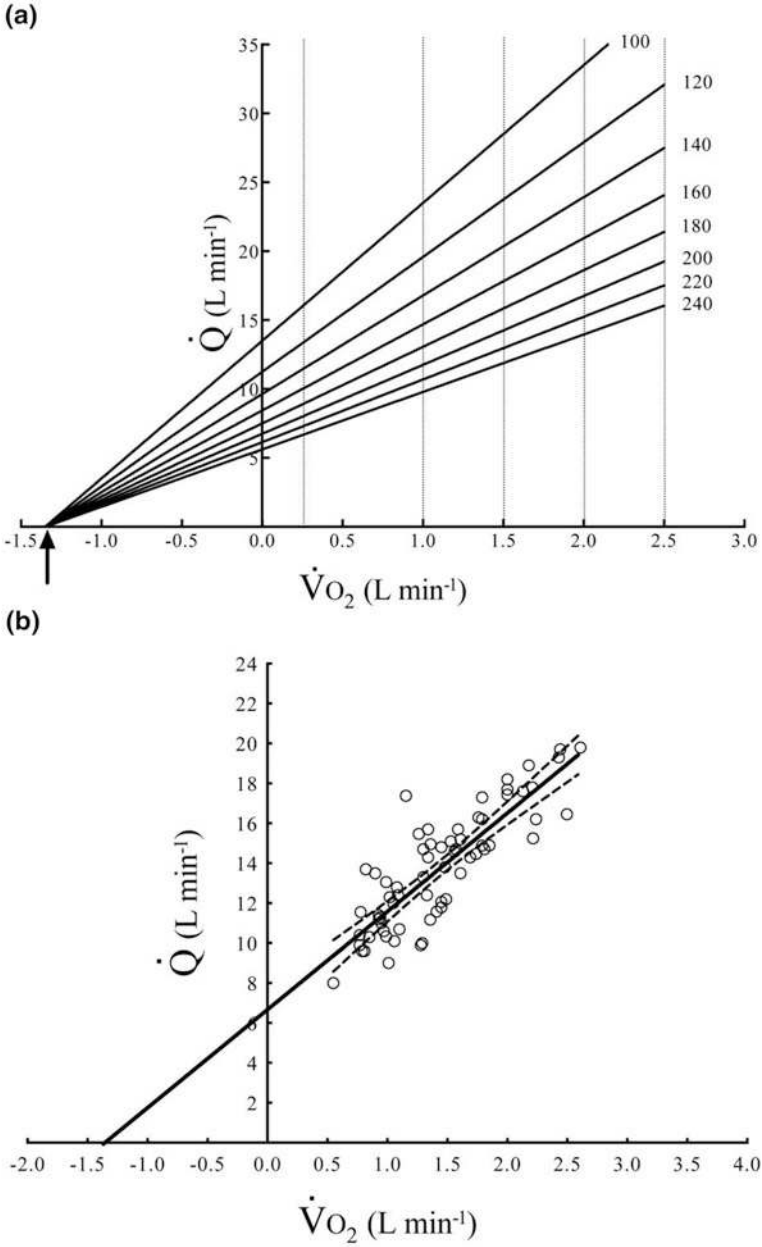


Fig. 2.14 *Panel a* Theoretical representation of the relationship between cardiac output ($\dot{Q}$) and oxygen uptake ($\dot{V}\,O_2$) at exercise steady state ($\dot{Q} - \dot{V}\,O_2$ diagram). The *lines* are isopleths for the indicated values of arterial oxygen concentration. They all converge on the same *x*-axis intercept, corresponding to the oxygen flow in mixed venous blood. *Panel b* An experimental $\dot{Q} - \dot{V}\,O_2$ diagram obtained during steady-state exercise in normoxia, using data from different sources in the literature. After Adami et al. (2014)

absence of SaO_2 changes, and thus who still operate on the flat part of the oxygen equilibrium curve, would have a $\dot{Q}$ versus $\dot{V}O_2$ relationship that coincides with a steeper CaO_2 isopleth on the $\dot{Q} - \dot{V}O_2$ diagram. The same would be the case in the presence of carbon monoxide poisoning (Gonzalez-Alonso et al. 2001; Vogel and Gleser 1972). On the opposite side, in case of polycythaemia, the $\dot{Q}$ versus $\dot{V}O_2$ relationship would coincide with a flatter CaO_2 isopleth. (Celsing et al. 1986; Ekblom et al. 1976; Ferretti et al. 1990, 1992).

Things are different in acute hypoxia, as shown in Fig. 2.15 which reports data obtained at an inspired oxygen fraction of 0.11. The regression analysis indicates $\dot{Q}\bar{v}O_2 = 1.12$ L min^{-1} and $CaO_2^{-1} = 6.73$ L of blood per L of oxygen, corresponding to a mean theoretical CaO_2 of 148.6 ml L^{-1}. However, at that level of hypoxia, subjects operate on the steep part of the oxygen equilibrium curve, so that any increase in $\dot{V}O_2$, and thus in $\dot{Q}$, carries along a shortening of capillary blood transit time, resulting in progressively lower SaO_2 values at the arterial end of lung capillaries, so that there are lower CaO_2 values in hypoxia the higher are $\dot{V}O_2$ and $\dot{Q}$. At any given hypoxic inspired oxygen fraction, the progressive SaO_2 reduction shifts the $\dot{Q}$ versus $\dot{V}O_2$ data towards an isopleth for lower CaO_2 values, so that (i) the apparent $\dot{Q}$ versus $\dot{V}O_2$ line has a higher slope than that for normoxia; and (ii) the same line points towards a higher *x*-axis intercept, indicative of an apparently lower $\dot{Q}\bar{v}O_2$ value (Adami et al. 2014). Anchisi et al. (2001) found lower $\dot{Q}\bar{v}O_2$ the

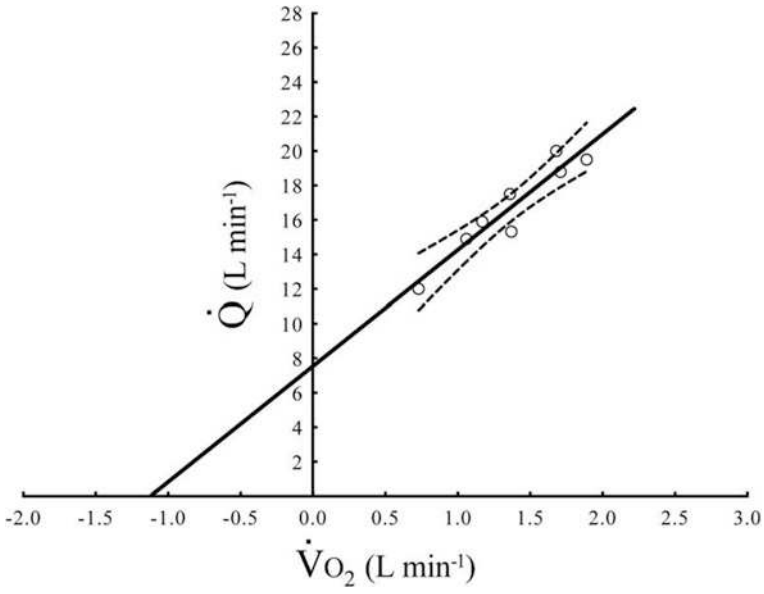


Fig. 2.15 An experimental $\dot{Q} - \dot{V}O_2$ diagram constructed for steady-state exercise in acute normobaric hypoxia, using data from different sources in the literature, all obtained at an inspired oxygen fraction of 0.11. After Adami et al. (2014)

lower was the $Sa\mathrm{O}_2$, as discussed here above, but they also found a positive linear relationship between these two parameters at exercise. This means that there is more than a mere shift across $Ca\mathrm{O}_2$ isopleths when the $\dot{Q}$ versus $\dot{V}\,\mathrm{O}_2$ relationship is modified by a fall of $Sa\mathrm{O}_2$ in hypoxia. There is also a right displacement of the x-axis intercept, implying a decrease of $\dot{Q}\,\bar{v}\mathrm{O}_2$. This is at variance with what appears when $Ca\mathrm{O}_2$ is modified by changing [Hb] (e.g. anaemia or polycythaemia) while keeping $Sa\mathrm{O}_2$ unchanged.

To explain the response characteristics revealed by the $\dot{Q} - \dot{V}\,\mathrm{O}_2$ diagram, we may call upon different mechanisms, depending on whether there is or not a change in $Sa\mathrm{O}_2$. Oxygen-sensing mechanisms may deserve high consideration. For instance, the conformation of the reduced haemoglobin determines the rise of NO in blood with consequent vasodilatation (Stamler et al. 1997). More recently, Crecelius et al. (2011a, b) proposed a synergistic effect of prostaglandins and NO in peripheral blood flow regulation during hypoxic exercise. Others suggested that in subjects with reduced $Ca\mathrm{O}_2$, peripheral blood flow may be increased by ATP-mediated vasodilatation (Ellsworth et al. 1995; Gonzalez-Alonso et al. 2002; Mortensen et al. 2011). Stickland et al. (2011) suggested a role for carotid chemoreceptors, directly related to variations of $Ca\mathrm{O}_2$. The above mechanisms, however, do not explain the effect of the $Sa\mathrm{O}_2$ fall in hypoxia, as pointed out by Stickland et al. (2011) who excluded a role for carotid chemoreceptors in regulating limb blood flow when $Ca\mathrm{O}_2$ was reduced because of a fall in $Sa\mathrm{O}_2$.

Conclusions

In this chapter, I have described the main relationships that at steady state represent the cardiorespiratory responses to exercise, which are tightly coupled with the metabolic responses to exercise, as a consequence of the concept that at steady state, the same $\dot{V}\,\mathrm{O}_2$ value is attained at all steps along the respiratory system, from ambient air to mitochondria. To end with, I will try a synthesis of the various relationships that I have discussed. To do so, I would start from the $\dot{Q} - \dot{V}\,\mathrm{O}_2$ diagram, where $\dot{Q}\,\bar{v}\mathrm{O}_2$ is defined as a constant, i.e. the x-axis intercept of a $\dot{Q}$ versus $\dot{V}\,\mathrm{O}_2$ line. Its algebraic formulation is summarized in Eq. (2.43). At the same time, the solution for $\dot{Q}$ of the ventilation–perfusion equation [Eq. (2.18)] is

$$\dot{Q} = \frac{\dot{V}_A P_A \mathrm{CO}_2}{CgRQ_L(Ca\mathrm{O}_2 - C\bar{v}\mathrm{O}_2)} \tag{2.44}$$

Inserting Eq. (2.43) in Eq. (2.44) yields

$$\frac{\dot{V}\,\mathrm{O}_2 + \dot{Q}\,\bar{v}\mathrm{O}_2}{Ca\mathrm{O}_2} = \frac{\dot{V}_A\,P_A\mathrm{CO}_2}{CgRQ_L(Ca\mathrm{O}_2 - C\bar{v}\mathrm{O}_2)} \tag{2.45}$$

Combining also Eq. (2.16) and rearranging, we get

$$\frac{\dot{V}_A\,P_A\,\mathrm{CO}_2}{CgRQ_L} + \dot{Q}\,\bar{v}\mathrm{O}_2 = \frac{\dot{V}_A\,P_A\,\mathrm{CO}_2\,Ca\mathrm{O}_2}{CgRQ_L(Ca\mathrm{O}_2 - C\bar{v}\mathrm{O}_2)} = \dot{Q}\cdot Ca\mathrm{O}_2 \tag{2.46}$$

This equation links ventilation, circulation and metabolism at exercise in a tight manner, such that **homeostasis of the respiratory system at exercise** is maintained around given values of the constant $\dot{Q}\,\bar{v}\mathrm{O}_2$. It tells that, as long as we are during steady-state exercise in normoxia, in which $P_A\mathrm{CO}_2$ (40 mmHg) and $Ca\mathrm{O}_2$ (200 ml L^{-1} for normal haemoglobin concentration) may be considered invariant, any increase in the exercise metabolic rate $\dot{E}$ and thus in $\dot{V}\,\mathrm{O}_2$ requires (i) an increase in $\dot{V}_A$ that is proportional to that in $\dot{V}\,\mathrm{O}_2$ only if RQ_L does not change, and (ii) an increase in $\dot{Q}$ that is not proportional to the corresponding increase in $\dot{V}\,\mathrm{O}_2$. Invariance of $Ca\mathrm{O}_2$ occurs only as long as we operate on the flat part of the oxygen equilibrium curve (diffusion limitation). As long as diffusion limitation appears, as is the case in deep hypoxia, also $Ca\mathrm{O}_2$ varies (drops), $\dot{Q}$ only partially corrects this drop, the constant $\dot{Q}\,\bar{v}\mathrm{O}_2$ takes a lower value, and all relations to $\dot{E}$ are modified except that with $\dot{V}_A$, whose characteristics remain related to changes in RQ_L only: the homeostasis of the respiratory system at exercise is modified. At intense exercise, when lactate accumulation also occurs and hyperventilation superimposes, a new steady state would be attained only at $P_A\mathrm{CO}_2$ values lower than 40 mmHg, depending on the intensity of the hyperventilation: the homeostasis of the respiratory system would again be modified. This new steady state, however, is never attained in fact, and the reasons for this are discussed in Chap. 3. Thus, in real life, the conditions described and discussed in this chapter are observed only during light exercise, below the so-called lactate threshold, or below the called critical power, two concepts that are developed in Chap. 5.

References

Adami A, Fagoni N, Ferretti G (2014) The $\dot{Q} - \dot{V}\,\mathrm{O}_2$ diagram: an analytical interpretation of oxygen transport in arterial blood during exercise in humans. Respir Physiol Neurobiol 193: 55–61

Anchisi S, Moia C, Ferretti G (2001) Oxygen delivery and oxygen return in humans exercising in acute normobaric hypoxia. Pflügers Arch 442:443–450

Armstrong RB, Delp MD, Goljan MF, Laughlin MH (1987) Distribution of blood flow in muscles of miniature swine during exercise. J Appl Physiol 62:1285–1298

Asmussen E, Nielsen M (1952) The cardiac output in rest and work determined simultaneously by the acetylene and the dye injection methods. Acta Physiol Scand 27:217–230

Åstrand PO, Cuddy TE, Saltin B, Stenberg J (1964) Cardiac output during submaximal and maximal work. J Appl Physiol 19:258–264

Baumgartner WA Jr, Jaryszak EM, Peterson AJ, Presson RG, Wagner WW (2003) Heterogeneous capillary recruitment among adjoining alveoli. J Appl Physiol 95:469–476
Bevegård S, Freyschuss U, Strandell T (1966) Circulatory adaptation to arm and leg exercise in supine and sitting position. J Appl Physiol 21:37–46
Bock AV, Vancaulert C, Dill DB, Fölling A, Hurxthal LM (1928) Studies in muscular activity. IV. The steady state and the respiratory quotient during work. J Physiol 66:162–174
Bonjour J, Capelli C, Antonutto G, Calza S, Tam E, Linnarsson D, Ferretti G (2010) Determinants of oxygen consumption during exercise on cycle ergometer: the effects of gravity acceleration. Respir Physiol Neurobiol 171:128–134
Capelli C, Rosa G, Butti F, Ferretti G, Veicsteinas A, di Prampero PE (1993) Energy cost and efficiency of riding aerodynamic bicycles. Eur J Appl Physiol 65:144–149
Cavagna GA, Kaneko M (1977) Mechanical work and efficiency in level walking and running. J Physiol 268:467–481
Cavagna GA, Thys H, Zamboni A (1976) The sources of external work in level walking and running. J Physiol 262:639–657
Celsing F, Nyström J, Pihlstedt P, Werner B, Ekblom B (1986) Effect of long-term anemia and retransfusion on central circulation during exercise. J Appl Physiol 61:1358–1362
Cerretelli P, di Prampero PE (1987) Gas exchange at exercise. In: Farhi LE, Tenney SM (eds) Handbook of physiology, the respiratory system IV. Bethesda, MD, pp 555–632 (Am Physiol Soc)
Clark AR, Tawhai MH, Hoffman EA, Burrowes KS (2011) The interdependent contributions of gravitational and structural features to perfusion distribution in a multiscale model of the pulmonary circulation. J Appl Physiol 110:943–955
Cottin F, Médigue C, Papelier Y (2008) Effect of heavy exercise on spectral baroreflex sensitivity, heart rate, and blood pressure variability in well-trained humans. Am J Physiol Heart Circ Physiol 295:H1150–H1155
Crecelius AR, Kirby BS, Richards JC, Garcia LJ, Voyles WF, Larson DG, Luckasen GJ, Dinenno FA (2011a) Mechanisms of ATP-mediated vasodilation in humans: modest role for nitric oxide and vasodilating prostaglandins. Am J Physiol Heart Circ Physiol 301:H1302–H1310
Crecelius AR, Kirby BS, Voyles WF, Dinenno FA (2011b) Augmented skeletal muscle hyperaemia during hypoxic exercise in humans is blunted by combined inhibition of nitric oxide and vasodilating prostaglandins. J Physiol 589:3671–3683
Delp MD, Laughlin MH (1998) Regulation of skeletal muscle perfusion during exercise. Acta Physiol Scand 162:411–419
Delp MD, O'Leary DS (2004) Integrative control of the skeletal muscle microcirculation in the maintenance of arterial pressure during exercise. J Appl Physiol 97:1112–1118
di Prampero PE (1981) Energetics of muscular exercise. Rev Physiol Biochem Pharmacol 89:143–222
di Prampero PE (1985) La locomozione umana su terra, in acqua, in aria: fatti e teorie. Edi Ermes, Milano
di Prampero PE (1986) The energy cost of human locomotion on land and in water. Int J Sports Med 7:55–72
di Prampero PE (2000) Cycling on earth, in space, on the moon. Eur J Appl Physiol 82:345–360
di Prampero PE, Ferretti G (1999) The energetics of anaerobic muscle metabolism: a reappraisal of older and recent concepts. Respir Physiol 118:103–115
di Prampero PE, Atchou G, Brückner JC, Moia C (1986) The energetics of endurance running. Eur J Appl Physiol 55:259–266
Dill DB (1965) Oxygen used in horizontal and grade walking and running on the treadmill. J Appl Physiol 20:19–22
Ekblom B, Hermansen L (1968) Cardiac output in athletes. J Appl Physiol 25:619–625
Ekblom B, Åstrand PO, Saltin B, Stenberg J, Wallström B (1968) Effect of training on circulatory response to exercise. J Appl Physiol 24:518–528
Ekblom B, Wilson G, Åstrand PO (1976) Central circulation during exercise after venesection and reinfusion of red blood cells. J Appl Physiol 40:379–383

Ellis CG, Wrigley SM, Groom AC (1994) Heterogeneity of red blood cell perfusion in capillary networks supplied by a single arteriole in resting skeletal muscle. Circ Res 75:357–368
Ellsworth ML, Forrester T, Ellis CG, Dietrich HH (1995) The erythrocyte as a regulator of vascular tone. Am J Physiol Heart Circ Physiol 269:H2155–H2161
Fagraeus L, Linnarsson D (1976) Autonomic origin of heart rate fluctuations at the onset of muscular exercise. J Appl Physiol 40:679–682
Farhi LE, Rahn H (1955) A theoretical analysis of the alveolar-arterial O_2 difference, with special reference to the distribution effect. J Appl Physiol 7:699–703
Ferretti G (2012) Da una catastrofe a un modello: la curva di dissociazione dell'ossiemoglobina. pH 1: 35–41
Ferretti G, Boutellier U, Pendergast DR, Moia C, Minetti AE, Howald H, di Prampero PE (1990) Muscular exercise at high altitude. IV. Oxygen transport system before and after exposure to chronic hypoxia. Int J Sports Med 11:S15–S20
Ferretti G, Kayser B, Schena F, Turner DL, Hoppeler H (1992) Regulation of perfusive O_2 transport during exercise in humans: effects of changes in haemoglobin concentration. J Physiol 455:679–688
Ferretti G, Licker MJ, Anchisi S, Moia C, Susta D, Morel DR (2005) The effects of beta1-adrenergic blockade on cardiovascular oxygen flow in normoxic and hypoxic humans at exercise. Eur J Appl Physiol 95:250–259
Ferretti G, Bringard A, Perini R (2011) An analysis of performance in human locomotion. Eur J Appl Physiol 111:391–401
Fick A (1870) Über die Messung des Blutquantums in den Herzventrikeln. Physikalisch Medizin Gesellschaft, Würzburg
Francescato MP, Girardis M, di Prampero PE (1995) Oxygen cost of internal work during cycling. Eur J Appl Physiol 72:51–57
Gaesser GA, Brooks GA (1975) Muscular efficiency during steady-rate exercise: effects of speed and work rate. J Appl Physiol 38:1132–1139
Geppert J, Zuntz N (1888) Über die Regulation der Atmung. Arch Ges Physiol 42:189–244
Girardis M, Linnarsson D, Moia C, Pendergast DR, Ferretti G (1999) Oxygen cost of dynamic leg exercise on a cycle ergometer: effects of gravity acceleration. Acta Physiol Scand 166:239–246
Gonzalez-Alonso J, Richardson RS, Saltin B (2001) Exercising skeletal muscle blood flow in humans responds to reduction in arterial oxyhaemoglobin, but not to altered free oxygen. J Physiol 530:331–341
Gonzalez-Alonso J, Olsen DB, Saltin B (2002) Erythrocyte and the regulation of human skeletal muscle blood flow and oxygen delivery: role of circulating ATP. Circ Res 91:1046–1055
Hagberg JM, Coyle EF (1984) Physiological comparison of competitive race walking and running. Int J Sports Med 5:74–77
Hartley LH, Vogel JA, Landowne L (1973) Central, femoral and brachial circulation during exercise in hypoxia. J Appl Physiol 34:87–90
Heinonen I, Nesterov SV, Kemppainen J, Nuutila P, Knuuti J, Laitio R, Kjaer M, Boushel R, Kalliokoski KK (2007) Role of adenosine in regulating the heterogeneity of skeletal muscle blood flow during exercise in humans. J Appl Physiol 103:2042–2048
Heinonen I, Duncker DJ, Knuuti J, Kalliokoski KK (2012) The effect of acute exercise with increasing workloads on inactive muscle blood flow and its heterogeneity in humans. Eur J Appl Physiol 112:3503–3509
Helgerud J (1994) Maximal oxygen uptake, anaerobic threshold and running economy in women and men with similar performances level in marathons. Eur J Appl Physiol 68:155–161
Helgerud J, Støren O, Hoff J (2010) Are there differences in running economy at different velocities for well-trained distance runners? Eur J Appl Physiol 108:1099–1105
Hermansen L, Ekblom B, Saltin B (1970) Cardiac output during submaximal and maximal treadmill and bicycle exercise. J Appl Physiol 29:82–86
Hill AV (1910) The possible effects of the aggregation of the molecules of haemoglobin on its dissociation curves. J Physiol 40: iv–vii

Holmér I (1974) Energy cost of arm stroke, leg kick and the whole stroke in competitive swimming styles. Eur J Appl Physiol 33:105–118
Hughes RL, Clode M, Edwards RH, Goodwin TJ, Jones NL (1968) Effect of inspired O_2 on cardiopulmonary and metabolic responses to exercise in man. J Appl Physiol 24:336–347
Jones AM, Doust JH (1996) A 1 % treadmill grade most accurately reflects the energetic cost of outdoor running. J Sports Sci 14:321–327
Koskolou MD, Calbet JAL, Rådegran G, Roach RC (1997) Hypoxia and cardiovascular response to dynamic knee extensor exercise. Am J Physiol Heart Circ Physiol 273:H1787–H1793
Krogh A (1922) The anatomy and physiology of capillaries. Yale University Press, New Haven
Lador F, Azabji Kenfack M, Moia C, Cautero M, Morel DR, Capelli C, Ferretti G (2006) Simultaneous determination of the kinetics of cardiac output, systemic O_2 delivery, and lung O_2 uptake at exercise onset in men. Am J Physiol Regul Integr Comp Physiol 290:1071–1079
Léger L, Mercier B (1984) Gross energy cost of horizontal treadmill and track running. Sports Med 1:270–277
Malliani A, Pagani M, Lombardi F, Cerutti S (1991) Cardiovascular neural regulation explored in the frequency domain. Circulation 84:482–492
Marconi C, Heisler N, Meyer M, Weitz H, Pendergast DR, Cerretelli P, Piiper J (1988) Blood flow distribution and its temporal variability in stimulated dog gastrocnemius muscle. Respir Physiol 74:1–13
Margaria R, Cerretelli P, Aghemo P, Sassi G (1963) Energy cost of running. J Appl Physiol 18:367–370
McMiken DF, Daniels JT (1976) Aerobic requirements and maximum aerobic power in treadmill and track running. Med Sci Sports 8:14–17
Minetti AE, Pinkerton J, Zamparo P (2001) From bipedalism to bicyclism: evolution in energetics and biomechanics of historic bicycles. Proc Roy Soc Lond B 268:1351–1360
Minetti AE, Moia C, Roi GS, Susta D, Ferretti G (2002) Energy cost of human locomotion at extreme uphill and downhill slopes. J Appl Physiol 93:1039–1046
Morgan DWl, Martin PE, Krahenbuhl GS (1989) Factors affecting running economy. Sports Med 7:310–330
Mortensen SP, Thaning P, Nyberg M, Saltin B, Hellsten Y (2011) Local release of ATP into the arterial inflow and venous drainage of human skeletal muscle: insight from ATP determination with the intravascular microdialysis technique. J Physiol 589:1847–1857
Nadel ER, Cafarelli E, Roberts MF, Wenger CB (1979) Circulatory regulation during exercise in different ambient temperatures. J Appl Physiol 46:430–437
Padilla S, Bourdin M, Barthélémy JC, Lacour JR (1992) Physiological correlates of middle-distance running performance. A comparative study between men and women. Eur J Appl Physiol 65:561–566
Pendergast DR, di Prampero PE, Craig AB Jr, Wilson DR, Rennie DW (1977) Quantitative analysis of the front crawl in men and women. J Appl Physiol 43:475–479
Perini R, Veicsteinas A (2003) Heart rate variability and autonomic activity at rest and during exercise in various physiological conditions. Eur J Appl Physiol 90:317–325
Perutz MF (1970) Stereochemistry of cooperative effects in haemoglobin. Nature 228:726–733
Piiper J, Scheid P (1981) Model for capillary-alveolar equilibration with special reference to O_2 uptake in hypoxia. Respir Physiol 46:193–208
Piiper J, Pendergast DR, Marconi C, Meyer M, Heisler N, Cerretelli P (1985) Blood flow distribution in dog gastrocnemius muscle at rest and during stimulation. J Appl Physiol 58:2068–2074
Pugh LGCE (1970) Oxygen intake in track and treadmill running with observations on the effect of air resistance. J Physiol Lond 207:823–835
Rahn H, Fenn WO (1955) A graphical analysis of the respiratory gas exchange. Am Physiol Soc, Washington DC
Rennie DW, di Prampero PE, Cerretelli P (1971) Effects of water immersion on cardiac output, heart rate and stroke volume of man at rest and during exercise. Med Sport Turin 24:223–228

Roach RC, Koskolou MD, Calbet JAL, Saltin B (1999) Arterial O_2 content and tension in regulation of cardiac output and leg blood flow during exercise in humans. Am J Physiol Heart Circ Physiol 276:H438–H445

Robinson BF, Epstein SE, Beiser GD, Braunwald E (1966) Control of heart rate by the autonomic nervous system: studies in man on the interrelation between baroreceptor mechanisms and exercise. Circ Res 19:400–411

Roca J, Hogan MC, Story D, Bebout DE, Haab P, Gonzalez R, Ueno O, Wagner PD (1989) Evidence for tissue diffusion limitation of in normal humans. J Appl Physiol 67:291–299

Rowell LB (1974) Human cardiovascular adjustments to exercise and thermal stress. Physiol Rev 54:75–159

Rowell LB, Brengelmann GL, Blackmon JR, Twiss RD, Kusumi F (1968) Disparities between aortic and peripheral pulse pressures induced by upright exercise and vasomotor changes in man. Circulation 37:954–964

Rowell LB, O'Leary DS, Kellogg DL Jr (1996) Integration of cardiovascular control systems in dynamic exercise. In: Handbook of physiology. Exercise: regulation and integration of multiple systems, Sect. 12, Chap. 17. Bethesda, MD, pp 770–838 (Am Physiol Soc)

Saltin B, Blomqvist G, Mitchell JH, Johnson RL, Wildenthal K, Chapman CB (1968) Response to exercise after bed rest and after training. Circulation 38(5):1–78

Seals DR, Victor RG (1991) Regulation of muscle sympathetic nerve activity during exercise in humans. Exerc Sports Sci Rev 19:313–349

Sheldahl LM, Tristani FE, Clifford PS, Hughes CV, Sobocinski KA, Morris RD (1987) Effect of head-out water immersion on cardiorespiratory response to dynamic exercise. J Am Coll Cardiol 10:1254–1258

Stamler JS, Jia L, Eu JP, McMahon TJ, Demchenko IT, Bonaventura J, Gernert K, Piantadosi CA (1997) Blood flow regulation by S-nitrosohemoglobin in the physiological oxygen gradient. Science 276:2034–2037

Stenberg J, Ekblom B, Messin R (1966) Hemodynamic response to work at simulated altitude, 4,000 m. J Appl Physiol 21:1589–1594

Stenberg J, Åstrand PO, Ekblom B, Royce J, Saltin B (1967) Hemodynamic response to work with different muscle groups, sitting and supine. J Appl Physiol 22:61–70

Stickland MK, Fuhr DP, Haykowsky MJ, Jones KE, Paterson DI, Ezekowitz JA, McMurtry MS (2011) Carotid chemoreceptor modulation of blood flow during exercise in healthy humans. J Physiol 589:6219–6230

Tam E, Rossi H, Moia C, Berardelli C, Rosa G, Capelli C, Ferretti G (2012) Energetics of running in top-level marathon runners from Kenya. Eur J Appl Physiol 112:3797–3806

Tanabe N, Todoran TM, Zenk GM, Bunton BR, Wagner WW, Presson RG (1998) Perfusion heterogeneity in the pulmonary acinus. J Appl Physiol 84:933–938

Termin B, Pendergast DR (2000) Training using the stroke frequency—velocity relationship to combine biomechanical and metabolic paradigms. J Swim Res 14:9–17

Vogel JA, Gleser MA (1972) Effect of carbon monoxide on oxygen transport during exercise. J Appl Physiol 32:234–239

Wagner PD, West JB (1972) Effects of diffusion impairment on O_2, and CO_2 time courses in pulmonary capillaries. J Appl Physiol 33:62–71

Woodson RD, Wills RE, Lenfant C (1978) Effect of acute and established anemia on O_2 transport at rest, submaximal and maximal work. J Appl Physiol 44:36–43

Zamparo P, Pendergast DR, Termin AB, Minetti AE (2002) How fins affect the economy and efficiency of human swimming. J Exp Biol 205:2665–2676

Zamparo P, Lazzer S, Antoniazzi C, Cedolin S, Avon R, Lesa C (2008) The interplay between propelling efficiency, hydrodynamic position and energy cost of front crawl in 8 to 19-year-old swimmers. Eur J Appl Physiol 104:689–699

Zamparo P, Gatta G, Capelli C, Pendergast DR (2009) Active and passive drag, the role of trunk incline. Eur J Appl Physiol 106:195–205

Zamparo P, Capelli C, Pendergast DR (2011) Energetics of swimming: a historical perspective. Eur J Appl Physiol 111:367–378

Chapter 3
Exercise Transients

Abstract The steady state of light constant-power submaximal exercise is attained after at least 3 min since the exercise start. Although the application of mechanical power is practically immediate, the rate of oxygen uptake $\left(\dot{V}\,O_2\right)$ increases at a remarkably slower rate: a metabolic transient phase occurs, during which $\dot{V}\,O_2$, despite increasing, is insufficient to provide all the metabolic power that is necessary to sustain ATP resynthesis, so that an oxygen deficit is incurred. The oxygen deficit consists of (i) an obligatory component, covered by phosphocreatine breakdown, reflecting the kinetics of glycolysis activation in the contracting muscles, and characterized by an invariant time constant independent of the exercise intensity and (ii) a facultative component, covered by anaerobic lactic metabolism (early lactate accumulation), due to the dissociation between cardiopulmonary response and muscular response at elevated powers, and characterized by a time constant depending on the exercise intensity. The kinetics of $\dot{V}\,O_2$ upon exercise onset is described with exponential equations. The implications of single- and double-exponential models are discussed. The former model carries along the assumption that the kinetics of $\dot{V}\,O_2$ determined at the mouth reflects the kinetics of $\dot{V}\,O_2$ in the contracting muscles. This correspondence, however, does not hold anymore when early lactate appears. The latter model, in particular, implies a rapid phase (phase I), which has been related to the fast cardiovascular responses at exercise start. A single-exponential model assumes also that the exercising muscles behave as dynamic linear first-order systems that, as such, admit only one transfer function. On this basis, ramp exercise and sinusoidal exercise, typically two unsteady-state conditions, are discussed. More recently, at powers higher than the critical power (see Chap. 5), the so-called slow component, or third phase of the $\dot{V}\,O_2$ kinetics, has been also characterized. The energetic meaning of the slow component is also discussed. Finally, some methodological aspects of single-breath analysis of pulmonary gas exchange are discussed.

G. Ferretti, *Energetics of Muscular Exercise*,
DOI 10.1007/978-3-319-05636-4_3

Contents

Introduction

The steady state of light constant-power submaximal exercise, which I discussed in Chap. 2, is attained after at least 3 min since the exercise start. Although the application of mechanical power is practically immediate, the rate of oxygen uptake or consumption $\left(\dot{V}\,O_2\right)$, which at the steady state represents the overall metabolic power, increases at a remarkably slower rate, as when charging a capacitance: a metabolic transient phase occurs before the attainment of the steady state, during which $\dot{V}\,O_2$, despite increasing, is insufficient to provide the metabolic power that is necessary to sustain ATP resynthesis at a rate corresponding to that of ATP hydrolysis supporting muscular contraction. As a consequence, during the transient, metabolic power must be generated also by anaerobic metabolism, coherently with Eq. (2.1) (see Chap. 2).

The historical view of the kinetics of $\dot{V}\,O_2$ increase upon exercise onset was discussed in Chap. 1 and is summarized in Eq. (1.4), which describes the time course of $\dot{V}\,O_2$ increase as a mono-exponential. This led to the creation of the concept of **oxygen deficit**, defined as the time integral of Eq. (1.4a). The oxygen deficit corresponds to the amount of metabolic energy that is derived from energy sources other than $\dot{V}\,O_2$ during the exercise transient. An implicit assumption underlies this mono-exponential model of the $\dot{V}\,O_2$—on kinetics of square wave constant-load exercise: the kinetics of $\dot{V}\,O_2$ as measured at the mouth corresponds to the kinetics of $\dot{V}\,O_2$ taking place in the working muscles, once possible changes in blood oxygen stores have been accounted for. This assumption implies equal time constants of $\dot{V}\,O_2$ increase at any level in the respiratory system, so that the time constant of $\dot{V}\,O_2$ is equal to that of muscle oxygen consumption, or of its mirror image, muscle phosphocreatine decrease. A second fundamental assumption

is that the muscle metabolic response to exercise start follows the laws of linear first-order systems. Although this may indeed be the case during light exercise, it is definitely not so during higher intensity exercise.

Soon afterwards, however, it became evident that a single-exponential model was insufficient for a satisfactory description of the $\dot{V}O_2$ response during the square wave exercise transient. Wasserman et al. (1974) were the first to realize that there might be a rapid component in the earliest phase of the exercise transient, which they attributed to a sudden increase in cardiac output $(\dot{Q})$. This rapid component became a preferential object of research in the field ever since, particularly by the British school led by Brian Whipp. It was integrated in the subsequent double-exponential model of the exercise transient, proposed by Barstow and Molé (1987). It also restricted the domain of application of the concept of a correspondence between $\dot{V}O_2$ response at the mouth and in muscle to the second exponential only, whose time delay was taken to represent the physiological delay between muscle and mouth $\dot{V}O_2$ increase.

In this chapter, I discuss first the energetics of the oxygen deficit, within the context of a mono-exponential model. These concepts still hold as long as, in a double-exponential context, accent is placed on the so-called primary component (or phase II) of the $\dot{V}O_2$ response. Then, I treat the implications of the double-exponential model and the cardiovascular transients, and I analyse the case of intense exercise, with the appearance of the so-called slow component, or phase III. Other exercise modalities than the square wave exercise will finally be considered.

The Energetics of the Oxygen Deficit During Light Exercise

The energy that $\dot{V}O_2$ is unable to provide during the exercise transient comes essentially from three sources: (i) phosphocreatine breakdown, providing what is called the **net alactic oxygen deficit**; (ii) "early" lactate accumulation (Cerretelli et al. 1979); (iii) body oxygen stores. These components of the oxygen deficit are not necessarily called upon all together. As exercise starts, no lactate accumulation occurs except in the intense exercise domain. This was clearly demonstrated in the isolated–perfused dog muscle preparation by Piiper et al. (1968), who found a relatively rapid time constant for $\dot{V}O_2$, faster than that usually observed in humans in the context of the single-exponential model of $\dot{V}O_2$ increase. Moreover, di Prampero and Margaria (1968) estimated a P/O_2 ratio close to 6.17 from the ratio of phosphocreatine split to oxygen deficit (both expressed in moles per kg of wet muscle), clearly suggesting a primary role for phosphocreatine and anaerobic alactic metabolism in the genesis of the oxygen deficit.

In fact during light aerobic exercise in normoxia, when no early lactate accumulation takes place and body oxygen stores do not vary, the entire amount of energy released to build the oxygen deficit comes from the hydrolysis of high-

energy phosphates, so that the energetics of the exercise transient can be summarized by the following equation:

$$\dot{E} \propto \overleftarrow{A\dot{T}P} = \overrightarrow{A\dot{T}P} = c\,\dot{V}\,\mathrm{O}_2 + a\,\dot{P}C \tag{3.1}$$

Equation (3.1) is nothing but a simplified version of the general equation of the energetics of muscular exercise (see Chap. 2, Eq. 2.1) for the specific case of a system in which only two metabolic energy sources are simultaneously active. In Eq. (3.1), $\dot{E}$ is the overall metabolic power, $\overleftarrow{A\,\dot{T}\,P}$ and $\overrightarrow{\mathrm{A\,\dot{T}\,P}}$ are the rates of ATP splitting and resynthesis, respectively, which during constant-power square wave exercise are equal, and the two constants a and c are proportionality constants indicating the moles of ATP resynthesized, respectively, by a mole of phosphocreatine hydrolyzed and a mole of oxygen consumed. The Lohmann's reaction tells that a is equal to 1. On the other hand, c is equal to the $\mathrm{P/O_2}$ ratio.

In case of constant-power square wave exercise, as long as during the exercise transient $\dot{V}\,\mathrm{O}_2$ goes up, $\dot{P}C$ goes down in such a way as to maintain the sum $c\,\dot{V}\,\mathrm{O}_2 + a\,\dot{P}C$ invariant. In the context of the mono-exponential model of $\dot{V}\,\mathrm{O}_2$ increase upon exercise onset, at the very start of exercise (exercise time 0), all the $\dot{E}$ above the resting metabolic rate is therefore from anaerobic alactic metabolism, so that Eq. (3.1) becomes

$$\dot{E}_\mathrm{o} \propto \overleftarrow{A\,\dot{T}\,P} = \overrightarrow{\mathrm{A\,\dot{T}\,P}} = a\,\dot{P}C_\mathrm{o} \tag{3.2}$$

where suffix 0 indicates the exercise time 0. This being so, then we have

$$a\,\dot{P}C_t = a\,\dot{P}C_0 \cdot \mathrm{e}^{-kt} \tag{3.3}$$

where t is time and k is the velocity constant (reciprocal of the time constant τ). In a system like the one represented by Eq. (3.1), if $\dot{E}$ is invariant, then k must take the same value for the $\dot{V}\,\mathrm{O}_2$ and the $\dot{P}C$ kinetics. Moreover, since at any t a positive value of $a\,\dot{P}C_\mathrm{t}$ implies a given finite reduction of muscle phosphocreatine concentration ([PC]), then the time course of muscle [PC] changes during the exercise transient is also described by a mono-exponential equation, whose k takes the same value as the one obtained from Eq. (3.3). Finally, the time integral of Eq. (3.3) provides the overall amount of phosphocreatine that has been hydrolyzed during the exercise transient in order to cover the oxygen deficit. This amount is directly proportional to the oxygen deficit and thus to the applied mechanical power, so that there must be a negative linear relationship between [PC] and $\dot{E}$.

These concepts have received wide experimental support. Values for τ comprised between 20 and 25 s were found for mono-exponential [PC] kinetics on the isolated–perfused dog muscle preparation (Piiper et al. 1968). The same authors demonstrated the negative linear relationship between [PC] and $\dot{E}$. Concerning humans, a remarkable breakthrough was generated by the technological evolution

of magnetic resonance spectroscopy, which allowed obtaining serial relative non-invasive determinations of high-energy phosphates in human muscle during contractions. This allowed the assessment of the kinetics of phosphocreatine decrease upon square wave exercise onset, for which Binzoni et al. (1992) obtained a τ value of 23.4 s. The same authors demonstrated also in humans the negative linear relationship between [PC] and $\dot{E}$. Similar results were later obtained by other authors (di Prampero et al. 2003; Francescato et al. 2013; Rossiter et al. 1999, 2002). This τ value for [PC] was also found to be independent of the exercise intensity (Binzoni et al. 1997), so that (i) the cumulative oxygen deficit of step-increasing powers up to a given level turns out equal to the oxygen deficit incurred if that very same level is attained in a unique step, and (ii) the oxygen deficit is directly proportional to the steady-state $\dot{V}O_2$, with τ as proportionality constant.

Single-leg extension exercise was also used as a tool to gain insight into the muscle oxygen consumption kinetics in humans (Grassi et al. 1996; Koga et al. 2005). These studies provided τ values similar to those for [PC]. A direct comparison between the τ of $\dot{V}O_2$ during single-leg exercise and the τ of [PC] on the same subjects during the same exercise transients further reinforced this notion (Rossiter et al. 1999) (Fig. 3.1). Finally, on the isolated–perfused dog muscle preparation, the τ of muscle oxygen consumption was found to be equal in conditions of normal and forced oxygen delivery and equal to that calculated for the kinetics of muscle phosphocreatine decrease (Grassi et al. 1998), demonstrating that there is at least some peripheral components of the kinetics of muscle oxygen consumption which are fully independent of muscle oxygen delivery.

More recently, however, faster mono-exponential τ values were obtained (Cautero et al. 2002; Lador et al. 2006) than in the classical studies (di Prampero 1981; Linnarsson 1974) with the same exercise mode and intensities, possibly as a consequence of improved signal-to-noise ratio in breath-by-breath $\dot{V}O_2$ computation (Capelli et al. 2001). The τ values for $\dot{V}O_2$ reported in those studies were also faster than those found for the mono-exponential phosphocreatine decrease upon exercise onset (Binzoni et al. 1992; di Prampero et al. 2003; Rossiter et al. 1999). These fast time constants suggest the possibility that the correspondence between lung $\dot{V}O_2$ and muscle oxygen consumption may not be so good under certain circumstances. It was then demonstrated that lung $\dot{V}O_2$ kinetics can be accelerated by prior exercise performance (Faisal et al. 2009), possibly as a consequence of maintained muscle vasodilation after completion of the first exercise bout (Faisal et al. 2010). Although, and especially when classical computational algorithms are employed, the lung $\dot{V}O_2$ kinetics may indeed result equivalent to the muscle oxygen consumption kinetics, this correspondence may be fortuitous: different mechanisms may be implicated in the two transients. This does not mean, however, that the above energetic interpretation of the oxygen deficit is to be rejected. This means only that the energetic analysis of the oxygen deficit performed on the basis of lung $\dot{V}O_2$ kinetics may provide an underestimate with respect to the oxygen deficit incurred in the contracting muscles. Nevertheless, I feel confident in stating

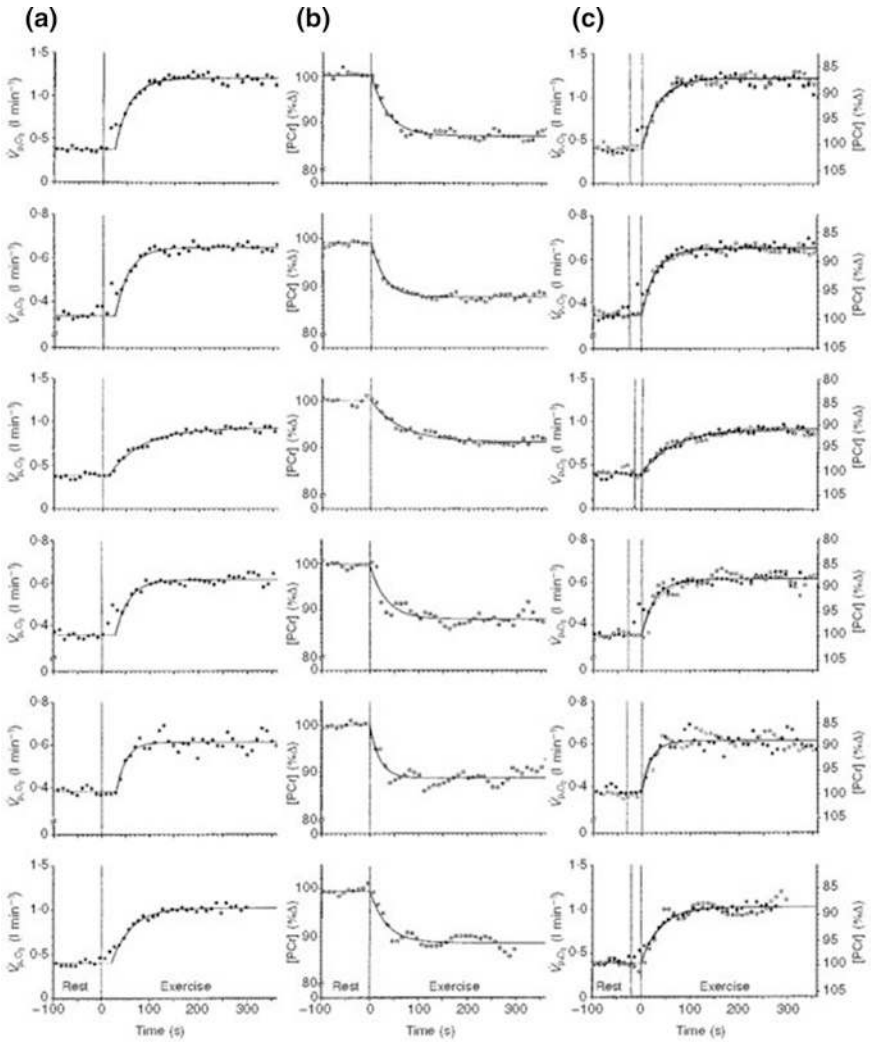


Fig. 3.1 Comparative kinetics of oxygen consumption $\dot{V}O_2$ and phosphocreatine concentration [PC] during constant-load exercise in six subjects. **a** $\dot{V}O_2$ as a function of time, with the phase II response fitted by a mono-exponential. **b** [PC] as a function of time, simultaneously determined on the same subjects. **c** demonstration of the identity of phase II $\dot{V}O_2$ (*black circle*) and [PC] (*white circle*) kinetics determined simultaneously during quadriceps exercise. The [PCr] scale is inverted to facilitate comparisons. From Rossiter et al. (1999)

that whenever the τ of lung $\dot{V}O_2$ kinetics is lower (faster) than or at most equal to that of muscle oxygen consumption, we deal with a dual energetic system like the one represented by Eq. (3.1): no early lactate accumulation occurs under these circumstances, and the kinetics of muscle [PC] is a mirror image of that of muscle oxygen consumption.

Also, the introduction of bi-exponential models of the pulmonary $\dot{V}O_2$ response at the exercise onset has contributed to a redefinition of the concept of a correspondence between lung $\dot{V}O_2$ and muscle oxygen consumption kinetics. In this context, the first exponential (rapid phase or phase I) is fully unrelated to the events occurring in contracting muscles (see below). The domain of application of the same reasoning as above on the oxygen deficit is restricted to the second exponential (primary phase of phase II) (Whipp and Ward 1990).

The Energetics of the Oxygen Deficit During Intense Exercise

As far as **early lactate** is concerned, Cerretelli et al. (1979) reported that the τ of a mono-exponential $\dot{V}O_2$ increase upon exercise onset is higher, the higher is the mechanical power applied, and thus, the higher is $\dot{E}$: they demonstrated in fact that τ is linearly related to the lactate accumulation in blood during the exercise transient, as described by the following:

$$\tau = \lambda[La]_e + \tau_0 \tag{3.4}$$

where $[La]_e$ is early lactate (net blood lactate accumulation during the exercise transient), λ is a constant indicating how much τ increases per unit increase of lactate in blood during the exercise transient (di Prampero and Ferretti 1999), and τ_0 is the time constant that would incur in the absence of early lactate accumulation. The constant λ is an inverse function of the steady-state $\dot{V}O_2$. From the data of Cerretelli et al. (1979), it results equal to 7.8 and 12.1 s mM^{-1} at a steady-state $\dot{V}O_2$ of 1.5 and 1.0 L min^{-1} (mechanical powers of 125 and 75 W), respectively (Fig. 3.2). These values allow computation of the oxygen deficit increase (in ml O_2 kg^{-1}) per unit increase in $[La]_e$ (in mM), which is nothing but the **energy equivalent of blood lactate accumulation** (see Chap. 6). This turns out equal to 2.19 and 2.89 ml kg^{-1} mM^{-1} for the 125 and 75 W powers, respectively, the latter value agreeing well with those reported in Chap. 6 (di Prampero 1981). On the other hand, the constant τ_0 corresponds to the time constant that one would observe in the two-component system described by Eq. (3.1) and thus to the time constant of muscle phosphocreatine decrease (see above). Considering the error due to extrapolation of a regression equation and neglecting possible though small changes in blood oxygen stores, the obtained value of τ_0 as from Fig. 3.2 (24.5 and 29.7 s for the two reported equations) corresponds very well to those reported from P-NMR studies for phosphocreatine decrease (Binzoni et al. 1992; di Prampero et al. 2003; Francescato et al. 2013; Rossiter et al. 1999, 2002).

Thus, above a given power, which I postulate to correspond to the critical power (Chap. 5), the overall oxygen deficit becomes larger than the net alactic oxygen deficit, so that τ becomes higher than that of muscle [PC] drop: the energy gap is

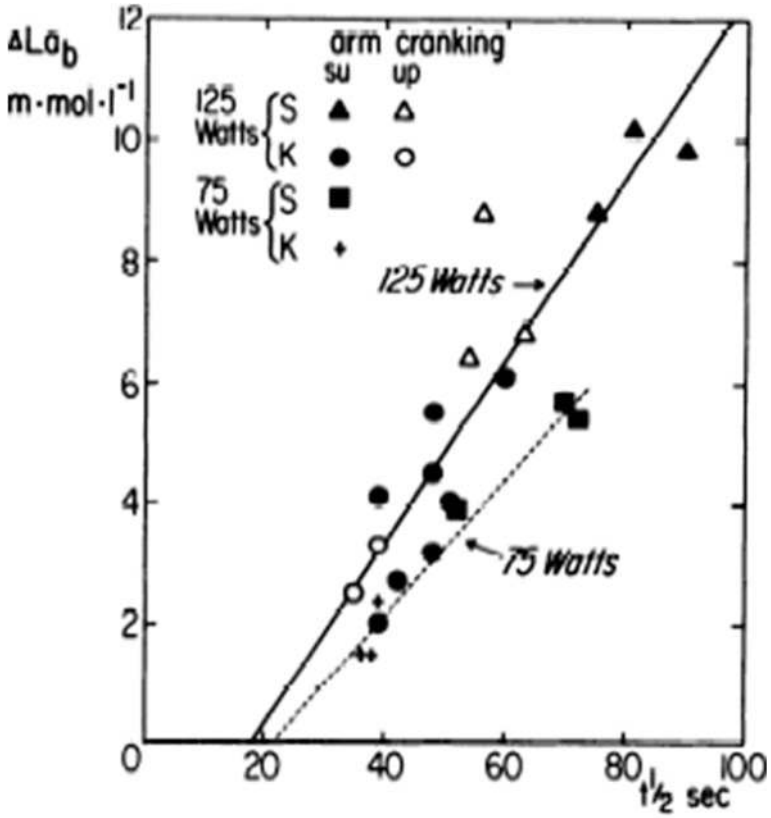


Fig. 3.2 Net blood lactate accumulation ($\Delta[La]_b$) at min 6 of square wave exercises of the type and intensity indicated on the graph as a function of the half-time ($t_{½}$) of the exponential oxygen uptake increase upon exercise onset. From Cerretelli et al. (1979). Note that $t_{½} = 0.75\ \tau$. Note also that the representation proposed by Cerretelli et al. (1979) corresponds to the solution of Eq. (3.4) for $[La]_b$, which they considered as the independent variable. In this representation, the constant τ_0 of Eq. (3.4) is given by the *x*-axis intercept of the reported relationships (in fact $t_{½,0}$ in the graph)

bridged by the appearance of early lactate accumulation. This being so, the difference between the overall oxygen deficit and the net alactic oxygen deficit can be precisely predicted from the amount of $[La]_e$ and the energy equivalent of blood lactate accumulation. It is of note that at such intense powers, the lung $\dot{V}O_2$ kinetics may indeed correspond to the muscle oxygen consumption kinetics, so that the overall oxygen deficit determined at the lungs would reflect the overall oxygen deficit incurred in the contracting muscles. But this does not inform on the alactic oxygen deficit. It is only the *x*-axis intercept of Fig. 3.2 (τ_0) that corresponds to the τ of the kinetics of muscle [PC] drop, if we assume that the effects of changes in oxygen stores are nil.

As a consequence of the diffusion–perfusion interaction equation for peripheral gas exchange (see Chap. 2) and of the reduction of capillary contact time, the amount of oxygen stored in the body during steady-state exercise is smaller, the higher is the exercise intensity, essentially because of lower oxygen concentration in mixed venous blood. Thus, the amount of energy constituting the oxygen deficit that is derived from oxygen stores becomes predictably smaller in a given transition from light to heavier work load than in an equivalent transition from rest to exercise. In fact, the τ of a mono-exponential lung $\dot{V}O_2$ kinetics was found to be lower (faster) in the former than in the latter case (di Prampero et al. 1970). Similarly, in acute normobaric hypoxia, a condition obviously characterized by decreased oxygen stores, the oxygen deficit was coherently smaller for equivalent early lactate accumulation (di Prampero et al. 1983). In other terms, oxygen stores may be viewed as a kind of buffer between contracting muscles and lungs, the size of which may slightly vary the lung $\dot{V}O_2$ kinetics. Of course, this does not mean that overall the lung $\dot{V}O_2$ kinetics is faster in hypoxia than in normoxia. In fact, it was shown to be slower in the former condition than in the latter (Engelen et al. 1996; Hughson and Kowalchuk 1995; Xing et al. 1991), as a consequence of increased early lactate accumulation at equivalent work load (Lador et al. 2013).

Mechanisms Underlying the Oxygen Deficit

The contraction of the net alactic oxygen deficit is a physiological necessity. It is unavoidable at exercise onset because the key enzymes of glycolysis need to be activated in order to sustain an increase in the rate of glycolytic energy fluxes. Phospho-fructo-kinase (PFK) is the key enzyme of glycolysis whose activity is modulated by the concentration of high-energy phosphates: a decrease in [PC] accelerates its kinetics as does an increase in inorganic phosphate concentration ([Pi]). The drop of [PC] carries along also an augmentation of adenosine diphosphate ([ADP]) and of [Pi], so that the so-called phosphorylation potential {[ATP]/([ADP] + [Pi])} is increased. This is a key controller of oxidative phosphorylation in the mitochondria (Korzeniewski 2003; Meyer and Foley 1996). Thus, the priming of aerobic metabolism requires an initial drop of [PC].

As exercise starts, immediately available ATP in the cytosol of the muscle fibres is used in the cross-bridge cycle and is immediately resynthesized by the Lohmann's reaction. The subsequent drop of muscle [PC] accelerates PFK activity, and thus the energy flux along the glycolytic pathway, and prompts the aerobic metabolism overall through a reduction of the phosphorylation potential. This chain of events supports the concept that the relatively slow increase of muscle oxygen consumption at exercise onset has a metabolic origin (di Prampero 1981; di Prampero and Ferretti 1999; Grassi 2000), as opposed to the alternative concept that the oxygen deficit is imposed by the delayed response of the respiratory system

(Hughson et al. 2001; Whipp and Ward 1982). In this context, the τ of the muscle [PC] fall upon exercise onset describes the τ of glycolysis activation.

However, the acceleration of glycolysis and of all subsequent metabolic pathways that are summarized in the concept of **aerobic metabolism** requires an adequate amount of oxygen to be made available in the mitochondria of the active muscle mass. This amount of oxygen is taken up from ambient air and transferred to the mitochondria along the respiratory system. A tight match between the rate of glycolysis acceleration and the rate of oxygen flow in the respiratory system upon exercise onset is needed in order to have equal τ values for the [PC] fall and the $\dot{V}O_2$ increase in the exercise transient. Only the respect of this condition warrants that we deal indeed with a dual energetic system (aerobic metabolism plus anaerobic alactic metabolism) in the exercise transient. More likely, however, during light aerobic exercise, the $\dot{V}O_2$ kinetics is faster than that of muscle oxygen consumption: although in this case the oxygen deficit incurred in the lungs is lower than, and so does not reflect the muscle oxygen deficit, nevertheless, we still deal with a dual energetic system, where differences in oxygen deficit between lungs and muscles are buffered by oxygen stores. The oxygen flow that the respiratory system is able to provide to the contracting muscle mass is sufficient to sustain the acceleration of glycolysis generated by the fall of [PC] at exercise start: in this case pyruvate, end product of glycolysis, can be entirely removed through the Krebs cycle and the new equilibrium is attained thanks to prompting of ATP resynthesis by aerobic metabolism only. Under these circumstances, the net alactic oxygen deficit represents indeed the entire oxygen deficit, a condition represented in Fig. 3.2 by the *x*-axis intercept of the regression line. This intercept defines the condition of **evenly aerobic metabolism**, in which all muscle fibres have sufficient oxygen delivery and oxidative capacity to sustain their aerobic metabolism.

By contrast, this is not so during intense exercise: in this case, the $\dot{V}O_2$ kinetics becomes slower than during light exercise (τ higher than τ_0), so that the $\dot{V}O_2$ response does not follow the rate at which glycolysis is activated by the reduction of phosphorylation potential and does not provide the necessary amount of oxygen in due time. The postulate, supported by the NMR experiments of Binzoni et al. (1997), is that the rate of glycolysis activation at exercise onset is independent of the developed mechanical power, whereas the $\dot{V}O_2$ kinetics depends on the exercise intensity. When the time constant of the latter becomes higher than that of the former, the amount of oxygen made available by the respiratory system during the exercise transient is insufficient to ensure complete pyruvate removal through aerobic metabolism: oxidative phosphorylation and the Krebs cycle are unable to follow glycolysis acceleration anymore, so that a bottleneck appears, tending to increase muscle pyruvate concentration. As a consequence, the equilibrium of the reaction of pyruvate reduction to lactate is displaced towards lactate production, and lactate accumulates in muscle, then in blood, whence the appearance of early lactate.

The amount of lactate that is accumulated during a high-intensity exercise transient is proportional to the difference between the progressively increasing τ of

the $\dot{V}O_2$ increase and the invariant τ of the [PC] fall (x-axis intercept of Fig. 3.2). The fraction of oxygen deficit that is due to early lactate accumulation—facultative component of the oxygen deficit—corresponds to the difference between the overall oxygen deficit and the fraction of oxygen deficit that is covered by [PC] hydrolysis. This last is the **obligatory component of the oxygen deficit** that is incurred anytime a human starts an exercise. For an invariant τ of the [PC] fall, as already pointed out, its amount depends only on the exercise intensity, i.e. on the mechanical power developed by muscle contraction. Conversely, the amount of energy provided by the facultative component of the oxygen deficit is directly proportional to the amount of early lactate that is accumulated, the proportionality constant being equal to the energy equivalent of blood lactate accumulation (see Chap. 6) (Lador et al. 2013 details given in Sect. 3.7).

A necessary consequence of the above reasoning is that the progressive increase of the τ of the $\dot{V}O_2$ kinetics at intense exercise should be related to a progressively slower kinetics of cardiopulmonary variables. These were poorly investigated until beat-by-beat methods became available. Their quantitative analysis was carried out essentially in the context of a double-exponential model. Thus, I will introduce this model before discussing the dynamics of the cardiovascular responses to exercise.

The Double-exponential Model of $\dot{V}O_2$ Kinetics

The double-exponential model, or two-phase model, of the $\dot{V}O_2$ kinetics was proposed by Barstow and Molé (1987) after an original idea of Wasserman et al. (1974) refined by Whipp et al. (1982). This model foresees that an exponential increase in $\dot{V}O_2$ (phase II), related to metabolic adaptation in skeletal muscle, is preceded by a faster $\dot{V}O_2$ increase in the first seconds of exercise (phase I), which Barstow and Molé (1987) also treated as an exponential and which the British school led by Brian Whipp attributed to a rapid, also immediate cardiovascular response upon exercise onset (see, e.g. Whipp and Ward 1982, 1990). In the context of this model, the $\dot{V}O_2$ kinetics (measured value minus resting value) upon exercise onset is described by the following:

$$\dot{V}O_2^t = A_1\left(1 - e^{-k_1 t}\right) + H(t-d)A_2\left(1 - e^{-k_2(t-d)}\right) \tag{3.5}$$

where $\dot{V}O_2^t$ is the net $\dot{V}O_2$ (measured value minus resting value) at time t, k_1 and k_2 are the velocity constants of the exponential $\dot{V}O_2$ increase in phase I and II, respectively (their reciprocals τ_1 and τ_2 being the corresponding time constants), d is the time delay, and A_1 and A_2 are the amplitudes of the $\dot{V}O_2$ increase during phase I and phase II, respectively. $H(t - d)$ is the associated Heaviside function, whose value is either 0 if $t < d$ or 1 if $t \geq d$.

Application of the double-exponential model to the analysis of the $\dot{V}O_2$ kinetics provides extremely rapid, functionally instantaneous τ_1 values, indicating a practically immediate upward translation of $\dot{V}O_2$ since the first breath. Higher τ_2 values are conversely obtained, similar to, although slightly faster than, the τ provided by the single-exponential model. This slight difference is a mere mathematical consequence of having introduced a time delay accounting for the time taken by venous blood to reach the pulmonary capillaries from the active muscles and thus corresponding to the time during which mixed venous oxygen concentration remains unchanged after exercise onset (Barstow and Molé 1987).

The double-exponential model represents a significant refinement with respect to the single-exponential model, including also phenomena that are unrelated to muscle oxygen consumption kinetics. By so doing, Lador et al. (2006) obtained faster τ_2 values than previously reported for the muscle [PC] decrease (Binzoni et al. 1992; di Prampero et al. 2003; Rossiter et al. 1999), thus explicitly introducing the concept of a possible dissociation between lung oxygen uptake and muscle oxygen consumption also during light aerobic exercise.

This may be the case also for the kinetics of leg oxygen flow, which Grassi et al. (1996) analysed with a single-exponential model. In their study, however, the time constant of leg oxygen flow was found to be only slightly faster than that of the leg $\dot{V}O_2$, but much slower than that of the muscle blood flow response at exercise onset, which is known to be extremely rapid (Rådegran and Saltin 1998; Toska and Ericksen 1994; Walloe and Wesche 1988). This data demonstrate that for some reasons, leg oxygen flow was unable to respond as fast as leg or muscle blood flow, suggesting that systemic oxygen flow, leg oxygen transfer and muscle oxygen consumption may be the consequence of different, independent, though optimized phenomena. Grassi et al. (1998) also demonstrated, on isolated–perfused dog gastrocnemii, that the time constant of the $\dot{V}O_2$ kinetics was the same in conditions of normal and forced oxygen delivery and equal to that calculated for the kinetics of muscle phosphocreatine decrease, further reinforcing the concept of an independent peripheral component of the kinetics of muscle oxygen consumption. This component, as discussed above, determines the net alactic oxygen deficit and is a necessary consequence of the mechanisms accelerating glycolysis at exercise onset.

Kinetics of Cardiac Output and Oxygen Delivery at Exercise Onset

The development of beat-by-beat techniques for the determination of cardiac output $(\dot{Q})$ led to demonstrate that the kinetics of $\dot{Q}$ at exercise onset is very fast, much faster than that of $\dot{V}O_2$ (Cummin et al. 1986; De Cort et al. 1991; Eriksen et al. 1990; Yoshida and Whipp 1994). Lador et al. (2006) modelled the kinetics of $\dot{Q}$ by extending the field of application of the dual exponential model of Barstow and

Molé (1987) to include its description. During light aerobic exercise, they obtained very low τ values not only for phase I, but also for phase II (τ_2 equal to 2.1 s as compared to 15.4 s for $\dot{V}\,O_2$). Since arterial oxygen concentration $(Ca\,O_2)$ did not vary during the exercise transient in normoxia, the same was the case for systemic oxygen delivery $\left(\dot{Q}\,aO_2\right)$

The rapid increase in $\dot{Q}$ is the consequence of the equally rapid increase in heart rate (f_H) and in stroke volume (Q_s). That the increase in f_H is a very rapid phenomenon is a well-known concept since long. Fagraeus and Linnarsson (1976) identified two components of it, one almost immediate, the second slower and slightly delayed. They attributed the former to the withdrawal of vagal tone at exercise start, the latter to the progressive increase of sympathetic activity. Vagal blockade with atropine is known to suppress in fact the rapid component of the f_H increase (Fagraeus and Linnarsson 1976). Coherently in hypoxia, when vagal activity is already reduced at rest, the amplitude of the f_H increase in phase I is smaller than in normoxia (Lador et al. 2008).

The evidence concerning Q_s is more elusive. The morphological evidence about heart innervation, indicating a presence of muscarinic receptors only in the sinus node, would suggest that vagal withdrawal would not act on Q_s. This being the case, the $\dot{Q}$ increase at exercise onset would be due only to the increase in f_H. Yet a rapid increase in Q_s was also demonstrated (Faisal et al. 2009; Lador et al. 2006, 2008), clearly opening the way to a possible role for the Frank-Starling mechanism in the Q_s increase at exercise start, likely activated by the sudden blood displacement from lower limbs to the heart due to muscle pump action. If this is so, then $\dot{Q}$ would be under dual control, neural (f_H increase via vagal withdrawal) and mechanical (Q_s increase via Frank-Starling mechanism).

The latter mechanism was proposed on the basis of animal studies (Sheriff et al. 1993), but direct evidence in healthy humans is still missing. Indirect evidence derives from experiments in supine posture, in which central blood volume is higher than in upright posture, showing that the phase I of $\dot{Q}$ and Q_s is not evident (Leyk et al. 1994; Wieling et al. 1996). In humans, the action of the Frank-Starling mechanism during exercise transients was clearly demonstrated only in heart transplant recipients, who do not show rapid f_H increase at exercise start because they have denervated hearts (Meyer et al. 1994). Experiments with human exposure to lower body negative pressure would be crucial to further clarify this issue.

A double-exponential treatment was already proposed for the kinetics of f_H, but not for that of Q_s. The use of an exponential model implies the assumption that the system behaves linearly. This may well be the case for f_H, as indicated by the classical linear relationship between f_H and power. This may not be so, however, for Q_s, whose response to exercise steady state is markedly nonlinear (Cerretelli and di Prampero 1987). So, applying an exponential model to the analysis of Q_s may be arbitrary. Lador et al. (2006) refrained from fitting parameters through Q_s data for this reason. Under these circumstances, a tool for a quantitative evaluation of the contribution of Q_s to the A_1 of $\dot{Q}$ is provided by the following equation:

$$\dot{Q}_r + \Delta\dot{Q} = (Q_{s,\mathrm{r}} + \Delta Q_s) * (f_{H,\mathrm{r}} + \Delta f_H) \tag{3.6}$$

where suffix r designates the resting value of the corresponding variable, whereas Δ indicates the corresponding respective increments during phase I as compared with rest, which, assuming exponential models, should correspond to the respective phase I amplitudes (A_1). The use of Eq. (3.6), however, implies that ΔQ_s would correspond to the A_1 of an exponential Q_s increase only if the Q_s kinetics upon exercise onset had the same time constant of the f_H kinetics, which is still undemonstrated.

The time constants of the phase I $\dot{Q}$ response are associated with an extremely rapid, and functionally instantaneous, phase I τ of $\dot{V}\,\mathrm{O}_2$ kinetics (Lador et al. 2006, 2008; Faisal et al. 2009). This would correspond to a practically immediate upward translation of $\dot{V}\,\mathrm{O}_2$ that is apparent since the first breath. Considering the time resolution in breath-by-breath analysis, the apparent phase I τ of $\dot{V}\,\mathrm{O}_2$ kinetics cannot be considered different from those obtained for the kinetics of $\dot{Q}$ and $\dot{Q}\,a\mathrm{O}_2$, thus refining and supporting quantitatively the observation (Cummin et al. 1986) of a close correspondence between the rapid increase of $\dot{Q}$ and ventilation at exercise onset. Application of the Fick principle helps in understanding the quantitative relations between the kinetics of $\dot{Q}$ or $\dot{Q}\,a\mathrm{O}_2$ and that of $\dot{V}\,\mathrm{O}_2$ during phase I. Because of a delay between muscle oxygen consumption and lung oxygen uptake, it can be assumed that during the first seconds of exercise, the composition of mixed venous blood remains unchanged, and thus, the arterial-venous oxygen difference $(Ca\mathrm{O}_2 - C\bar{v}\,\mathrm{O}_2)$ stays equal to that at rest (Barstow and Molé 1987; Weissman et al. 1982). This being so, any increase in $\dot{V}\,\mathrm{O}_2$ during phase I would be due only to an increase in $\dot{Q}$. Lador et al. (2006) found that the A_1 of $\dot{Q}$ was on average 4.3 L min^{-1}. For an average resting $(Ca\mathrm{O}_2 - C\bar{v}\,\mathrm{O}_2)$ of 87 ml L^{-1}, this would carry along a corresponding immediate $\dot{V}\,\mathrm{O}_2$ increase of 374 ml min^{-1}, which is very close to the observed amplitude of phase I for $\dot{V}\,\mathrm{O}_2$, reported in the same study (355 $\pm$ 148 ml min^{-1}), indicating that the A_1 for $\dot{V}\,\mathrm{O}_2$ is indeed entirely accounted for by the $\dot{Q}$ increase during phase I, as previously proposed (Wasserman et al. 1974; Whipp et al. 1982).

Lador et al. (2006) found faster τ_2 of $\dot{Q}$ and $\dot{Q}\,a\mathrm{O}_2$ than that of $\dot{V}\,\mathrm{O}_2$, with equal time delay. Thus, the amount of oxygen made available to the contracting muscle mass in phase II overrides the oxygen demand, determining a transient decrease in $(Ca\mathrm{O}_2 - C\bar{v}\,\mathrm{O}_2)$, with consequent transient increase of the oxygen stores in the venous reservoir. The phase II increase in $\dot{Q}$ was attributed to the progressive activation of sympathetic flow to the heart. In hypoxia (Lador et al. 2013), the τ_2 of $\dot{Q}$ was higher than in normoxia. This may be, at least in part, a consequence of a slower f_H increase in hypoxia in response to sympathetic activation. Some studies, however, have shown unchanged f_H kinetics in hypoxia with respect to normoxia despite slower $\dot{V}\,\mathrm{O}_2$ response (Cleuziou et al. 2005; Engelen et al. 1996).

The $\dot{V}O_2$ Kinetics in Hypoxia

Several studies reported higher time constants for the primary component (phase II) of the $\dot{V}O_2$ response in hypoxia than in normoxia, independently of the applied model (mono-or bi-exponential) (Cleuziou et al. 2005; Engelen et al. 1996; Hughson and Kowalchuk 1995; Lador et al. 2013; Springer et al. 1991). Only one study, however, reported at the same time the values of early lactate accumulation (Lador et al. 2013). I therefore refer to these data for the present analysis.

The average cumulative volume of oxygen (VO_2) that is transferred at the alveolar level during a constant-load exercise is given by the following:

$$VO_2 = \int_0^t d\dot{V}O_2 dt \tag{3.7}$$

where t is the exercise time. At the same time, the changes in venous blood oxygen stores (ΔVvO_2) occurring during the transient can be calculated as follows (Barstow et al. 1990):

$$\Delta VvO_2 = \left[\left(\frac{\dot{V}O_2}{\dot{Q}}\right)_r - \left(\frac{\dot{V}O_2}{\dot{Q}}\right)_{ss}\right] V_v \tag{3.8}$$

where suffixes ss and r refer to the steady-state and pre-exercise resting conditions, respectively, and V_v is the venous blood volume, assumed invariant within the exercise transient and equal to 3 L (Barstow et al. 1990). From the data of Lador et al. (2013), average ΔVvO_2 turned out equal to 260 and to 230 ml in normoxia and hypoxia, respectively. These values can then be added to $\dot{V}O_2$, to obtain the volume of oxygen actually extracted by the contracting muscles (VO_{2M}) in the two conditions. Since the metabolic requirements of muscle contraction at a given steady mechanical power are independent of exercise time, the difference between the overall metabolic energy (expressed in oxygen equivalents) consumed during a given exercise time and VO_{2M} defines a muscular oxygen deficit (DO_{2M}), which is equal to (di Prampero 1981; di Prampero and Ferretti 1999)

$$DO_{2M} = DO_{2AL} + DO_{2LA} \tag{3.9}$$

where DO_{2AL} is the alactic oxygen deficit, i.e. the obligatory component of DO_{2M}, and DO_{2LA} is that facultative component of DO_{2M}, represented by early lactate. DO_{2AL} results from an exponential muscle $\dot{V}O_2$ kinetics that, in evenly aerobic conditions, i.e. when DO_{2LA} is nil, has an equal time constant to that of the mono-exponential kinetics of muscle phosphocreatine decrease upon exercise onset (Binzoni and Cerretelli 1991). As already pointed out, this time constant in humans ranges between 20 and 25 s, as demonstrated by magnetic resonance spectroscopy experiments, and is invariant and independent of the mechanical power imposed (Binzoni et al. 1992, 1997; di Prampero et al. 2003; Francescato et al. 2008;

Rossiter et al. 1999, 2002). As a consequence, $D\,O_{2AL}$ turns out directly proportional to the steady-state $\dot{V}\,O_2$.

In the study of Lador et al. (2013), the evenly aerobic condition is represented by the experiments in normoxia, in which no increase in $[La]_b$ was observed during the exercise transient, and the estimated time constant of muscle $\dot{V}\,O_2$ kinetics, after accounting for changes in blood oxygen stores, corresponded well to that reported in the above-mentioned studies for muscle phosphocreatine kinetics. In this condition, $D\,O_{2M} = D\,O_{2AL}$

Things are not so in hypoxia, in which case $D\,O_{2M}$ turns out larger than in normoxia. Since exercise was carried out at the same power in both conditions, and thus steady state $\dot{V}\,O_2$ was the same, $D\,O_{2AL}$ was necessarily equal in hypoxia as in normoxia. Consequently, the increase in $D\,O_{2M}$ in hypoxia is exclusively due to an increase in $D\,O_{2LA}$, whence the experimental finding of a net increase of lactate concentration during the exercise transient. The energy furnished by $D\,O_{2LA}$ in hypoxia must be equal to the difference in $D\,O_{2M}$ between hypoxia and normoxia. The ratio between $D\,O_{2LA}$ and the net average lactate accumulation (1.3 mM in the study of Lador et al. 2013), expressed per unit of body mass, turns out equal to 2.5 ml O_2 mM^{-1} kg^{-1}, a value fairly close to the range normally admitted for the energy equivalent of blood lactate accumulation (di Prampero 1981).

The rate of substrate flux dictates the rate at which muscle $\dot{V}\,O_2$ increases in evenly aerobic conditions (Bowtell et al. 2007; Connett et al. 1985; Korzeniewski and Zoladz 2002). In this case, the phase II kinetics of $\dot{Q}$ and $\dot{Q}aO_2$ is faster than that of muscle oxygen consumption. However, as soon as in an exercise transient the increase in $\dot{Q}\,aO_2$ becomes as slow as or slower than the rate at which substrate flux increases, as was the case hypoxia in the study of Lador et al. (2013), and I would say is the case anytime the evenly aerobic condition is broken around the so-called lactate threshold, then muscle $\dot{V}\,O_2$ kinetics would be imposed by the former instead of the latter and would be slowed down. Pyruvate accumulates in contracting muscle fibres, thus promoting muscle, then blood lactate accumulation. To sum up, any slowing of $\dot{Q}aO_2$ kinetics entails a slowing of both the kinetics of $\dot{V}\,O_2$ and of muscle oxygen consumption.

The Slow Component

When exercise is carried out at a power higher than the so-called lactate threshold, beside the appearance of early lactate, a new component of the $\dot{V}\,O_2$ kinetics becomes evident, defined as the **slow component** of the $\dot{V}\,O_2$ response to exercise (Camus et al. 1988; Paterson and Whipp 1991; Poole et al. 1988; Whipp and Wasserman 1972). When the slow component appears, no steady state is attained during constant-load exercise: $\dot{V}\,O_2$ keeps increasing until it attains its maximum, and exercise is terminated (Poole et al. 1988). However, Jones et al. (2010)

demonstrated that the slow component may appear also at moderate exercise, slightly below the critical power, so that a steady state may still be attained at a level, which is lower than the maximum $\dot{V}O_2$ but higher than the phase II steady state. This may justify treating the slow component as a third exponential of the $\dot{V}O_2$ kinetics, whose amplitude would be nil at light exercise in evenly aerobic conditions, becoming positive above the lactate threshold, possibly higher, the higher is the mechanical power, yet unmeasurable due to the achievement of a $\dot{V}O_2$ level equivalent to the maximum, which by definition cannot be overridden. This option was anyway retained by Barstow and Molé (1991), who proposed two distinct exponential models differing by the size and meaning of the admitted time delay. Time constants higher than 100 s were reported by these authors for the exponential assumed to characterize the slow component (phase III of the $\dot{V}O_2$ kinetics).

The mechanisms behind the slow component are far from being understood. They are nonetheless related to alterations in the *milieu interne* of the contracting muscle mass, possibly as a consequence of early lactate accumulation, and to the onset of peripheral fatigue (Jones et al. 2011). Initially, what we call nowadays the slow component was attributed to the increase of the energy cost of ventilation and to the metabolic effects of increasing body temperature (Hagberg et al. 1978). These two factors, however, intervene across the entire power range from rest to maximum, which is not the case for the slow component. Other mechanisms had to be called upon. Some of these were reviewed by Poole et al. (1994a), including the potential metabolic effect of increased catecholamine concentration (other factor, however, active along the entire power range), work performed by non-locomotory muscles, differences in contraction efficiency between type I and type II fibres, differentially recruited at progressively increasing powers according to the Henneman principle. Several studies with single-leg extension exercise suggested localization of the slow component within the active muscle mass (Koga et al. 2005; Krustrup et al. 2009; Poole et al. 1991), with associated "slow component" for muscle [PC] decrease (Rossiter et al. 2002), a deranging finding indeed for the suggested link between the slow component and the dynamics of ATP turnover in the cross-bridge cycle.

The resulting change of perspective has led Jones et al. (2011) to consider three intrinsic mechanisms potentially explaining the onset of the slow component: (i) a progressive increase in muscle temperature, (ii) the onset of acidosis related to lactate accumulation and (iii) alterations in P/O_2 coupling leading to possible changes in the P/O_2 ratio. The first of these mechanisms can easily be excluded, on both theoretical (muscle temperature increases at all powers) and experimental grounds (Ferguson et al. 2006). The last of these mechanisms has been proposed following the different muscle fibre recruiting patterns, with type II fibre activation being added to type I fibre activation only at intense powers (Henneman principle), as demonstrated by neurophysiological (Sale 1987) and fibre glycogen-depletion studies (Krustrup et al. 2004), on the hypothesis that type II fibres have lower mechanical efficiency during contraction and lower P/O_2 ratio than type I fibres.

Such a mechanism, however, does not per se imply the necessity of a slow component, as long as at a given intense power, type II fibres are recruited since the exercise start: in this case, lowered efficiency would carry along a higher phase II steady state rather than the addition of a phase III with time delay, as postulated in the model of Barstow and Molé (1991). In fact, this hypothesis was contradicted by the findings of Zoladz et al. (2008).

Muscle pH is significantly decreased only during intense exercise, when a continuous increase in lactate concentration takes place. The link between acidosis and slow component is not due to a direct action of lactate itself, as long as continuous lactate infusion into working dogs did not modify the time course of oxygen consumption (Poole et al. 1994b). The link may be indirect, or better, acidosis may be an epiphenomenon, associated with the onset of the slow component, but not a mechanistic cause of it. The lactic acid concentration in the body fluids results from the balance between lactate production and removal. During intense exercise, the latter is due exclusively, or very nearly so, to its oxidation, the first step of which is the reversible transformation of lactate to pyruvate. When lactate production equals lactate removal, the lactate concentration in body fluids stays constant, and $\dot{V}O_2$ is an overall measure of the whole body energy expenditure, independent of the magnitude of lactate production and removal and of the absolute lactate concentration. On the contrary, during intense exercise, the lactate concentration in the body fluids keeps increasing with time, indicating that the overall energy balance includes a fraction of energy deriving from anaerobic lactic metabolism, which is proportional to the net rate of lactate accumulation and which is largely due to the recruitment also of type II fibres. These are characterized by relatively poor aerobic potential, as demonstrated by their low mitochondrial density (Howald et al. 1985), and thus during intense exercise, these are in **hypoaerobic condition** (di Prampero and Ferretti 1999), in which active muscle fibres produce more pyruvate than can be oxidized in the Krebs cycle, so that lactate concentration keeps increasing steadily inside them and lactate is liberated in the intracellular space. At the same time, type I fibres are in a **hyperaerobic condition**, in which the active fibres can take up lactate from the extracellular space and oxidize it, in addition to the amount of lactate produced by themselves, a phenomenon tending to decrease lactate concentration in extracellular space. The combination of a hypoaerobic type II fibre with an adjacent hyperaerobic type I defines an **unevenly aerobic condition**, wherein some of the lactate produced in excess by hypoaerobic fibres can be oxidized by the hyperaerobic fibres nearby (Fig. 3.3). This process requires an increase in muscle lactate concentration, entailing a pH decrease. If an equilibrium is attained between the hypoaerobic and the hyperaerobic fibre, lactate concentration, after an initial rise (early lactate), stabilizes at a higher level. This may be the case around the critical power: higher lactate, lower pH, both stable, less efficient contraction due to type II fibre recruitment (Han et al. 2003; Stienen et al. 1996) and appearance of phase III $\dot{V}O_2$ response, which attains a steady state whose level is higher the larger the number of active type II fibres. It is noteworthy that this analysis bears an analogy with

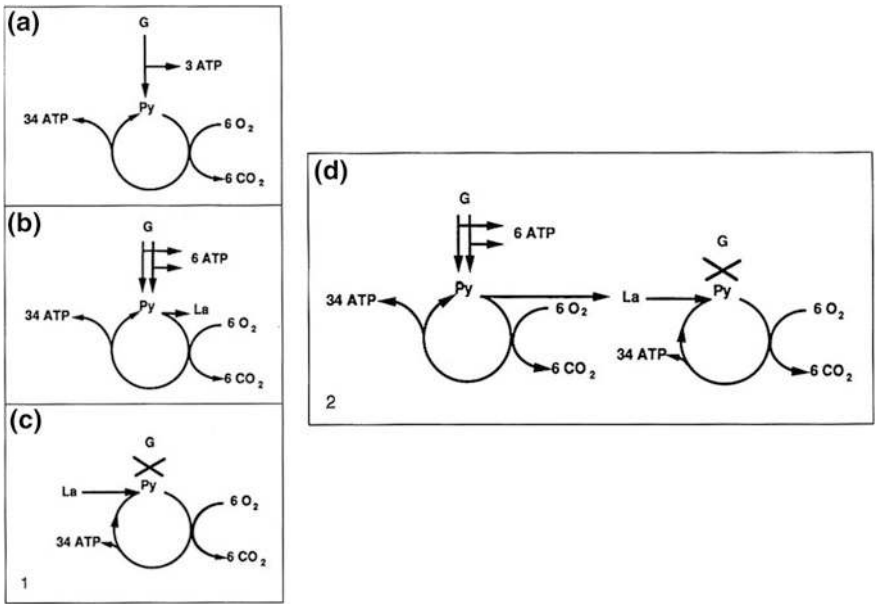


Fig. 3.3 **a** Muscle fibre in evenly aerobic condition. The pyruvate (Py) formed from glycogen (G) is fully oxidized to carbon dioxide and water within the same fibre. Each glycogen unit participating in the process yields 3 units of ATP in the glycolytic pathway and 34 units of ATP in the Krebs cycle and consumes 6 units of oxygen. The P/O_2 ratio amounts thus to (34 + 3)/6 = 6.17. **b** Muscle fibre in hypoaerobic condition. The amount of pyruvate formed at the outcome of the glycolytic path is greater than what can be oxidized in the Krebs cycle. The excess pyruvate is transformed into lactate. The P/O_2 ratio turns out higher than in evenly aerobic condition: (34 + 6)/6 = 6.67. **c** Muscle fibre in hyperaerobic condition. The fibre takes up lactate from the extracellular space and transforms it into pyruvate, which is fed into the Krebs cycle in the absence of glycogen breakdown. The P/O_2 ratio turns out lower than in evenly aerobic condition: 34/6 = 5.67. **d** A couple of muscle fibres in unevenly aerobic condition. The coupling of a hypoaerobic fibre with a hyperaerobic fibre generates a fully aerobic condition across the two fibres. The P/O_2 ratio of this system is equal to that incurring in evenly aerobic condition: (34 + 34 + 6)/12 = 6.17. The arrow connecting the two fibres indicates that lactate concentration is highest in the hypoaerobic fibre, intermediate in the extracellular fluid and lowest in the associated hyperaerobic fibre. From di Prampero and Ferretti (1999)

Brooks' theory of the lactate shuttle (Brooks 1986, 2000, 2009), which looks at the same phenomenon from a slightly different perspective.

By contrast, at powers near the maximum aerobic power, the activity of type II hypoaerobic fibres exceeds that of type I hyperaerobic fibres: more lactate is produced by the former than can be oxidized by the latter: muscle lactate concentration keeps going up, muscle pH keeps decreasing, type II fibres fatigue and perhaps the muscle tries to recruit a larger number of motor units, which may contribute to a continuously increasing phase III: after a given time, which is shorter, the higher is the applied power, the maximal $\dot{V}O_2$ is attained and exercise must end within short (Fig. 3.4).

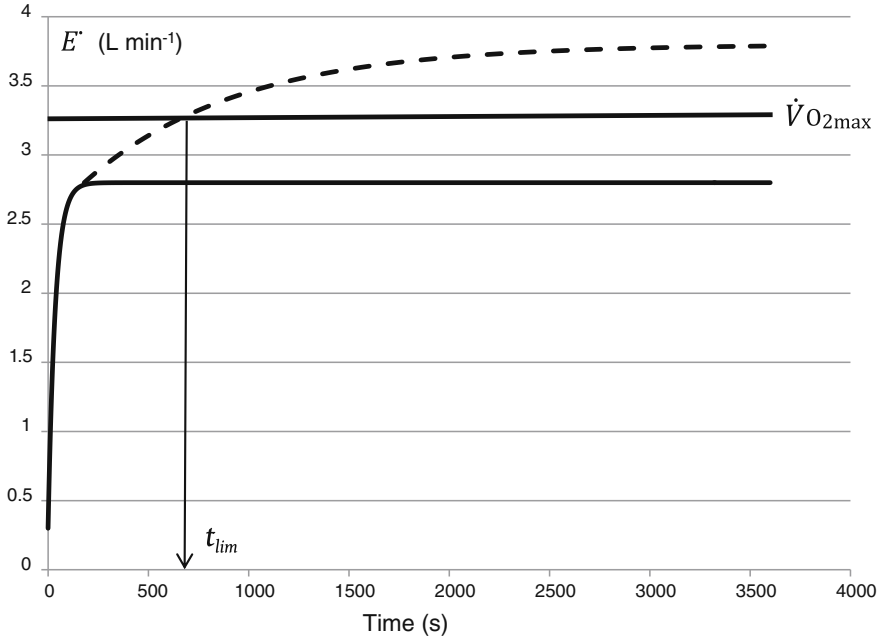


Fig. 3.4 Example of kinetics of oxygen flow $\dot{V}O_2$ upon constant-load exercise onset, with identification of the primary component (phase II, *continuous curve*) and of the slow component (phase III, *dashed curve*). An exponential phase III implies superposition of a further $\dot{V}O_2$ increase above the steady state of phase II until the new steady state. This would be attained, however, at a $\dot{V}O_2$ higher than the maximal oxygen consumption $\left(\dot{V}O_{2max}\right)$, which cannot be overcome. Thus, the $\dot{V}O_2$ increase due to phase III stops at the attainment of $\dot{V}O_{2max}$. This sets the maximal time that can be sustained at a given power (t_{lim}), indicated in the graph by the *vertical arrow*

To sum up, behind the slow component, there may be a mixture of fibre type functional characteristics, fatigue, predominance of hypoaerobic fibres leading to lactate accumulation, decreased efficiency of muscle contraction during intense exercise. The general picture underlined here above carries along numerous corollaries, namely that (i) early lactate starts being accumulated at powers below the critical power; (ii) the critical power may correspond, or at least be close, to the power eliciting maximal lactate steady state (Greco et al. 2012; Pringle and Jones 2002); (iii) the amplitude of the slow component (phase III of the $\dot{V}O_2$ response) is greater, the higher is the applied power; (iv) the power–duration relationship above the critical power is connected with the quantitative characteristics of phase III. Moreover, as underlined also in Chap. 6, the energetic significance of lactate accumulation is related to the rate at which its concentration changes in the body fluids and not to its absolute concentration. The typical plot of blood lactate concentration as a function of exercise intensity does not mean that above a given threshold (e.g. 4 mM), the energy requirement of the exercise is met in part by anaerobic lactic energy sources: a continuous anaerobic lactic contribution to the

energy requirement can be demonstrated only if the lactate concentration keeps increasing during the exercise (di Prampero and Ferretti 1999).

The slow component represents a challenge to the classical notion of a linear $\dot{V}O_2$ versus power relationship from rest to maximal exercise. This concept was already discussed in Chap. 2. In fact, the appearance of the slow component may flex this relationship upwards in the high-intensity exercise domain. Here, I add that, in the context of an exponential model of the $\dot{V}O_2$ kinetics including slow component, we may be able to compute a phase II amplitude, present at all powers between rest and maximal exercise, redefining the classical steady-state concept for $\dot{V}O_2$, and a phase III amplitude, appearing above the critical power (see Chap. 5), or likewise above the lactate threshold, whose steady state might be attained at $\dot{V}O_2$ levels higher than the maximum, and therefore invisible experimentally. The provocative hypothesis is that these two phases do not refer to same phenomena: in this case, only the former would represent the metabolic power sustaining muscle contraction in aerobic conditions, its amplitude being directly proportional to the applied mechanical power.

The Effect of Priming Exercise

The kinetics of $\dot{Q}aO_2$, variable which is dictated by $\dot{Q}$ and CaO_2 (invariant in normoxia), can logically be accelerated if the blood flow to the contracting muscle mass is artificially elevated before a square wave exercise. The easiest way to attain such an acceleration of the $\dot{Q}aO_2$ kinetics is to perform an intense exercise a few minutes before the start of the "experimental" exercise session. During recovery after intense exercise, the decrease of blood flow is relatively slow, so that the second exercise is initiated when muscle blood flow has not yet returned to its resting value. In this case, one should expect a $\dot{V}O_2$ kinetics characterized by a smaller τ_2 than that which one would find if the same exercise was started from a resting blood flow condition. This was demonstrated to be so in several studies (see, e.g. Burnley et al. 2001, 2002; Gerbino et al. 1996; MacDonald et al. 1997; Perrey et al. 2003), but the observation is not universal (Burnley et al. 2000; Scheuermann et al. 2002; Wilkerson et al. 2004). In particular, the priming exercise effect does not appear when priming exercise is carried out at a power below the lactate threshold (Carter et al. 2005; Gerbino et al. 1996), thus in evenly aerobic conditions. Above the lactate threshold, the effect depends on the intensity of exercise (Bailey et al. 2009; Tordi et al. 2003) and on the time of recovery between the two exercise bouts (Burnley et al. 2006). Some authors have reported that the effect is specific to the slow component (Koppo and Bouckaert 2001; Sahlin et al. 2005), with contradictory results regarding the primary component (Burnley et al. 2000; Faisal et al. 2009; Tordi et al. 2003).

The mechanisms behind the priming exercise effect are still poorly understood. Several hypotheses have been put forward, which include the interaction of various mechanisms. Among these, increased muscle oxygen delivery may play a crucial role for its potentially direct effect (DeLorey et al. 2007; Endo et al. 2005; Faisal et al. 2009), although enhanced activity of muscle oxidative enzymes and alterations of motor unit recruitment patterns have also been considered (for a review of these alternative hypotheses, see Poole and Jones 2012). According to Faisal et al. (2009), greater oxygen delivery with increased leg blood flow after prior heavy exercise (Fukuba et al. 2007), or an elevation in pyruvate dehydrogenase and intracellular lactate and acetyl CoA concentrations (Gurd et al. 2006), may generate an increase in PO_2 following elevated oxygen delivery.

The effect of priming exercise on the $\dot{V}O_2$ kinetics as determined at the lungs does not appear when studying the kinetics of muscle oxygen consumption during blood flow manipulations in the isolated–perfused muscle preparation (Grassi et al. 1998). Therefore, the acceleration of the $\dot{V}O_2$ kinetics associated with the performance of priming exercise during heavy exercise is a consequence of something occurring in the respiratory system upstream of the contracting muscle fibres.

The phenomenon is typical of intense exercise, in which early lactate accumulation occurs. It appears associated with faster kinetics of $\dot{Q}aO_2$. As long as it accelerates the $\dot{V}O_2$ kinetics, priming exercise improves the performance time at any power above the critical power (Burnley et al. 2011; Ferguson et al. 2010), without changing the critical power. Since the critical power is tightly matched with the maximal aerobic power (Adami et al. 2013), this is unaffected as well. In sum, I propose that the effect of priming exercise has to do with the interaction between cardiopulmonary oxygen flow and muscle oxygen consumption. This would explain why it is unlike during light exercise: in this condition, the kinetics of $\dot{Q}aO_2$ is anyway fast enough to ensure a sufficient amount of oxygen to sustain aerobic metabolism. In intense exercise, the faster $\dot{Q}aO_2$ kinetics generated by keeping up of muscle blood flow after the priming exercise accelerates the priming component of the $\dot{V}O_2$ kinetics, reduces its slow component and likely reduces early lactate accumulation, thus improving the matching between respiration and metabolism in the exercise transient. In other terms, the effects of priming exercise represent a further demonstration of the important role played by the cardiopulmonary response in dictating the $\dot{V}O_2$ response at exercise onset and of the dissociation between muscular and lung $\dot{V}O_2$ response.

Ramp and Sinusoidal Exercise

Equation (1.4a) assumes that the exercising muscles behave as dynamic linear first-order systems that, as such, admit only one transfer function. By analogy, Eq. (3.5) requires two transfer functions, one characterizing phase I, the other characterizing phase II. If we accept that phase II reflects muscle oxygen consumption, once

allowance is made for the buffer function of blood oxygen stores, it follows that aerobic metabolism is dictated by the rate of a single first-order reaction. A corollary of this postulate is that oxygen flow along the respiratory system does not limit the kinetics of muscle oxygen consumption, at least in the light and moderate exercise domains. In these conditions, the τ of any $\dot{V}O_2$ response should be the same, independent of the exercise protocol used.

As a consequence, when a ramp exercise protocol is investigated in the submaximal exercise range, both the power and the $\dot{V}O_2$ increase linearly with time, but the latter lags behind the former by a time equal to the time constant of the $\dot{V}O_2$ response. The ratio between the two slopes is equal to the mechanical efficiency of exercise. Similarly, when a sinusoidal exercise protocol is investigated, the $\dot{V}O_2$ response follows a sinusoidal pattern. But this pattern is not in phase with that of mechanical power, but is out of phase by a time corresponding to the time constant of the $\dot{V}O_2$ response. These predictions have received solid experimental support (Haouzi et al. 1993; Hughson et al. 1991; Niizeki et al. 1995; Swanson and Hughson 1988; Whipp et al. 1981), especially in the light exercise domain (Haouzi et al. 1993).

Elements suggesting dissociation from this model, however, intervene in the high-intensity exercise domain. The accumulation of early lactate, the appearance of the slow component, the changes in τ and the slowing of the $\dot{Q}aO_2$ kinetics with increasing power suggest nonlinearity at high-intensity exercise. In the context of the double-exponential model, the same concepts may apply to the primary component of the $\dot{V}O_2$ kinetics.

The Problem of Gas Flow Analysis on a Breath-by-Breath Basis

The study of the dynamic response of metabolic and pulmonary variables upon exercise onset is strongly affected by the recording and computational techniques used. The first need was to improve the time resolution up to the single breath, the duration of which is a physiological barrier. This was initially achieved in 1966, when Auchincloss et al. (1966) published their algorithm for single-breath determination of $\dot{V}O_2$. Attempts at improving the time resolution beyond the single-breath duration could rely only on computational manipulations, such as superposition of several trials and interpolation procedures. The second need was to improve the signal-to-noise ratio during the exercise transient, in order to reduce the error of fitting procedures, a key step in the calculation of parameters of exponential equations.

The algorithm by Auchincloss et al. (1966) requires a correct determination of the changes in the amount of gas stored in the lungs over each breath. This quantity cannot be measured, so they estimated it by imposing fixed pre-defined values of end-expiratory lung volumes. To this purpose, they used pre-measured values of functional residual capacity. Subsequently, several authors introduced variants to the Auchincloss algorithm (Busso and Robbins 1997; Swanson and Sherrill 1983;

Wessel et al. 1979), in order to improve the definition of end-expiratory lung volumes. However, di Prampero and Lafortuna (1989) demonstrated the impossibility of attaining a correct estimate of end-expiratory lung volume at each breath and, thus, of reducing the experimental error by acting on the Auchincloss algorithm, whose value was undermined by an elusive variable. A remarkable computational improvement was achieved after Capelli et al. (2001) had resumed an alternative quite forgotten algorithm (Grønlund 1984), which got rid of the need of estimating end-expiratory lung volume. Using Grønlund's algorithm, Capelli et al. (2001) demonstrated a two-time improvement of the signal-to-noise ratio in breath-by-breath determination of alveolar gas transfer as compared with Auchincloss-like algorithms. Moreover, Cautero et al. (2002) demonstrated that Grønlund's algorithm was able to provide lower τ_2 values than any variant of Auchincloss algorithm, no matter what value was attributed to the end-expiratory lung volumes, suggesting that the primary component might indeed be faster than previously admitted.

Such algorithm improvements, however, did not act on the time resolution, the second fundamental aspect in the study of gas exchange dynamics. In fact, application of the double-exponential model of Barstow and Molé (1987) provides extremely low τ_1 values, so low (so fast), that it was systematically undersampled because it was resolved within one, at most two breaths, from exercise start. The first attempts at improving the time resolution made use of interpolation methods on the 1 s basis (Beaver et al. 1981; Hughson et al. 1993; Lamarra et al. 1987). All these attempts are equivalent to the introduction of filters which distort the physiological signal, thus introducing a further source of error, which tends to increase the value of the calculated time constants. Lamarra et al. (1987), who first proposed and discussed a stepwise interpolation procedure, were aware of this problem, as they recognized that the step interpolation generated "mean physiological responses that are smoothed by a filter whose time constant is the mean breath duration (typically 3-4 s for these studies)". For this reason, they restricted application of their procedure to the analysis of phase II, whose time constant was at least one order of magnitude greater than the interpolation interval. Hughson et al. (1993), in order to circumvent the limits of the stepwise interpolation, introduced a linear interpolation procedure, on the assumption of a continuous, linear $\dot{V}O_2$ increase within the same breath. Yet the filter effect is still maintained, especially in the determination of τ_1, whose values may be within the duration of a single breath. Although the smaller data scatter with Hughson's than with Lamarra's interpolation indicated that the former was indeed a more precise method than the latter, the linear interpolation still remained an intrinsically inaccurate method.

More recently, at least in the light exercise domain, mere stacking of multiple repetitions was proposed and treated as if the data were from the same rest-to-exercise transient (Bringard et al. 2014; Francescato et al. 2014a, b). With this procedure, possible signal distortion was prevented by using superposition of raw data obtained during several identical $\dot{V}O_2$ on transients, on the assumption that each repetition on a given subject is representative of the same physiological situation. This approach increases the number of observations encompassed by a

fitting procedure without artificial data manipulations, thus reinforcing the fitting by mere addition of data. A comparison of the results obtained by means of the stacking procedure with those obtained with the interpolation procedures (Bringard et al. 2014), for the same $\dot{V}O_2$ computational algorithm (Grønlund's), showed equivalent τ_2 values, but lower (faster) τ_1 values with stacking than with interpolation. It is not unlike that the $\dot{V}O_2$ kinetics upon exercise onset be faster than usually reported as a consequence of insufficient or inadequate data treatment tools.

In spite of what precedes, Keir et al. (2014) recently argued on the need for performing anyway a 1-s interpolation procedure in the treatment of the primary component of $\dot{V}O_2$ kinetics on the assertion of narrower confidence intervals than with stacking. Lamarra et al. (1987), who first proposed interpolation techniques, underlined the signal distortion, and thus the conceptual error introduced by these techniques and the need for circumventing it. This need has a conceptual origin whose value is independent of statistics. One may well obtain good, even better statistics with interpolation than with stacking, at least as far as the primary component is concerned. The problem here is that the conceptual error implicit in interpolation techniques, even if they provide accurate time constants for the primary component (Bringard et al. 2014), should be avoided even at the price of somewhat weaker statistics. The study of gas exchange kinetics is less a matter of statistics than of ideas. A conceptual error remains an error even if it receives statistical support and provides accurate data.

Conclusions

The synthesis that can be made after the above analysis of the dynamics of exercise transients is that the picture evolves as the applied mechanical power is increased.

During light exercise, all active muscle fibres (essentially type I slow fibres) operate in evenly aerobic conditions. In this case, oxygen delivery matches (or even exceeds) oxygen consumption, the Krebs cycle washes out all the pyruvate produced by glycolysis and no lactate accumulation occurs. The time constant of the $\dot{V}O_2$ kinetics (mono-exponential model) or the time constant of the primary component of the $\dot{V}O_2$ kinetics (phase II, bi-exponential model) approximates that of muscle oxygen consumption, once allowance is made for the buffer function exerted by oxygen stores. The oxygen deficit consists only of its obligatory component, namely anaerobic alactic metabolism, whence the correspondence between muscle [PC] kinetics as determined by NMR studies and muscle oxygen consumption kinetics.

As the power goes up, the metabolic rate increases and more muscle fibres are to be recruited: type II fibres, with lower mitochondrial volume and oxidative potential, start to be activated. The maximal oxygen consumption of these fibres is lower than that of type I slow fibres, so that those fibres start accumulating lactate (hypoaerobic condition), while these fibres do not yet. This phenomenon may be accentuated by the

progressive slowing of the kinetics of cardiovascular variables, which reduces the amount of oxygen relative to the energy demand that is made available to the contracting muscle fibres at a given time during the transient. As a consequence, muscle, and subsequently blood, lactate concentrations increase. However, since a type I fibre can take up the lactate produced by a neighbouring type II fibre (hyperaerobic condition, di Prampero and Ferretti 1999), a new equilibrium is attained, with steady blood lactate concentration higher than at rest (early lactate).

By further increasing power, this equilibrium can no more be sustained, because both the metabolism of type I fibres and the lactate production by type II fibres, which are recruited at a progressively greater extent, increase. Although the power is still lower than the maximal aerobic power, muscle and blood lactate concentration keep increasing with time, muscle pH drops, fibres (especially type II fibres) fatigue, their efficiency decreases and perhaps more fibres need to be recruited: the slow component (phase III) appears. This may occur above a power that is called the critical power, which is discussed in Chap. 5. Associated with the critical power is the concept of maximal lactate steady state. These phenomena progressively reduce the time that can be sustained at a given power, thus dictating the power–duration relationship above the critical power (Chap. 5). At even higher powers, also type I fibres attain their maximal oxygen consumption: in this condition, all active muscle fibres produce lactate, and subjects exercise at powers higher than the maximal aerobic power. All fibres become hypoaerobic, and supramaximal exercise (Chap. 6) is performed. The implications that this state of things have on the concept of maximal aerobic power are discussed in Chap. 4.

References

Adami A, Sivieri A, Moia C, Perini R, Ferretti G (2013) Effects of step duration in incremental ramp protocols on peak power and maximal oxygen consumption. Eur J Appl Physiol 113:2647–2653

Auchincloss JH Jr, Gilbert R, Baule GH (1966) Effect of ventilation on oxygen transfer during early exercise. J Appl Physiol 21:810–818

Bailey SJ, Vanhatalo A, Wilkerson DP, DiMenna FJ, Jones AM (2009) Optimizing the "priming" effect: influence of prior exercise intensity and recovery duration on O_2 uptake kinetics and severe-intensity exercise tolerance. J Appl Physiol 107:1743–1756

Barstow TJ, Molé PA (1987) Simulation of pulmonary O_2 uptake during exercise transients in humans. J Appl Physiol 63:2253–2261

Barstow TJ, Molé PA (1991) Linear and non-linear characteristics of oxygen uptake kinetics during heavy exercise. J Appl Physiol 71:2099–2106

Barstow TJ, Lamarra N, Whipp BJ (1990) Modulation of muscle and pulmonary O_2 uptakes by circulatory dynamics during exercise. J Appl Physiol 68:979–989

Beaver WL, Lamarra N, Wasserman K (1981) Breath-by-breath measurement of true alveolar gas exchange. J Appl Physiol 51:1662–1675

Binzoni T, Cerretelli P (1991) Muscle ^{31}P-NMR in humans: estimate of bias and qualitative assessment of ATPase activity. J Appl Physiol 71:1700–1704

Binzoni T, Ferretti G, Schenker K, Cerretelli P (1992) Phosphocreatine hydrolysis by ^{31}P-NMR at the onset of constant-load exercise in humans. J Appl Physiol 73:1643–1649

Binzoni T, Hiltbrand E, Yano T, Cerretelli P (1997) Step vs. progressive exercise: the kinetics of phosphocreatine hydrolysis in human muscle. Acta Physiol Scand 159:209–215
Bowtell JL, Marwood S, Bruce M, Constantin-Teodosiu D, Greenhaff DL (2007) Tricarboxylic acid cycle intermediate pool size: functional importance for oxidative metabolism in exercising human skeletal muscle. Sport Med 37:1071–1088
Bringard A, Adami A, Moia C, Ferretti G (2014) A new interpolation-free procedure for breath-by-breath analysis of oxygen uptake in exercise transients. Eur J Appl Physiol 114:1983–1994
Brooks GA (1986) Lactate production under fully aerobic conditions: the lactate shuttle during rest and exercise. Fed Proc 45:2924–2929
Brooks GA (2000) Intra-and extra-cellular lactate shuttles. Med Sci Sports Exerc 32:790–799
Brooks GA (2009) Cell-cell and intracellular lactate shuttles. J Physiol 587:5591–5600
Burnley M, Jones AM, Carter H, Doust JH (2000) Effects of prior heavy exercise on phase II pulmonary oxygen uptake kinetics during heavy exercise. J Appl Physiol 89:1387–1396
Burnley M, Doust JH, Carter H, Jones AM (2001) Effects of prior exercise and recovery duration on oxygen uptake kinetics during heavy exercise in humans. Exp Physiol 86:417–425
Burnley M, Doust JH, Jones AM (2002) Effects of prior heavy exercise, prior sprint exercise and passive warming on oxygen uptake kinetics during heavy exercise in humans. Eur J Appl Physiol 87:424–432
Burnley M, Doust JH, Jones AM (2006) Time required for the restoration of normal heavy exercise $\dot{V}O_2$ kinetics following prior heavy exercise. J Appl Physiol 101:1320–1327
Burnley M, Davison G, Baker JR (2011) Effects of priming exercise on $\dot{V}O_2$ kinetics and the power-duration relationship. Med Sci Sports Exerc 43:2171–2179
Busso T, Robbins PA (1997) Evaluation of estimates of alveolar gas exchange by using a tidally ventilated nonhomogenous lung model. J Appl Physiol 82:1963–1971
Camus G, Atchou G, Brückner JC, Giezendanner D, di Prampero PE (1988) Slow upward drift of $\dot{V}O_2$ during constant-load cycling in untrained subjects. Eur J Appl Physiol 58:197–202
Capelli C, Cautero M, di Prampero PE (2001) New perspectives in breath-by-breath determination of alveolar gas exchange in humans. Pflügers Arch 441:566–577
Carter H, Grice Y, Dekerle J, Brickley G, Hammond AJP, Pringle JSM (2005) Effect of prior exercise above and below critical power on exercise to exhaustion. Med Sci Sports Exerc 37:721–775
Cautero M, Beltrami AP, di Prampero PE, Capelli C (2002) Breath-by-breath alveolar oxygen transfer at the onset of step exercise in humans. Eur J Appl Physiol 88:203–213
Cerretelli P, di Prampero PE (1987) Gas exchange at exercise. In: Farhi LE, Tenney SM (eds) Handbook of physiology, the respiratory system IV. Bethesda, MD, pp 555–632 (Am Physiol Soc)
Cerretelli P, Pendergast DR, Paganelli WC, Rennie DW (1979) Effects of specific muscle training on $\dot{V}O_2$ on-response and early blood lactate. J Appl Physiol 47:761–768
Cleuziou C, Perrey S, Lecoq AM, Candau R, Courteix D, Obert P (2005) Oxygen uptake kinetics during moderate and heavy intensity exercise in humans: the influence of hypoxia and training status. Int J Sport Med 26:356–362
Connett RJ, Gayeski TE, Honig CR (1985) Energy sources in fully aerobic rest-work transition: a new role for glycolysis. Am J Physiol Heart Circ Physiol 248:H922–H929
Cummin AR, Iyawe VI, Mehta N, Saunders KB (1986) Ventilation and cardiac output during the onset of exercise, and during voluntary hyperventilation, in humans. J Physiol 370:567–583
De Cort SC, Innes JA, Barstow TJ, Guz A (1991) Cardiac output, oxygen consumption and arterio-venous oxygen difference following a sudden rise in exercise level in humans. J Physiol 441:501–512
DeLorey DS, Kowalchuk JM, Heenan AP, duManoir GR, Paterson DH (2007) Prior exercise speeds pulmonary O_2 uptake kinetics by increases in both local muscle O_2 availability and O_2 utilization. J Appl Physiol 103:771–778
di Prampero PE (1981) Energetics of muscular exercise. Rev Physiol Biochem Pharmacol 89:143–222

di Prampero PE, Ferretti G (1999) The energetics of anaerobic muscle metabolism: a reappraisal of older and recent concepts. Respir Physiol 118:103–115
di Prampero PE, Lafortuna CL (1989) Breath-by-breath estimate of alveolar gas transfer variability in man at rest and during exercise. J Physiol 415:459–475
di Prampero PE, Margaria R (1968) Relationship between O_2 consumption, high energy phosphates and the kinetics of O_2 debt in exercise. Pflügers Arch 304:11–19
di Prampero PE, Davies CTM, Cerretelli P (1970) An analysis of O_2 debt contracted in submaximal exercise. J Appl Physiol 29:547–551
di Prampero PE, Boutellier U, Pietsch P (1983) Oxygen deficit and stores at the onset of muscular exercise in humans. J Appl Physiol 55:146–153
di Prampero PE, Francescato MP, Cettolo V (2003) Energetics of muscle exercise at work onset: the steady-state approach. Pflügers Arch 445:741–746
Endo M, Okada Y, Rossiter HB, Ooue A, Miura A, Koga S, Fukuba Y (2005) Kinetics of pulmonary $\dot{V}O_2$ and femoral artery blood flow and their relationship during repeated bouts of heavy exercise. Eur J Appl Physiol 95:418–430
Engelen M, Porszasz J, Riley M, Wasserman K, Maehara K, Barstow TJ (1996) Effects of hypoxic hypoxia on O_2 uptake and heart rate kinetics during heavy exercise. J Appl Physiol 81:2500–2508
Eriksen M, Waaler BA, Walloe L, Wesche J (1990) Dynamics and dimensions of cardiac output changes in humans at the onset and the end of moderate rhythmic exercise. J Physiol 426:423–437
Fagraeus L, Linnarsson D (1976) Autonomic origin of heart rate fluctuations at the onset of muscular exercise. J Appl Physiol 40:679–682
Faisal A, Beavers KR, Robertson AD, Hughson RL (2009) Prior moderate and heavy exercise accelerate oxygen uptake and cardiac output kinetics in endurance athletes. J Appl Physiol 106:1553–1563
Faisal A, Beavers KR, Hughson RL (2010) O_2 uptake and blood pressure regulation at the onset of exercise: interaction of circadian rhythm and priming exercise. Am J Physiol Heart Circ Physiol 299:H1832–H1842
Ferguson RA, Krustrup P, Kjaer M, Mohr M, Ball D, Bangsbo J (2006) Effect of temperature on skeletal muscle energy turnover during dynamic knee-extensor exercise in humans. J Appl Physiol 101:47–52
Ferguson C, Rossiter HB, Whipp BJ, Cathcart AJ, Murgatroyd SR, Ward SA (2010) Effect of recovery duration from prior exhaustive exercise on the parameters of the power-duration relationship. J Appl Physiol 108:866–874
Francescato MP, Cettolo V, di Prampero PE (2008) Influence of phosphagen concentration on phosphocreatine breakdown kinetics. Data from human gastrocnemius muscle. J Appl Physiol 105:158–164
Francescato MP, Cettolo V, di Prampero PE (2013) Oxygen uptake kinetics at work onset: role of cardiac output and of phosphocreatine breakdown. Respir Physiol Neurobiol 185:287–295
Francescato MP, Cettolo V, Bellio R (2014a) Confidence intervals for the parameters estimated from simulated O_2 uptake kinetics: effects of different data treatments. Exp Physiol 99:187–195
Francescato MP, Cettolo V, Bellio R (2014b) Assembling more O_2 uptake responses: is it possible to merely stack the repeated transitions? Respir Physiol Neurobiol 200:46–49
Fukuba Y, Endo MY, Ohe Y, Hirotoshi Y, Kitano A, Shiragiku C, Miura A, Fukuda O, Ueoka H, Miyachi M (2007) Central circulatory and peripheral O_2 extraction changes as interactive facilitators of pulmonary O_2 uptake during a repeated high-intensity exercise protocol in humans. Eur J Appl Physiol 99:361–369
Gerbino A, Ward SA, Whipp BJ (1996) Effects of prior exercise on pulmonary gas-exchange kinetics during high-intensity exercise in humans. J Appl Physiol 80:99–107
Grassi B (2000) Skeletal muscle $\dot{V}O_2$ on-kinetics: set by O_2 delivery or by O_2 utilization? New insights into an old issue. Med Sci Sports Exerc 32:108–116
Grassi B, Poole DC, Richardson RS, Knight DR, Erickson BK, Wagner PD (1996) Muscle O_2 uptake kinetics in humans: implications for metabolic control. J Appl Physiol 80:988–998

Grassi B, Gladden LB, Samaja M, Stary CM, Hogan MC (1998) Faster adjustment of O_2 delivery does not affect $\dot{V}O_2$ on kinetics in isolated in situ canine muscle. J Appl Physiol 85:1394–1403

Greco CC, Caritá RA, Dekerle J, Denadai BS (2012) Effect of aerobic training status on both maximal lactate steady state and critical power. Appl Physiol Nutr Metab 37:736–743

Grønlund J (1984) A new method for breath-to-breath determination of oxygen flux across the alveolar membrane. Eur J Appl Physiol 52:167–172

Gurd BJ, Peters SJ, Heigenhauser GJF, LeBlanc PJ, Doherty TJ, Paterson DH, Kowalchuk JM (2006) Prior heavy exercise elevates pyruvate dehydrogenase activity and speeds O_2 uptake kinetics during subsequent moderate-intensity exercise in healthy young adults. J Physiol 577:985–996

Hagberg JM, Mullin JP, Nagle FJ (1978) Oxygen consumption during constant-load exercise. J Appl Physiol 45:381–384

Han YS, Geiger PC, Cody MJ, Macken RL, Sieck GC (2003) ATP consumption rate per cross bridge depends on myosin heavy chain isoform. J Appl Physiol 94:2188–2196

Haouzi P, Fukuba Y, Casaburi R, Stringer W, Wasserman K (1993) O_2 uptake kinetics above and below the lactic acidosis threshold during sinusoidal exercise. J Appl Physiol 75:1683–1690

Howald H, Hoppeler H, Claassen H, Mathieu O, Straub R (1985) Influences of endurance training on the ultrastructural composition of the different muscle fiber types in humans. Pflügers Arch 403:369–376

Hughson RL, Kowalchuk JM (1995) Kinetics of oxygen uptake for submaximal exercise in hyperoxia, normoxia, and hypoxia. Can J Appl Physiol 20:198–210

Hughson RL, Cuervo LA, Patla AE, Winter DA, Xing HC, Dietrich BH, Swanson GD (1991) Time domain analysis of oxygen uptake during pseudorandom binary sequence exercise tests. J Appl Physiol 71:1620–1626

Hughson RL, Cochrane JE, Butler GC (1993) Faster O_2 uptake kinetics at onset of supine exercise with than without lower body negative pressure. J Appl Physiol 75:1962–1967

Hughson RL, Tschakovsky ME, Houston ME (2001) Regulation of oxygen consumption at the onset of exercise. Exerc Sport Sci Rev 29:129–133

Jones AM, Vanhatalo A, Burnley M, Morton RH, Poole DC (2010) Critical power: implications for the determination of $\dot{V}O_{2max}$ and exercise tolerance. Med Sci Sports Exerc 42:1876–1890

Jones AM, Grassi B, Christensen PM, Krustrup P, Bangsbo J, Poole DC (2011) Slow component of $\dot{V}O_2$ kinetics: mechanistic bases and practical applications. Med Sci Sports Exerc 43:2046–2062

Keir DA, Murias JM, Paterson DH, Kowalchuk JM (2014) Breat-by-breath pulmonary O_2 kinetics: effect of data processing on confidence in estimating model parameters. Exp Physiol 99:1511–1522

Koga S, Poole DC, Shiojiri T, Kondo N, Fukuba Y, Miura A, Barstow TJ (2005) Comparison of oxygen uptake kinetics during knee extension and cycle exercise. Am J Physiol Regul Integr Comp Physiol 288:R212–R220

Koppo K, Bouckaert J (2001) The effect of prior high-intensity cycling exercise on the $\dot{V}O_2$ kinetics during high-intensity cycling exercise is situated at the additional slow component. Int J Sports Med 22:21–26

Korzeniewski B (2003) Regulation of oxidative phosphorylation in different muscles and various experimental conditions. Biochem J 375:799–804

Korzeniewski B, Zoladz JA (2002) Influence of rapid changes in cytosolic pH on oxidative phosphorylation in skeletal muscle: theoretical studies. Biochem J 365:249–258

Krustrup P, Söderlund K, Mohr M, Bangsbo J (2004) Slow-twitch fiber glycogen depletion elevates moderate-exercise fast-twitch fiber activity and O_2 uptake. Med Sci Sports Exerc 36:973–982

Krustrup P, Jones AM, Wilkerson DP, Calbet JA, Bangsbo J (2009) Muscular and pulmonary O_2 uptake kinetics during moderate and high-intensity sub-maximal knee-extensor exercise in humans. J Physiol 587:1843–1856

Lador F, Azabji-Kenfack M, Moia C, Cautero M, Morel DR, Capelli C, Ferretti G (2006) Simultaneous determination of the kinetics of cardiac output, systemic O_2 delivery and lung O_2 uptake at exercise onset in man. Am J Physiol Regul Integr Comp Physiol 290:1071–1079

Lador F, Tam E, Azabji-Kenfack M, Cautero M, Moia C, Morel DR, Capelli C, Ferretti G (2008) Phase I dynamics of cardiac output, systemic O_2 delivery and lung O_2 uptake at exercise onset in men in acute normobaric hypoxia. Am J Physiol Regul Integr Comp Physiol, 295:R624–R632

Lador F, Tam E, Adami A, Azabji-Kenfack M, Bringard A, Cautero M, Moia C, Morel DR, Capelli C, Ferretti G (2013) Cardiac output, O_2 delivery and $\dot{V}O_2$ kinetics during step exercise in acute normobaric hypoxia. Respir Physiol Neurobiol 186:206–213

Lamarra N, Whipp BJ, Ward SA, Wasserman K (1987) Effect of interbreath fluctuations on characterizing exercise gas exchange kinetics. J Appl Physiol 62:2003–2012

Leyk D, Essfeld D, Hoffmann U, Wunderlich HG, Baum K, Stegemann J (1994) Postural effect on cardiac output, oxygen uptake and lactate during cycle exercise of varying intensity. Eur J Appl Physiol 68:30–35

Linnarsson D (1974) Dynamics of pulmonary gas exchange and heart rate changes at start and end of exercise. Acta Physiol Scand Suppl 415:1–78

MacDonald MJ, Pedersen PK, Hughson RL (1997) Acceleration of $\dot{V}O_2$ kinetics in heavy submaximal exercise by hyperoxia and prior high-intensity exercise. J Appl Physiol 83:1318–1325

Meyer M, Rahmel A, Marconi C, Grassi B, Cerretelli P, Cabrol C (1994) Adjustment of cardiac output to step exercise in heart transplant recipients. Z Kardiol 83(Suppl 3):103–109

Meyer RA, Foley JM (1996) Cellular processes integrating the metabolic response to exercise. In: Handbook of physiology. Exercise: regulation and integration of multiple systems. Bethesda, MD, pp 841–869 (Am Physiol Soc, Section 12, Chapter 18)

Niizeki K, Takahashi T, Miyamoto Y (1995) A model analysis of asymmetrical response of pulmonary $\dot{V}O_2$ during incremental and decremental ramp exercise. J Appl Physiol 79:1816–1827

Paterson DH, Whipp BJ (1991) Asymmetries of oxygen uptake transients at the on-and offset of heavy exercise in humans. J Physiol 443:575–586

Perrey S, Scott J, Mourot L, Rouillon JD (2003) Cardiovascular and oxygen uptake kinetics during sequential heavy cycling exercises. Can J Appl Physiol 28:283–298

Piiper J, di Prampero PE, Cerretelli P (1968) Oxygen debt and high-energy phosphates in the gastrocnemius muscle of the dog. Am J Physiol 215:523–531

Poole DC, Jones AM (2012) Oxygen uptake kinetics. Compr Physiol 2:933–996

Poole DC, Ward SA, Gardner GW, Whipp BJ (1988) Metabolic and respiratory profile of the upper limit for prolonged exercise in man. Ergonomics 31:1265–1279

Poole DC, Schaffartzik W, Knight DR, Derion T, Kennedy B, Guy HJ, Prediletto R, Wagner PD (1991) Contribution of exercising legs to the slow component of oxygen uptake kinetics in humans. J Appl Physiol 71:1245–1260

Poole DC, Barstow TJ, Gaesser GA, Willis WT, Whipp BJ (1994a) $\dot{V}O_2$ slow component: physiological and functional significance. Med Sci Sports Exerc 26:1354–1358

Poole DC, Gladden LB, Kurdak S, Hogan MC (1994b) L-(+)-Lactate infusion into working dog gastrocnemius: no evidence lactate per se mediates $\dot{V}O_2$ slow component. J Appl Physiol 76:787–792

Pringle JS, Jones AM (2002) Maximal lactate steady state, critical power and EMG during cycling. Eur J Appl Physiol 88:214–226

Rådegran G, Saltin B (1998) Muscle blood flow at onset of dynamic exercise in man. Am J Physiol Heart Circ Physiol 274:H314–H322

Rossiter HB, Ward SA, Doyle VL, Howe FA, Griffiths JA, Whipp BJ (1999) Inferences from pulmonary O_2 uptake with respect to intramuscular [phosphocreatine] kinetics during moderate exercise in humans. J Physiol 518:921–932

Rossiter HB, Ward SA, Kowalchuk JM, Howe FA, Griffiths JR, Whipp BJ (2002) Dynamic asymmetry of phosphocreatine concentration and O_2 uptake between the on-and off-transients of moderate-and high-intensity exercise in humans. J Physiol 541:991–1002

Sahlin K, Sørensen JB, Gladden LB, Rossiter HB, Pedersen PK (2005) Prior heavy exercise eliminates $\dot{V}O_2$ slow component and reduces efficiency during submaximal exercise in humans. J Physiol 564:765–773

Sale DG (1987) Influence of exercise and training on motor unit activation. Exerc Sport Sci Rev 15:95–151

Scheuermann BW, Bell C, Paterson DH, Barstow TJ, Kowalchuk JM (2002) Oxygen uptake kinetics for moderate exercise are speeded in older humans by prior heavy exercise. J Appl Physiol 92:609–616

Sheriff DD, Rowell LB, Scher AM (1993) Is rapid rise in vascular conductance at onset of dynamic exercise due to muscle pump? Am J Physiol Heart Circ Physiol 265:H1227–H1234

Springer C, Barstow TJ, Wasserman K, Cooper DM (1991) Oxygen uptake and heart rate responses during hypoxic exercise in children and adults. Med Sci Sports Exerc 23:71–79

Stienen GJ, Kiers JL, Bottinelli R, Reggiani C (1996) Myofibrillar ATPase activity in skinned human skeletal muscle fibres: fibre type and temperature dependence. J Physiol 493:299–307

Swanson GD, Hughson RL (1988) On the modeling and interpretation of oxygen uptake kinetics from ramp work rate tests. J Appl Physiol 65:2453–2458

Swanson GD, Sherrill DL (1983) A model evaluation of estimates of breath-to-breath alveolar gas exchange. J Appl Physiol 55:1936–1941

Tordi N, Perrey S, Harvey A, Hughson RL (2003) Oxygen uptake kinetics during two bouts of heavy cycling separated by fatiguing sprint exercise in humans. J Appl Physiol 94:533–541

Toska K, Ericksen M (1994) Peripheral vasoconstriction shortly after onset of moderate exercise in humans. J Appl Physiol 77:1519–1525

Walloe L, Wesche J (1988) Time course and magnitude of blood flow changes in the human quadriceps muscle during and following rhythmic exercise. J Physiol 405(257–273):1988

Wasserman K, Whipp BJ, Castagna J (1974) Cardiodynamic hyperpnea: hyperpnea secondary to cardiac output increase. J Appl Physiol 36:457–464

Weissman C, Abraham B, Askanazi J, Milic-Emili J, Hyman AI, Kinney JM (1982) Effect of posture on the ventilatory response to CO_2. J Appl Physiol 53:761–765

Wessel HU, Stout RL, Bastanier CK, Paul MH (1979) Breath-by-breath variation of FRC: effect on O_2 and CO_2 measured at the mouth. J Appl Physiol 46:1122–1126

Whipp BJ, Ward SA (1982) Cardiopulmonary coupling during exercise. J Exp Biol 100:175–193

Whipp BJ, Ward SA (1990) Physiological determinants of pulmonary gas exchange kinetics during exercise. Med Sci Sports Exerc 22:62–71

Whipp BJ, Wasserman K (1972) Oxygen uptake kinetics for various intensities of constant-load work. J Appl Physiol 33:351–356

Whipp BJ, Davis JA, Torres F, Wasserman K (1981) A test to determine parameters of aerobic function during exercise. J Appl Physiol 50:217–221

Whipp BJ, Ward SA, Lamarra N, Davis JA, Wasserman K (1982) Parameters of ventilatory and gas exchange dynamics during exercise. J Appl Physiol 52:1506–1513

Wieling W, Harms MP, ten Harkel AD, van Lieshout JJ, Sprangers RL (1996) Circulatory response evoked by a 3s bout of dynamic leg exercise in humans. J Physiol 494:601–611

Wilkerson DP, Koppo K, Barstow TJ, Jones AM (2004) Effect of prior multiple-sprint exercise on pulmonary O_2 uptake kinetics following the onset of perimaximal exercise. J Appl Physiol 97:1227–1236

Xing HC, Cochrane JE, Yamamoto Y, Hughson RL (1991) Frequency domain analysis of ventilation and gas exchange kinetics in hypoxic exercise. J Appl Physiol 71:2394–2401

Yoshida T, Whipp BJ (1994) Dynamic asymmetries of cardiac output transients in response to muscular exercise in man. J Physiol 480:355–359

Zoladz JA, Gladden LB, Hogan MC, Nieckarz Z, Grassi B (2008) Progressive recruitment of muscle fibers is not necessary for the slow component of $\dot{V}O_2$ kinetics. J Appl Physiol 105:575–580

Chapter 4
Maximal Oxygen Consumption

Abstract As soon as the concept of maximal oxygen consumption ($\dot{V}O_{2max}$) was created, it was clear that $\dot{V}O_{2max}$ was limited somewhere along the respiratory system. The quest for the single factor limiting $\dot{V}O_{2max}$ went on for long, with highly contradictory outcomes. The way of looking at $\dot{V}O_{2max}$ limitation, however, changed drastically some 30 years ago. The resumption of the oxygen cascade theory as a tool for a holistic description of the respiratory system led to the development of multifactorial models of $\dot{V}O_{2max}$ limitation. Two such models are currently available, one created by Pietro Enrico di Prampero and the other by Peter Wagner. These models are described in detail and criticized. The evidence supporting the predictions generated by the two models is presented. Demonstration is provided that the two models converge indeed on the same conclusion, namely that most of the limitation to $\dot{V}O_{2max}$ in normoxia is provided by cardiovascular oxygen transport. However, the same models show that the role of peripheral oxygen diffusion and utilization as limiting factors is such that it cannot be neglected. The special case of $\dot{V}O_{2max}$ in hypoxia is then presented, and the effects of a nonlinear oxygen equilibrium curve are discussed. It is acknowledged that as long as we operate on the flat portion of the oxygen equilibrium curve, the lungs do not limit $\dot{V}O_{2max}$, but as soon as the steep part of the curve is attained, the lungs take over a significant fraction of $\dot{V}O_{2max}$ limitation. Finally, the case of prolonged bed rest is discussed as an example of $\dot{V}O_{2max}$ changes induced by simultaneous multiple modifications occurring at various levels along the respiratory system.

Contents

G. Ferretti, *Energetics of Muscular Exercise*,
DOI 10.1007/978-3-319-05636-4_4

Introduction

The concept of maximal oxygen consumption ($\dot{V}O_{2max}$) was created when it was observed that the linear relationship between oxygen uptake ($\dot{V}O_2$) and mechanical power ($\dot{w}$) attains a plateau which cannot be overcome despite further increases of $\dot{w}$ (Herbst 1928; Hill and Lupton 1923) (Fig. 4.1). The $\dot{V}O_2$ plateau implied limitation of oxygen flow at some levels along the respiratory system. The quest for the factors that limit $\dot{V}O_{2max}$ has not ceased ever since. For a long time, the discussion on $\dot{V}O_{2max}$ limitation focused on the identification of a single limiting step. A long-lasting debate between two opposed fields, that of central (cardiovascular)

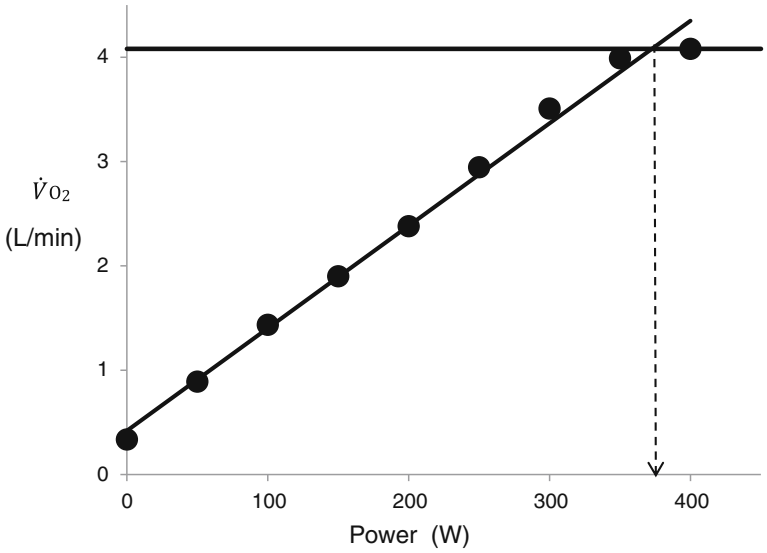


Fig. 4.1 An example of a relationship between oxygen uptake ($\dot{V}O_2$) and power during a classical discontinuous protocol for $\dot{V}O_{2max}$ measurements. The reported data refer to a trained top-level cyclist tested in Geneva. The line through the points is the regression line calculated on the submaximal $\dot{V}O_2$ values. The horizontal line indicates the $\dot{V}O_{2max}$ plateau. The vertical dashed arrow indicates the maximal aerobic power. From Ferretti (2014)

limitation and that of peripheral (muscular) limitation characterized 50 years of research in exercise physiology, without significant synthesis.

A revolution in the approach to the subject of $\dot{V}O_{2max}$ limitation occurred after Taylor and Weibel (1981) resumed the oxygen cascade theory as a tool for describing oxygen transfer from ambient air to the mitochondria in mammals. Although their aim was to analyse the structural constraints of respiratory systems under maximal stress in animals encompassing a wide range of body size, that idea brought some exercise physiologists to consider the multiple factors that contribute to $\dot{V}O_{2max}$ limitation under a holistic perspective. The quest for the single limiting step came to an end and the way to the creation of the multifactorial models of $\dot{V}O_{2max}$ limitation (di Prampero 1985, 2003; di Prampero and Ferretti 1990; Ferretti and di Prampero 1995; Wagner 1992, 1993, 1996a, b). These models have characterized the last 20 years of debate on this issue. $\dot{V}O_{2max}$ and the multifactorial models of $\dot{V}O_{2max}$ limitation are the objects of this chapter.

The Unifactorial Vision of $\dot{V}O_{2max}$ Limitation

The descriptive physiology of $\dot{V}O_{2max}$ has been the object of thousands of papers, the results of which have been summarized in numerous review articles (Blomqvist and Saltin 1983; Cerretelli and di Prampero 1987; Cerretelli and Hoppeler 1996; Ferretti 2014; Jones and Lindstedt 1993; Lacour and Flandrois 1977; Levine 2008; Saltin 1977; Scheuer and Tipton 1977; Stamford 1988; Taylor 1987; Tesch 1985; Weibel 1987; Weibel et al. 1992). In short, $\dot{V}O_{2max}$ is (i) up to twice higher in endurance athletes than in sedentary individuals; (ii) higher in men than in women; (iii) decreased by ageing, with athletes maintaining higher $\dot{V}O_{2max}$ values than non-athletic individuals along the entire lifespan; (iv) reduced by inactivity (e.g. bed rest) or by hypoxia; (v) increased by endurance training, whether with continuous or interval-training protocols, depending on the overall training volume. Training also slows down the $\dot{V}O_{2max}$ decline with age.

These effects on $\dot{V}O_{2max}$ are associated with consensual and quantitatively similar changes in maximal cardiac output ($\dot{Q}_{max}$) (Blomqvist and Saltin 1983; Cerretelli and di Prampero 1987; Clausen 1977; Ekblom et al. 1968). Also the effects of acute manipulations of the cardiovascular oxygen transport system on $\dot{V}O_{2max}$ were widely investigated. $\dot{V}O_{2max}$ was found to be lower in acute anaemia than in normaemia (Celsing et al. 1987; Krip et al. 1997; Woodson et al. 1978) and higher in acute polycythaemia than in normaemia (Buick et al. 1980; Celsing et al. 1987; Ekblom et al. 1975, 1976; Spriet et al. 1986; Turner et al. 1993), and after erythropoietin administration (Russell et al. 2002; Thomsen et al. 2007). $\dot{V}O_{2max}$ is reduced also when small quantities of carbon monoxide are added to inspired air (Ekblom and Huot 1972; Pirnay et al. 1971; Vogel and Gleser 1972). The relationship between $\dot{V}O_{2max}$ and $\dot{Q}_{max}$ is linear and highly significant (Blomqvist and

Saltin 1983; Cerretelli and di Prampero 1987), as is that between $\dot{V}O_{2max}$ and leg blood flow during single-leg extension exercise (Calbet et al. 2004, 2007; Richardson et al. 1995b). Finally, if sufficient blood flow is delivered to the contracting muscle mass, specific muscle $\dot{V}O_{2max}$ can increase well above the levels attained at maximal exercise in normal blood flow condition (Andersen and Saltin 1985; Richardson et al. 1995a; Rowell et al. 1986). On this basis, a large number of exercise physiologists concluded that at least during exercise with large muscle groups, the single factor limiting $\dot{V}O_{2max}$ is cardiovascular oxygen transport (Blomqvist and Saltin 1983; Clausen 1977; Ekblom 1969, 1986; Mitchell and Blomqvist 1971; Rowell 1974; Saltin and Rowell 1980; Saltin and Strange 1992; Scheuer and Tipton 1977; Sutton 1992).

However, focusing on active muscles showed that (i) the smaller is the active muscle mass, the lower is $\dot{V}O_{2max}$ (Åstrand and Saltin 1961; Bergh et al. 1976; Davies and Sargeant 1974; Secher et al. 1974); (ii) specific endurance training of one leg increases $\dot{V}O_{2max}$ during exercise with that leg only (Saltin et al. 1976); (iii) endurance athletes have a greater fraction of oxidative type I muscle fibres, a greater muscle capillary density and a higher activity of muscle oxidative enzymes than sedentary individuals (Brodal et al. 1977; Costill et al. 1976; Gollnick et al. 1972; Howald 1982; Tesch and Karlsson 1985; Zumstein et al. 1983); (iv) muscle capillary supply, muscle mitochondrial volume and muscle oxidative enzyme activities are increased by physical training (Andersen and Henriksson 1977; Gollnick et al. 1973; Henriksson 1977; Holloszy and Coyle 1984; Hoppeler et al. 1985; Howald et al. 1985; Ingjer 1979) and decreased by prolonged inactivity (Berg et al. 1993; Booth 1982; Hikida et al. 1989). Furthermore, and most importantly, the $\dot{V}O_{2max}$ of altitude-acclimatized subjects who are staying in chronic hypoxia, after sudden exposure to normoxic gas mixtures, does not return to the pre-acclimatization levels (Cerretelli 1976). On these bases, some authors concluded that muscle oxidative capacity, rather than cardiovascular oxygen transport, limits $\dot{V}O_{2max}$ (Cerretelli 1980; Lindstedt et al. 1988; Taylor 1987; Weibel 1987), especially during exercise with small muscle groups (Davies and Sargeant 1974; Kaijser 1970; Saltin 1977). More recently, this view was supported also by experiments with single-leg extension exercise (Rådegran et al. 1999; Richardson et al. 1995b; Roach et al. 1999). With the same experimental model, Calbet et al. (2009) demonstrated also a different $\dot{V}O_{2max}$ decrease in hypoxia when exercise was performed with small rather than big muscle masses. In a minority of cases, such as extreme hypoxia (West 1983) and in athletes with very high $\dot{V}O_{2max}$ values (Dempsey et al. 1984; Dempsey and Wagner 1999), the lungs were also accounted for as limiting step.

The debate on the single factor that limits $\dot{V}O_{2max}$ in humans went on for a long time, remaining essentially unresolved. Still in 1992, Saltin and Strange (1992) noted that no consensus existed on what limits $\dot{V}O_{2max}$. The concept of a mono-factorial $\dot{V}O_{2max}$ limitation was so deeply rooted in the world of exercise physiology, that even an important recent review on $\dot{V}O_{2max}$ maintained a mono-factorial focus (Levine 2008). However, the revolution generated by the introduction of

multifactorial models of $\dot{V}O_{2max}$ limitation has transformed the inconclusive debate on the cardiovascular versus muscular limitation of $\dot{V}O_{2max}$ into an old-fashioned reminiscence of the past, similarly to what has happened to tape recorders for experimental data collection.

The Oxygen Cascade at Maximal Exercise

The theory of the oxygen cascade represents an attempt at developing a comprehensive, integrative view of the respiratory system as a gas transporter from ambient air to the mitochondria or vice versa. The basic concept, which can be taken as the axiom behind multifactorial models of $\dot{V}O_{2max}$ limitation, describes oxygen as flowing along the respiratory system driven by oxygen pressure gradients against several in-series resistances, in analogy with water flow in pipes or current in high-resistance electric lines. The overall driving pressure is the pressure gradient between inspired air and the mitochondria. Oxygen partial pressure can be measured at various levels along the respiratory system: the measured values decrease as long as we proceed from the mouth to the mitochondria. These measurement sites allow definition of clear and physiologically significant resistances to flow. A representation of the oxygen flow from ambient air to the mitochondria is depicted in Fig. 1.3 (see Chap. 1). The set of equations describing the flow of oxygen across each resistance provides a simple quantitative description of the oxygen cascade theory. A more detailed nonlinear algebraic solution of the oxygen conductance equations can be found elsewhere (Shephard 1969). At steady state, all these equations have equal solutions for oxygen flow (see Chap. 1), which, at maximal exercise, corresponds to $\dot{V}O_{2max}$, i.e. the maximal flow of oxygen that the incurring overall pressure gradient can sustain against the total resistance to oxygen flow. This resistance decreases as long as the body metabolism is increased, because of the concomitant elevation of ventilation, diffusion capacity, cardiovascular oxygen flow and muscle blood flow. The resistance at maximal exercise, opposing to $\dot{V}O_{2max}$, is the minimal resistance opposed by the respiratory system to oxygen flow.

Two variants of the oxygen cascade theory at maximal exercise have been proposed, depending on whether the cardiovascular oxygen transport step is considered merely convective or not. A convective cardiovascular step implies that the driving force of oxygen flow across this step is the gradient set by the mean capillary oxygen partial pressures ($P_{\bar{c}}O_2$) in the lungs and in muscles, which can be calculated by Bohr's integration at the respective capillaries. In this case, the cardiovascular system would be seen as an element connecting two distant resistances, not as a resistive step in se. If conversely cardiovascular oxygen transport is not considered convective, the driving force across it would be the difference between arterial and mixed venous oxygen partial pressures (P_aO_2 and $P_{\bar{v}}O_2$, respectively), thus making blood circulation one of the many in-series resistances of a hydraulic system.

Both interpretations of cardiovascular oxygen transport can be considered viable because there is a still unresolved quantitative step in the oxygen cascade theory:

the effects of the heterogeneity of distribution of the ventilation/perfusion ratio ($\dot{V}_A/\dot{Q}$) in the lungs, which generates the difference between mean alveolar oxygen partial pressure (P_AO_2) and P_aO_2. The best analytical tool conceived for the description of oxygen transfer between alveoli and arterial blood is the **diffusion–perfusion interaction equation for the lung** (Piiper and Scheid 1981), which nevertheless does not include the effect of $\dot{V}_A/\dot{Q}$ heterogeneity on P_aO_2. The genesis of the two above-mentioned interpretations of cardiovascular oxygen transport is a consequence of the manner this unresolved step of the oxygen cascade is treated, and these two interpretations are at the basis of the two main multifactorial models of $\dot{V}O_{2max}$ limitation, respectively conceived by Pietro Enrico di Prampero and by Peter Wagner (Fig. 4.2). This generated some apparent conceptual and analytical differences in the respective formulations, which led to consider the two models as conflicting. It was recently demonstrated that this was not the case indeed, at least as long as the analysis is restricted to the trait of the respiratory system distal to arterial blood (Ferretti 2014). This restriction is acceptable in normoxia, as long as it is admitted that there is no limitation of $\dot{V}O_{2max}$ imposed by pulmonary ventilation and lung diffusion in this condition.

Fig. 4.2 From left to right, Peter Wagner, Fabio Benfenati (then President of the Italian Physiological Society), Arsenio Veicsteinas, Pietro Enrico di Prampero, Guido Ferretti, Fabio Esposito, Carlo Capelli and Paolo Cerretelli. Wagner and di Prampero are the creators of the two multifactorial models of $\dot{V}O_{2max}$ limitation. Picture taken at the 62° annual meeting of the Italian Physiological Society, which took place in Sorrento, Italy, on 25–27 September 2011. Courtesy of Arsenio Veicsteinas

An Analysis of di Prampero's Model

di Prampero's model (di Prampero 1985, 2003; di Prampero and Ferretti 1990; Ferretti and di Prampero 1995) looks at the respiratory system from ambient air to the mitochondria as a hydraulic model of in-series resistances and assumes steady-state condition at maximal exercise. If this is so, for a system characterized by n resistances in series, we have:

$$\dot{V} = \frac{\Delta P_1}{R_1} = \frac{\Delta P_2}{R_2} = \cdots = \frac{\Delta P_n}{R_n} = \frac{\Delta P_\mathrm{T}}{R_\mathrm{T}} \tag{4.1}$$

where $\dot{V}$ is the gas flow, ΔP is the pressure gradient sustaining $\dot{V}$ across the ith resistance R and ΔP_T is the overall pressure gradient. At maximal exercise, $\dot{V}$ is $\dot{V}\,\mathrm{O_{2max}}$ and ΔP_T is the difference between the inspired and the mitochondrial partial pressure of oxygen, $P_I\mathrm{O_2} - P_m\mathrm{O_2}$. Since $P_m\mathrm{O_2}$ tends to 0 mmHg (Gayeski and Honig 1986; Richardson et al. 2001; Wagner 2012), ΔP_T can be set equal to $P_I\mathrm{O_2}$ with negligible error. Of course, ΔP_T is the sum of the pressure gradients across each resistance:

$$\Delta P_T = \Delta P_1 + \Delta P_2 + \cdots + \Delta P_n \tag{4.2}$$

In this case, the fraction of the overall limitation imposed by the ith resistance to oxygen flow is given by:

$$F_i = \frac{R_i}{R_\mathrm{T}} \tag{4.3}$$

whence

$$\frac{R_1}{R_\mathrm{T}} + \frac{R_2}{R_\mathrm{T}} + \cdots + \frac{R_n}{R_\mathrm{T}} = F_1 + F_2 + \cdots + F_n = 1 \tag{4.4}$$

indicating that the overall limitation to oxygen flow in this model is equal to the sum of the fractional limitations imposed by each of the resistances in the system.

The portrait of the oxygen cascade presented in Fig. 1.3 allows identification of five resistances of clear physiological meaning, namely from proximal (ambient air) to distal (mitochondria), (i) the ventilatory resistance (R_V), (ii) the lung resistance (R_L), which refers to the transfer of oxygen from the alveoli to the arterial blood, (iii) the cardiovascular resistance (R_Q), (iv) the tissue resistance (R_t), which refers to oxygen transfer from peripheral capillaries to muscle fibres and (v) the mitochondrial resistance (R_m), related to mitochondrial oxygen flow and utilization. Although these resistances are related to general concepts that can easily be perceived, discrimination between R_t and R_m is virtually impossible, because they are strongly interrelated on a structural basis. Therefore, for subsequent analysis, they

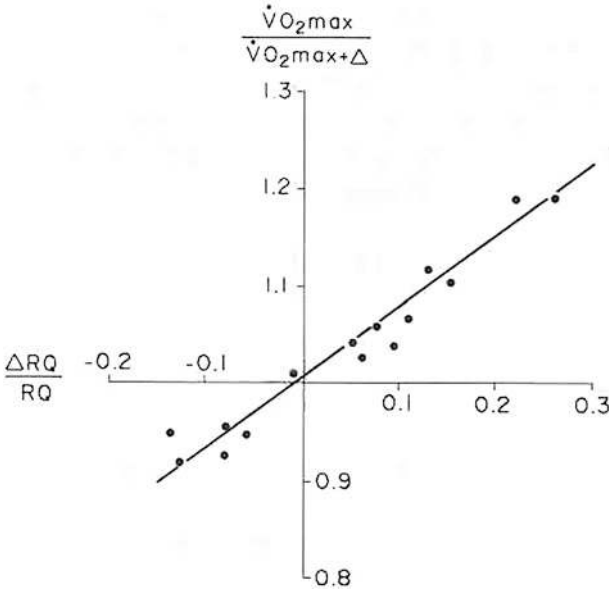


Fig. 4.3 Graphical representation of Eq. (4.13). The changes in $\dot{V}\,O_{2max}$ that follow an acute manoeuvre acting on the cardiovascular resistance to oxygen flow (Rq) are expressed as the ratio of the $\dot{V}\,O_{2max}$ before to the $\dot{V}\,O_{2max}$ after the manoeuvre at stake ($\dot{V}\,O_{2max} + \Delta$). This ratio is plotted as a function of the ratio between the induced change in R_Q (ΔR_Q) and the R_Q before the manoeuvre. Points are mean values from different sources in the literature. The continuous straight line is the corresponding regression equation (y = 1.006 + 0.7 x, r = 0.97, n = 15). The slope of the line, equal to 0.7, indicates that 70 % of the overall limitation to $\dot{V}\,O_{2max}$ is imposed by cardiovascular oxygen transport. Modified after di Prampero and Ferretti (1990)

are merged to form a lumped peripheral resistance (R_p). For the specific case of $\dot{V}\,O_{2max}$, Eq. (4.1) can thus be rewritten as follows:

$$\dot{V}\,O_{2max} = \frac{(P_I O_2 - P_A O_2)}{R_V} = \frac{(P_A O_2 - P_a O_2)}{R_L} = \frac{(P_a O_2 - P_{\bar{v}} O_2)}{R_Q} = \frac{P_{\bar{v}} O_2}{R_p} = \frac{P_I O_2}{R_T} \tag{4.5}$$

Of these resistances, only two are characterized by precisely defined physiological variables, namely R_V and R_Q, which are, respectively, equal to:

$$R_V = \frac{1}{\dot{V}_A \cdot \beta_g} \tag{4.6a}$$

$$R_Q = \frac{1}{\dot{Q} \cdot \beta_b} \tag{4.6b}$$

where $\dot{V}_A$ is alveolar ventilation and $\dot{Q}$ is cardiac output. The other two variables are the oxygen transfer coefficient for air (β_g) and for blood (β_b), i.e. the volume of

oxygen that can be displaced across a gradient of a unit of pressure. In STPD condition, β_g is equal to 1.16 ml mmHg^{-1} and is an invariant constant. Concerning β_b, it is equal to:

$$\beta_b = \frac{(Ca\mathrm{O}_2 - C\bar{v}\mathrm{O}_2)}{(Pa\mathrm{O}_2 - P\bar{v}\mathrm{O}_2)} \tag{4.7}$$

that is the average slope of the oxygen equilibrium curve. Therefore, constant β_b is not an invariant value, for it depends on the oxygen pressure range on which blood operates. The other three resistances cannot be translated into equivalent physiological expressions. R_L, R_t and R_m were set proportional, respectively, to a factor including lung diffusing capacity corrected for the effect of $\dot{V}_A/\dot{Q}$ heterogeneity, to muscle capillary density and to muscle mitochondrial volume (di Prampero and Ferretti 1990).

When a manipulation, either chronic or acute, affects $\dot{V}\,\mathrm{O}_{2\mathrm{max}}$ without affecting $P_I\mathrm{O}_2$, and thus ΔP_T, the observed increase in $\dot{V}\,\mathrm{O}_{2\mathrm{max}}$ is the result of changes in one or more of the resistances in series. Thus, the model was devised in such a manner as to provide a value for the fraction of the overall $\dot{V}\,\mathrm{O}_{2\mathrm{max}}$ limitation which any given in-series resistance is responsible for. For instance, aerobic training provides a given $\dot{V}\,\mathrm{O}_{2\mathrm{max}}$ increase, $\Delta\dot{V}\,\mathrm{O}_{2\mathrm{max}}$, because some resistances (at least three in this case, namely R_Q, R_t and R_m) have decreased, and so has R_T. Thus, after training has induced a measurable increase in $\dot{V}\,\mathrm{O}_{2\mathrm{max}}$ with respect to the value before training, Eq. (4.5) can be rewritten as follows:

$$\dot{V}\,\mathrm{O}_{2\mathrm{max}} + \Delta\dot{V}\,\mathrm{O}_{2\mathrm{max}} = \frac{P_I\mathrm{O}_2}{(R_\mathrm{T} + \Delta R_\mathrm{T})} \tag{4.8}$$

If we divide Eq. (4.5) by Eq. (4.8), we get:

$$\frac{\dot{V}\,\mathrm{O}_{2\mathrm{max}}}{\left(\dot{V}\,\mathrm{O}_{2\mathrm{max}} + \Delta\dot{V}\,\mathrm{O}_{2\mathrm{max}}\right)} = 1 + \frac{\Delta R_\mathrm{T}}{R_\mathrm{T}} \tag{4.9}$$

which, since ΔR_T is the sum of the changes in the *i*th resistances in series, it can also take the following form:

$$\frac{\dot{V}\,\mathrm{O}_{2\mathrm{max}}}{(\dot{V}\,\mathrm{O}_{2\mathrm{max}} + \Delta\dot{V}\,\mathrm{O}_{2\mathrm{max}})} = 1 + \frac{(\Delta R_\mathrm{V} + \Delta R_\mathrm{L} + \Delta R_\mathrm{Q} + \Delta R\mathrm{p})}{R_\mathrm{T}} \tag{4.10}$$

As a consequence of Eqs. (4.3) and (4.4), the induction of a change in any resistance by a manoeuvre specifically acting on it yields:

$$\frac{\Delta R_i}{R_\mathrm{T}} = F_i \cdot \frac{\Delta R_i}{R_i} \tag{4.11}$$

So, Eq. (4.10) can be rewritten as follows:

$$\frac{\dot{V}\,O_{2max}}{\left(\dot{V}\,O_{2max}+\Delta\dot{V}\,O_{2max}\right)}=1+F_V\frac{\Delta R_V}{R_V}+F_L\frac{\Delta R_L}{R_L}+F_Q\frac{\Delta R_Q}{R_Q}+F_p\frac{\Delta R_p}{R_p} \quad (4.12)$$

Equation (4.12) has four unknowns and as such cannot be solved. However, if we take a condition wherein only one resistance is varied by an acute manipulation, as is the case, according to di Prampero and Ferretti (1990), for R_Q after acute blood reinfusion or withdrawal, three terms of Eq. (4.12) annihilate. Thus, we remain with a simplified version of it, with only one unknown. For the specific case of changes in R_Q only, Eq. (4.12) takes therefore the following form:

$$\frac{\dot{V}\,O_{2max}}{\left(\dot{V}\,O_{2max}+\Delta\dot{V}\,O_{2max}\right)}=1+F_Q\frac{\Delta R_Q}{R_Q} \quad (4.13)$$

Equation (4.13) allows computation of F_Q, provided we know the $\dot{V}\,O_{2max}$ before and after the manoeuvre, the R_Q before the manoeuvre and the absolute change in R_Q induced by the manoeuvre. An analytical solution of Eq. (4.13), using data from different sources in the literature, is reported in Fig. 4.3, where the ratio between the $\dot{V}\,O_{2max}$ values before and after the manoeuvre (left-hand branch of Eq. 4.13) is plotted as a function of the ratio between ΔR_Q and R_Q. Equation (4.13) tells that this relationship is linear, with y-intercept equal to 1 and slope equal to F_Q. From linear regression analysis of the data shown in Fig. 4.3, di Prampero and Ferretti (1990) obtained $F_Q = 0.70$. This means that R_Q provides 70 % of the fractional limitation of $\dot{V}\,O_{2max}$.

An F_Q value equal to 0.70 implies that **the respiratory system does not have linear behaviour**. In fact, for a linear respiratory system, the ratio of any given R_i to R_T would be equal to the ratio of the pressure gradient over that R_i to the overall pressure gradient, so that:

$$F_Q=\frac{(PaO_2-P\bar{v}O_2)}{P_IO_2} \quad (4.14)$$

from which we would have obtained $F_Q = 0.50$ instead of 0.70 (di Prampero and Ferretti 1990). The source of nonlinearity, and thus the source of this discrepancy, was identified in the effects of the oxygen equilibrium curve on β_b, as shown in Fig. 4.4. Assume that an acute manoeuvre acts directly on R_V only, e.g. reducing it. This would increase P_AO_2, and thus PaO_2, but would not change the associated CaO_2, because in normoxia our blood operates on the flat portion of the oxygen equilibrium curve. Therefore, since $P\bar{v}O_2$ undergoes only small changes, β_b would be reduced, and thus R_Q would be increased. In sum, because of the shape of the oxygen equilibrium curve, as long as we are in normoxia, a specific manoeuvre acting only on R_V cannot have effects on $\dot{V}\,O_{2max}$, because any change in R_V would

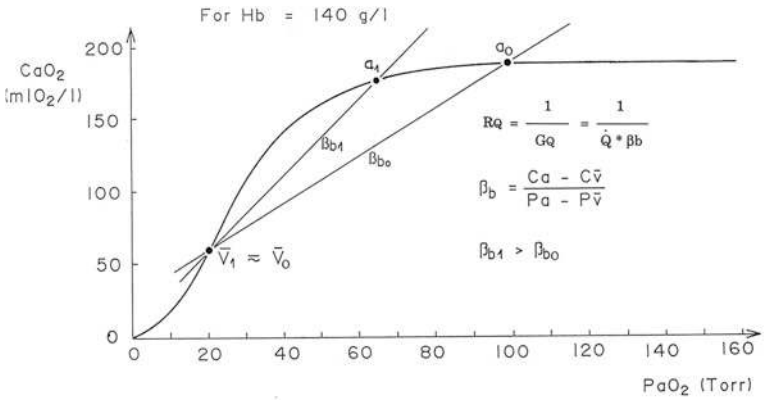


Fig. 4.4 Average oxygen equilibrium curve. Two arterial and mixed venous points are reported, applying to normaemia (a_0, $\bar{v}_0$) and hypoxaemia (a_1, $\bar{v}_1$). The two straight lines connecting the two couples of points have a slope equal to the respective oxygen transport coefficients for blood (β_b), which is higher in hypoxaemia than in normaemia. As a consequence, when an increase in the ventilatory resistance R_V entails a decrease in arterial oxygen partial pressure, β_b becomes higher and the cardiovascular resistance R_Q lower. These two phenomena compensate each other, so that no changes in $\dot{V}O_{2max}$ are induced by an acute change in R_V: the lungs do not limit $\dot{V}O_{2max}$ in normoxia. Modified after di Prampero (1985)

be counteracted by an opposite change in R_Q: **in normoxia, R_V and R_L do not limit $\dot{V}O_{2max}$**. Using a different terminology, this is the case when perfusion limitation characterises the alveolar-capillary gas transfer. Thus, the effects of the respiratory system on $\dot{V}O_{2max}$ can be fully described by a two-site model wherein the effective limitation is located distally to PaO_2. This explains why $F_Q = 0.7$ instead of 0.5, so that we necessarily have $F_p = 0.3$, partly attributable to F_t, partly to F_m. According to Ferretti et al. (1997a), the differences in $\dot{V}O_{2max}$ would be minimal, if we assume, on one extreme, $R_t = R_p$, and on the other extreme, $R_m = R_p$, and that it makes no difference to assume R_t and R_m in series or in parallel. Direct experimental assessment of the parameters of Eq. (4.13) confirmed that F_Q in normoxia is between 0.65 and 0.76 (Bringard et al. 2010; Turner et al. 1993).

Experimental Testing of di Prampero's Model

The nonlinear behaviour of the respiratory system implies that within the context of di Prampero's model (i) R_V and R_L do limit $\dot{V}O_{2max}$ in hypoxia; (ii) F_Q in hypoxia is less than 0.7; (iii) the decrease of $\dot{V}O_{2max}$ in hypoxia is larger in subjects with high $\dot{V}O_{2max}$ in normoxia; (iv) only subjects with high $\dot{V}O_{2max}$ in normoxia undergo an increase in $\dot{V}O_{2max}$ in hyperoxia; (v) exercise with small muscle masses reduces F_Q and increases F_p; (vi) the fall of $\dot{V}O_{2max}$ in hypoxia is smaller, the

smaller is the contracting muscle mass. Moreover, since the cause of the nonlinear behaviour of the respiratory system is related to the shape of the oxygen equilibrium curve, there must be a linear relationship between $\dot{V}\,O_{2max}$ and SaO_2.

To investigate the roles played by R_V and R_L in normoxia and hypoxia, Esposito and Ferretti (1997) changed the air density of the inspired gas mixture by replacing nitrogen with helium, thus reducing R_V. Although $\dot{V}_A$ increased in both cases, $\dot{V}\,O_{2max}$ did not change when breathing the He–O_2 mixture in normoxia, going up only in hypoxia. Similar results were recently obtained also by Ogawa et al. (2010). Consistently, no effects of respiratory muscle training were shown on $\dot{V}\,O_{2max}$ in normoxia, but a positive effect was observed in hypoxia (Downey et al. 2007; Esposito et al. 2010).

On two groups of subjects, one with high, the other with low $\dot{V}\,O_{2max}$ in normoxia, Ferretti et al. (1997b) found that, in the former with respect to the latter group, (i) the decrease in $\dot{V}\,O_{2max}$ in hypoxia was larger, and (ii) a significant increase in $\dot{V}\,O_{2max}$ in hyperoxia occurred. Moreover, they found a highly significant linear relationship between $\dot{V}\,O_{2max}$, expressed relative to the value in hyperoxia set equal to 100 %, and SaO_2, which was identical in both groups, in agreement with the above predictions. According to Wehrlin and Hallén (2006), the $\dot{V}\,O_{2max}$ of endurance athletes is so high that the decrease of $\dot{V}\,O_{2max}$ in hypoxia becomes linear. Coherent with this picture is also the finding that the $\dot{V}\,O_{2max}$ decrease in hypoxia is smaller the stronger is the ventilatory response to hypoxia (Benoit et al. 1995; Gavin et al. 1998; Kayser et al. 1994; Marconi et al. 2004).

An Analysis of Wagner's Model

Peter Wagner (1993) constructed a three-equation system with three unknowns (P_AO_2, P_aO_2 and $P_{\bar{v}}O_2$) by combining the mass conservation equation for blood (Fick principle) and the two diffusion–perfusion interaction equations (Piiper and Scheid 1981; Piiper et al. 1984). At steady state, all these equations must have equal solutions for $\dot{V}\,O_{2max}$. The algebraic development of the system led to three equations allowing a solution for P_AO_2, P_aO_2 and $P_{\bar{v}}O_2$. These equations lead to a unique, necessary $\dot{V}\,O_{2max}$ value for any combination of known values of P_IO_2, $\dot{V}_A$, D_L, $\dot{Q}$, β_b and D_t at maximal exercise (Wagner 1993). Wagner's system of equations implies a vision of the oxygen cascade with two mass balance equations responsible for convective oxygen transfer, associated with two conductive components, described by the diffusion–perfusion interaction equations. This vision is conceptually different from di Prampero's, who conceived a pure hydraulic system of in-series resistances. Proximally, the interaction of a convective component with a diffusive component sets the maximal flow of oxygen in arterial blood ($\dot{Q}aO_{2max}$), and this is the first step in the system. Distally, the interaction of a convective component (Fick principle) with a diffusive component (the diffusion–perfusion

interaction equation setting oxygen flow from peripheral capillaries to the muscle fibres) sets $\dot{V}\,O_{2max}$.

The Fick equation can take either of the following solutions:

$$\dot{V}\,O_{2max} = \dot{Q} \cdot (CaO_2 - C\bar{v}O_2) = \dot{Q} \cdot \beta_b \cdot (P_aO_2 - P_{\bar{v}}O_2) \tag{4.15}$$

The term β_b in Eq. (4.15) implies a nonlinear negative relationship between $\dot{V}\,O_{2max}$ and $P_{\bar{v}}O_2$ (**convective curve**), the algebraic expression of which depends on the solution that is given to the oxygen equilibrium curve. Concerning the diffusive component, it is described by the following equation:

$$\dot{V}\,O_{2max} = DtO_2 \cdot (P_{\bar{c}}O_2 - P_mO_2) \tag{4.16}$$

where DtO_2 is tissue diffusing capacity for oxygen and P_mO_2 is again equal to 0 mmHg. However, the right branches of Eqs. (4.15) and (4.16) do not share any term, so that they cannot as such be compared on the same plot. To circumvent this obstacle, Wagner assumed direct proportionality between $P_{\bar{v}}O_2$ and $P_{\bar{c}}O_2$, arguing that the segment of the oxygen equilibrium curve between these two pressure values is essentially linear, so that within that segment β_b can be considered invariant. On this basis, he reformulated Eq. (4.16) as follows:

$$\dot{V}\,O_{2max} = DtO_2 \cdot K_p \cdot P_{\bar{v}}O_2 \tag{4.17}$$

where K_p is the dimensionless constant relating $P_{\bar{v}}O_2$ and $P_{\bar{c}}O_2$. Equation (4.17) implies a positive linear relationship between $\dot{V}\,O_{2max}$ and $P_{\bar{v}}O_2$ (**diffusion line**), which Roca et al. (1989) determined experimentally. The slope of the line is equal to the product $DtO_2 \cdot K_p$, which Ferretti (2014) called Wagner's constant, K_W. Equations (4.15) and (4.17) generate analytical relationships that, if we plot $\dot{V}\,O_{2max}$ on the y-axis and $P_{\bar{v}}O_2$ on the x-axis, can be represented on the same graph and directly compared (Fig. 4.5). In this figure, the resulting $\dot{V}\,O_{2max}$ for any combination of $\dot{Q}aO_{2max}$ and K_W corresponds to the intersection of the two functions, which occurs at a precise value of $P_{\bar{v}}O_2$.

Experimental Testing of Wagner's Model

Concerning the diffusive component, a decrease in DtO_2 implies, in Fig. 4.5, a decrease in K_W, whence a drop of $\dot{V}\,O_{2max}$ and an increase in $P_{\bar{v}}O_2$. The reverse is caused by an increase in DtO_2. This is virtually impossible to test in humans with acute manoeuvres acting on DtO_2, the most important determinant of K_W. Moreover, DtO_2 is affected by haemoglobin concentration (Schaffartzik et al. 1993). Wagner (1996a) predicted quite accurately the effects of chronic alterations of DtO_2 on $\dot{V}\,O_{2max}$ and $P_{\bar{v}}O_2$ in patients affected by chronic obstructive pulmonary disease,

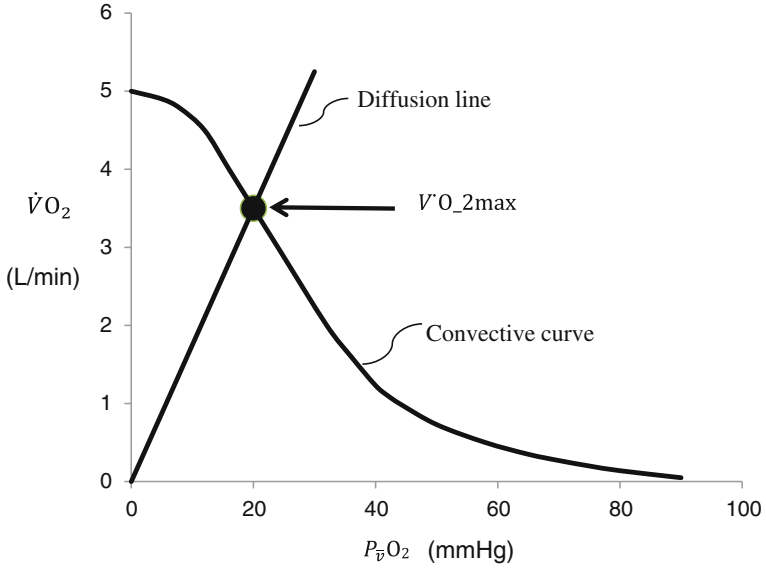


Fig. 4.5 Graphical representation of Wagner's model. Oxygen uptake ($\dot{V}O_2$) is plotted as a function of mixed venous oxygen pressure ($P_{\bar{v}}O_2$). The curve with negative slope is Wagner's convective curve. The straight line with positive slope is Wagner's diffusion line, whose slope is equal to Wagner's constant K_W. The convective curve intercepts the y-axis at a $\dot{V}O_2$ equal to arterial oxygen flow ($\dot{Q}aO_2$), which is the case when $K_W = \infty$. The same curve intercepts the x-axis when $P_{\bar{v}}O_2$ is equal to arterial oxygen pressure, which is the case when $K_W = 0$. The $\dot{V}O_{2max}$ value is found on the crossing of the convective curve with the diffusion line (full dot). After Ferretti (2014)

once allowance was made for the simultaneous impairment of cardiovascular oxygen transport. If direct proportionality between K_W and muscle capillary density is assumed, an analysis of literature data of muscle morphometry and $\dot{V}O_{2max}$ of altitude-acclimatized climbers (Hoppeler et al. 1990; Oelz et al. 1986) or endurance-trained subjects (Hoppeler et al. 1985) led to $P_{\bar{v}}O_2$ values coherent with Wagner's predictions (Ferretti 2014).

On the convective curve, an increase in the product of $\dot{Q}$ times β_b carries along an increase in both $\dot{V}O_{2max}$ and $P_{\bar{v}}O_2$. This explains, in Wagner's model, the effects of acute polycythaemia and anaemia on $\dot{V}O_{2max}$ (Ekblom et al. 1976; Woodson et al. 1978): the convective curve is displaced upwards and becomes steeper. The intercept on the x-axis of the convective curve corresponds to the P_aO_2 point, i.e. the point at which $P_{\bar{v}}O_2 = P_aO_2$. Hyperoxia displaces this point to the right, implying a slightly higher $\dot{V}O_{2max}$, because the rightward displacement of the P_aO_2 point increases the slope of the convective curve (makes it less negative), so that the diffusion line is intercepted at a higher $\dot{V}O_{2max}$ value. The reverse occurs in hypoxia. The y-intercept of the convective curve corresponds to the $\dot{Q}aO_{2max}$ point,

representing the condition in which $\dot{V}\,O_{2max} = \dot{Q}aO_{2max}$ (Wagner 1995, 1996a). The case of hypoxia is treated in a separate paragraph (see **Of Maximal Oxygen Consumption in Hypoxia**). Controversial is the case of hyperoxia. Although Fig. 4.5 predicts an increase in $\dot{V}\,O_{2max}$, such an increase was rarely observed in humans, the only clear effects having been observed in individuals with elevated $\dot{V}\,O_{2max}$, who are subject to the Dempsey effect (Dempsey and Wagner 1999; Dempsey et al. 1984; Powers et al. 1989). Richardson et al. (1999) were able to observe a $\dot{V}\,O_{2max}$ increase during single-leg exercise only when they used pure oxygen breathing. The thoroughbred horse, a highly athletic animal characterized by deep hypoxaemia at maximal exercise, was proposed as the nicest example supporting the prediction of elevated $\dot{V}\,O_{2max}$ in hyperoxia (Wagner 1996a; Wagner et al. 1989, 1996). This apparent discrepancy between theoretical predictions and experimental data is hard to explain, and the hypotheses put forward so far are scarcely convincing, so that the issue still remains open.

In the context of Wagner's model, athletes have elevated $\dot{V}\,O_{2max}$ because they have high K_W and a simultaneously upward displacement of the convective curve. The opposite occurs with muscle disuse and with ageing. Changing haemoglobin oxygen affinity changes the shape of the convective curve.

A Critical Comparison of the Two Models

The two models share the notion that $\dot{V}\,O_{2max}$ is set by multiple factors, despite their different vision of the oxygen cascade theory. Both models have difficulties in dealing with that black box related to the effects of $\dot{V}_A/\dot{Q}$ heterogeneity. Wagner skipped it by stating that they are negligible in normoxia, di Prampero artificially included them in R_L, but without a specific quantitative analysis. The different approach to the oxygen cascade theory entailed some conceptual differences between the two models, as summarized in Table 4.1. The exclusion by both models of a $\dot{V}\,O_{2max}$ limitation imposed by pulmonary ventilation and oxygen diffusion capacity in healthy non-athletic humans in normoxia implied that both finally focused only on what goes on distally to P_aO_2. This facilitates a comparison of the two models. The critical comparison of the two models which I propose herewith is based on the reasoning developed elsewhere (Ferretti 2014).

Equations (4.15) and (4.17) are common to the two models. The former defines *RQ*, since, because of Eq. (4.6b):

$$\dot{V}\,O_{2max} = \dot{Q} \cdot \beta_b \cdot (P_aO_2 - P_{\bar{v}}O_2) = \frac{1}{R_Q} \cdot (P_aO_2 - P_{\bar{v}}O_2) \tag{4.18}$$

Table 4.1 Main apparent differences between the two multifactorial models of $\dot{V}\,O_{2max}$ limitation

Wagner's model	di Prampero's model
Blood oxygen transport	
Purely convective element	One of many resistances in series
Hydraulic model of in-series resistances	
Partially applicable	Fully applicable
Pressure gradient at alveolar level	
$P_AO_2 - P_{\bar{c}}O_2$	$P_AO_2 - P_aO_2$
Pressure gradient in blood circulation	
No oxygen pressure difference	$P_aO_2 - P_{\bar{v}}O_2$
Peripheral diffusion	
Imposed by mean capillary pressure	Imposed by $P_{\bar{v}}O_2$
Role of $P_{\bar{v}}O_2$	
End point of the diffusion process	Driving pressure for diffusion

P_AO_2, alveolar oxygen partial pressure; $P_{\bar{c}}O_2$, mean capillary oxygen partial pressure; P_aO_2, arterial oxygen partial pressure; $P_{\bar{v}}O_2s$, mixed venous oxygen partial pressure

In turn, Eq. (4.17), for $P_mO_2 = 0$ mmHg, defines R_p, since

$$\dot{V}\,O_{2max} = DtO_2 \cdot K_p \cdot P_{\bar{v}}O_2 = K_W \cdot P_{\bar{v}}O_2 = \frac{1}{R_p} \cdot P_{\bar{v}}O_2 \tag{4.19}$$

which indicates that Wagner's constant K_W is the reciprocal of R_p, i.e. G_p. As a consequence of Eqs. (4.18) and (4.19), Fig. 4.5 can receive a different, novel interpretation. According to Eq. (4.19), the slope of the diffusive line becomes equal to G_p, or $1/R_p$. The y-intercept of the same line on the origin of the axes, where $P_{\bar{v}}O_2 = 0$ mmHg, indicates that all oxygen delivered to the active muscle mass is extracted, so that $F_p = 0$. Concerning the convective curve, Eq. (4.18) implies a nonlinear relationship in which the slope is equal to $-\dot{Q} \cdot \beta_b$, i.e. $-G_Q$, or $-1/R_Q$. The y-axis intercept of this line, equal to $\dot{Q}\,aO_2$, implies that $\dot{V}\,O_{2max} = \dot{Q}\,aO_{2max}$ and, according to di Prampero's model, $F_Q = 1$. This means that Wagner's model includes two terms that characterize di Prampero's model: R_Q and R_p, and the respective fractional limitations.

If we accept that indeed the lungs do not limit $\dot{V}\,O_{2max}$ in normoxia, the simplified version of di Prampero's model, describing the flow of oxygen downstream of the lungs, can be treated as linear, so that

$$F_Q = \frac{(P_aO_2 - P_{\bar{v}}O_2)}{P_aO_2} = \frac{R_Q}{(R_Q + R_p)} \tag{4.20}$$

whence

$$\frac{1}{F_{\mathrm{Q}}} = \frac{(R_{\mathrm{Q}} + R_{\mathrm{p}})}{R_{\mathrm{Q}}} = 1 + \frac{R_{\mathrm{p}}}{R_{\mathrm{Q}}} = 1 + \frac{G_Q}{G_{\mathrm{p}}} \tag{4.21}$$

Equation (4.21) expresses F_{Q} in terms of ratio between the slopes of Eqs. (4.18) and (4.19). Moreover, we know that

$$\dot{Q}\, a\mathrm{O}_{2\max} = \dot{Q} \cdot Ca\mathrm{O}_2 = \dot{Q} \cdot \beta_b \cdot P_a\mathrm{O}_2 \tag{4.22}$$

Dividing Eq. (4.18) by Eq. (4.22), we get the following equation:

$$\frac{\dot{V}\,\mathrm{O}_{2\max}}{\dot{Q}\, a\mathrm{O}_{2\max}} = \frac{\dot{Q} \cdot (Ca\mathrm{O}_2 - C\bar{v}\mathrm{O}_2)}{\dot{Q} \cdot Ca\mathrm{O}_2} = \frac{\dot{Q} \cdot \beta_b \cdot (P_a\mathrm{O}_2 - P_{\bar{v}}\mathrm{O}_2)}{\dot{Q} \cdot \beta_b \cdot P_a\mathrm{O}_2} = \frac{(P_a\mathrm{O}_2 - P_{\bar{v}}\mathrm{O}_2)}{P_a\mathrm{O}_2} \tag{4.23}$$

which is just a different way of expressing Eq. (4.20), whence

$$\frac{\dot{V}\,\mathrm{O}_{2\max}}{\dot{Q}\, a\mathrm{O}_{2\max}} = F_{\mathrm{Q}} \tag{4.24}$$

This implies that F_{Q} **in normoxia is equal to the oxygen extraction coefficient!**

Equation (4.24) confirms that if $\dot{V}\,\mathrm{O}_2 = \dot{Q}\, a\mathrm{O}_2$ (y-axis intercept of the convective curve in Fig. 4.5), $F_{\mathrm{Q}} = 1$ and thus $F_{\mathrm{p}} = 0$: all oxygen delivered to peripheral capillaries is consumed by mitochondria. On the contrary, when $\dot{V}\,\mathrm{O}_2 = 0$ (x-axis intercept of the convective curve in Fig. 4.5, where $P_{\bar{v}}\mathrm{O}_2 = P_a\mathrm{O}_2$), $F_{\mathrm{Q}} = 0$, and thus $F_{\mathrm{p}} = 1$, and $R_{\mathrm{p}} = \infty$ or $K_{\mathrm{W}} = 0$ (diffusive curve coincident with the x-axis): no oxygen flows from capillaries to mitochondria. All intermediate solutions of Eq. (4.24) fall somewhere between these two extremes on the convective curve, at the intersection with the corresponding diffusive line. The closer is the intersection to the $P_a\mathrm{O}_2$ point, the lower is K_{W}, and thus the higher are R_{p} and F_{p} and the lower is F_{Q}. The relationship between F_{Q} and $P_{\bar{v}}\mathrm{O}_2$ (Fig. 4.6) is nothing but a representation the convective curve, on a plot where $\dot{V}\,\mathrm{O}_2$ is expressed relative to $\dot{Q}\, a\mathrm{O}_2$.

The diffusion–perfusion interaction equation for peripheral capillaries (Piiper et al. 1984) is as follows:

$$P_{\bar{v}}\mathrm{O}_2 = P_a\mathrm{O}_2 \cdot e^{-D_{\mathrm{t}}/(\dot{Q} \cdot \beta_b)} \tag{4.25}$$

Combining Eqs. (4.15) and (4.25), we then obtain the following equation:

$$\dot{V}\,\mathrm{O}_{2\max} = \dot{Q}_{\max} \cdot \beta_b \cdot P_a\mathrm{O}_2 \left[1 - e^{-D_{\mathrm{t}}/(\dot{Q} \cdot \beta_b)}\right] = \dot{Q}\, a\mathrm{O}_{2\max} \cdot \left[1 - e^{-D_{\mathrm{t}}/(\dot{Q} \cdot \beta_b)}\right] \tag{4.26}$$

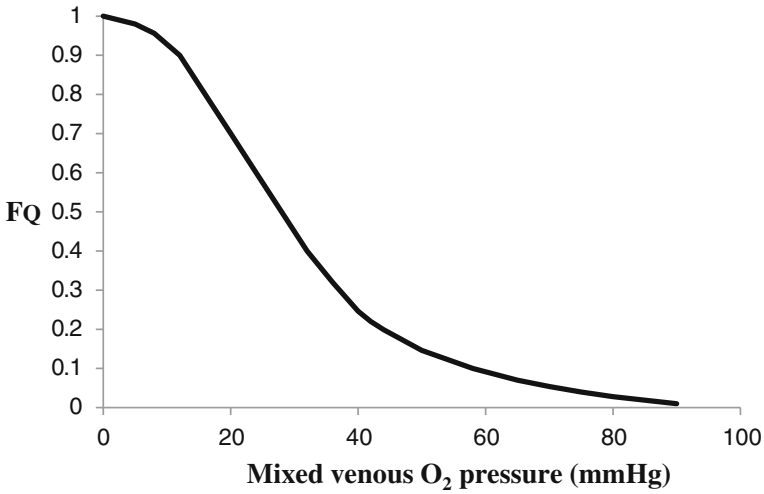


Fig. 4.6 Fractional limitation to $\dot{V}\,O_{2max}$ imposed by the cardiovascular oxygen transport system (F_Q) in normoxia as a function of mixed venous oxygen pressure. From Ferretti (2014)

whence

$$\frac{\dot{V}\,O_{2max}}{\dot{Q}\,aO_{2max}} = F_Q = 1 - e^{-D_t/(\dot{Q}\cdot\beta_b)} \tag{4.27}$$

and

$$F_p = 1 - F_Q = \frac{P_{\bar{v}}O_2}{P_aO_2} = e^{-D_t/(\dot{Q}\cdot\beta_b)} \tag{4.28}$$

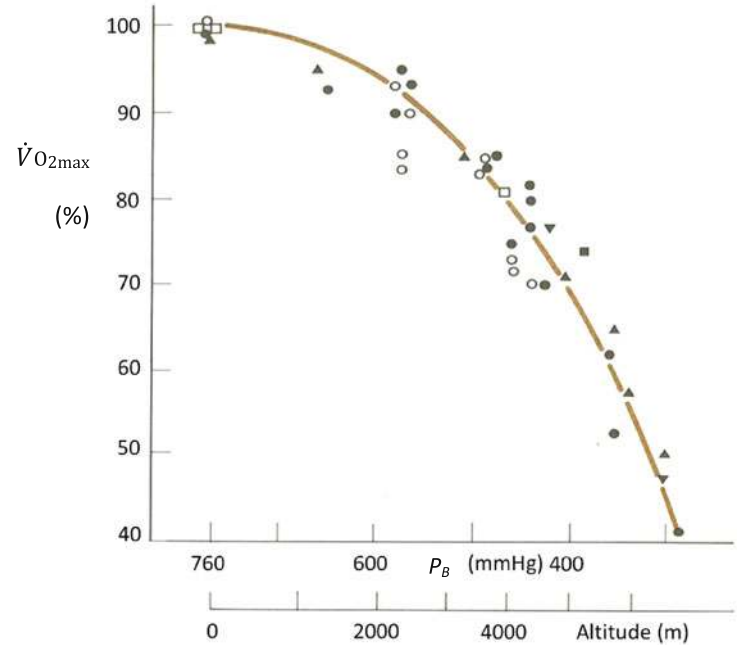
This implies that the exponent of Eq. (4.25) is the natural logarithm of F_p, an equivalence allowing inclusion of the diffusion–perfusion interaction equation for peripheral capillaries in di Prampero's model, and representing a further step towards a more complete representation of the quantitative relations describing oxygen flow at maximal exercise. Incidentally, I note that F_Q is a constant whose value is invariant in normoxia, and so is, according to Eq. (4.27), the $D_t/(\dot{Q}\cdot\beta_b)$ ratio. This provides further theoretical support to Wagner's assumption of a direct proportionality between $P_{\bar{v}}O_2$ and $P_{\bar{c}}O_2$.

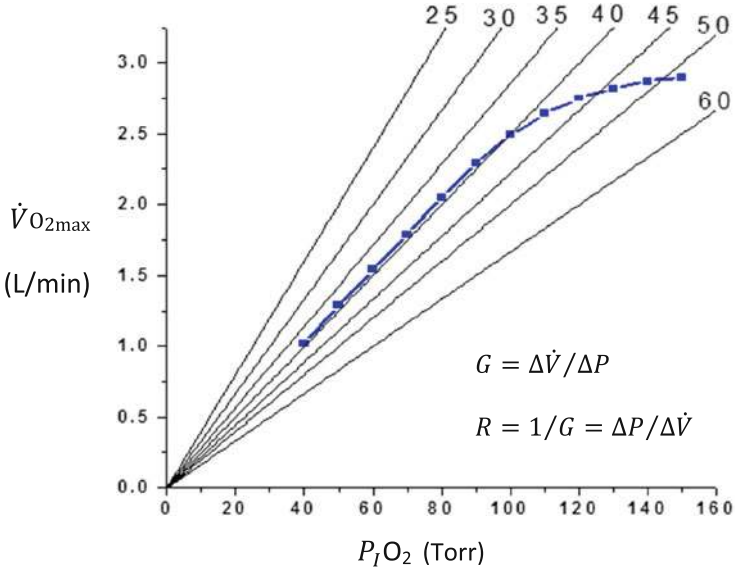
This analysis justifies the statement that di Prampero's model and Wagner's model converge on the same conclusion, namely that both cardiovascular oxygen transport and muscle oxygen diffusion and utilization are necessary determinants of $\dot{V}\,O_{2max}$, the former being responsible for the larger fraction of the overall $\dot{V}\,O_{2max}$ limitation (some 70 %, according to di Prampero and Ferretti 1990).

Of Maximal Oxygen Consumption in Hypoxia

$\dot{V}O_{2max}$ decreases in hypoxia, both acute and chronic (see for review Cerretelli 1980; Ferretti 1990; Cerretelli and Hoppeler 1996; Ferretti 2014). Conversely, exposure to elevated inspired oxygen pressures leads only to slight, if any, increases in $\dot{V}O_{2max}$, the effect being evident only in endurance athletes (Ferretti et al. 1997b), who are subject to the Dempsey effect. It is smaller, the smaller is the active muscle mass (Cardus et al. 1998). The main cause of the $\dot{V}O_{2max}$ decrease in hypoxia is the drop of P_IO_2. However, the $\dot{V}O_{2max}$ decrease is small at altitudes below 3000 m above sea level, much smaller than one would expect after the curves of barometric pressure decrease at altitude (West et al. 1983). I already mentioned some aspects of nonlinear behaviour of the respiratory system as a consequence of the shape of the oxygen equilibrium curve, and the linear relationship between $\dot{V}O_{2max}$ and SaO_2: this implies that a linear decrease of $\dot{V}O_{2max}$ in hypoxia appears only as we have a drop of SaO_2. This does not occur as long as blood operates on the flat portion of the oxygen equilibrium curve. We need a decrease in P_aO_2 as big as that required to attain the steep part of the oxygen equilibrium curve before finding significant falls of $\dot{V}O_{2max}$. In other terms, as P_IO_2 decreases, and thus P_aO_2 decreases, β_b goes up, because the decrease in P_aO_2 is not accompanied by an equivalent decrease in CaO_2: as a consequence, R_Q falls. This reduces R_T, thus correcting for the effect of the decrease in P_IO_2. It is only after the steep part of the oxygen equilibrium curve has been attained, that P_IO_2 and R_Q do not change anymore and the drop of $\dot{V}O_{2max}$ becomes linear (see Fig. 4.7). The curve describing the $\dot{V}O_{2max}$ decrease in hypoxia is a kind of mirror image of the oxygen equilibrium curve (Ferretti et al. 1997b). Ferretti and di Prampero (1995) analysed the interrelations between R_Q and R_V in hypoxia, showing that as we approximate the steep part of the oxygen equilibrium curve, the role of the lungs in limiting $\dot{V}O_{2max}$ becomes more important: these authors calculated that in extreme hypoxia F_Q may decrease down to 0.20 with F_V going up to about 0.35. This analysis led to several predictions that could be tested experimentally. The effects of hypoxia on $\dot{V}O_{2max}$ were indeed found to be, as predicted: (i) larger the higher is the subject's $\dot{V}O_{2max}$ in normoxia (Ferretti et al. 1997b; Gavin et al. 1998; Koistinen et al. 1995; Wehrlin and Hallén 2006), because of the Dempsey effect; (ii) smaller the more intense is the ventilatory response to hypoxia (Giesbrecht et al. 1991; Marconi et al. 2004; Ogawa et al. 2007).

A most fundamental work on the determinants of $\dot{V}O_{2max}$ at altitude was carried out by Cerretelli (1976), who showed that, if altitude-acclimatized polycythaemic subjects living at the Everest base camp are given to breathe a gas mixture containing a P_IO_2 equivalent to that existing at sea level (acute normoxia), their $\dot{V}O_{2max}$, that was expected to become higher than that measured in Milano before the Mount Everest expedition, did not even return to the level observed in Milano. Those were still times of a mono-factorial vision of $\dot{V}O_{2max}$ limitation, so this finding was taken as a demonstration that the muscles, rather than the


$\dot{V}O_{2max}$
(%)
100
90
80
70
60
50
40
760
600
P_B (mmHg) 400
0
2000
4000
Altitude (m)


$\dot{V}O_{2max}$
(L/min)
25
30
35
40
45
50
60
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
20
40
60
80
100
120
140
160
$G = \Delta\dot{V}/\Delta P$
$R = 1/G = \Delta P/\Delta\dot{V}$
P_IO_2 (Torr)

◀**Fig. 4.7** *Top panel* Fall of maximal oxygen consumption ($\dot{V}O_{2max}$) at altitude. $\dot{V}O_{2max}$ is expressed relative to the value observed at sea level, set equal to 100 %. Two *x*-axes are shown, one indicating barometric pressure (P_B), the other, below, indicating altitude. Open and full dots refer, respectively, to acute and chronic hypoxia. Data from Cerretelli (1980). *Bottom panel* Same curve as on top, calculated for a sea level $\dot{V}O_{2max}$ of 2.8 L min^{-1} (Cerretelli and di Prampero 1987), where P_B is replaced by the inspired oxygen pressure (P_IO_2), corresponding to the overall oxygen pressure gradient. The straight lines converging on the origin of the axes have a slope ($\Delta\dot{V}/\Delta P$) equal to the overall oxygen conductance of the respiratory system (G). The modest $\dot{V}O_{2max}$ decrease at low altitude is a consequence of the simultaneous increase in G (decrease in resistance R), due to the effects of the shape of the oxygen equilibrium curve. From Ferretti (2014)

cardiovascular system, were limiting $\dot{V}O_{2max}$ at altitude. This conclusion prompted several morphological studies, unanimously showing the reduction of muscle oxidative capacity as a consequence of altitude acclimatization (for a review, se Cerretelli and Hoppeler 1996; Hoppeler et al. 2008). Great surprise at the time was generated by the observation that the climbers who reached the highest summits on Earth without supplementary oxygen had relatively low $\dot{V}O_{2max}$ in normoxia, much lower than that of endurance athletes (Oelz et al. 1986). In fact, since athletes undergo a bigger fall of $\dot{V}O_{2max}$ in hypoxia, the differences in $\dot{V}O_{2max}$ which we may observe at sea level disappear on the top of Mount Everest.

In the context of multifactorial models of $\dot{V}O_{2max}$ limitation, the data by Cerretelli (1976) deserve a different interpretation. Administering oxygen at 150 mmHg to Cerretelli's subjects at Everest base camp was tantamount to changing three parameters pertaining to the oxygen conductance equation: (i) the overall oxygen gradient was higher, because the P_IO_2 was increased; (ii) the maximal $\dot{Q}$ was increased (it was measured indeed); and (iii) β_b was lowered. In fact, the increase in P_IO_2 induced a subsequent increase in P_AO_2 and in P_aO_2, so that the arterial blood point was moved onto the flat part of the oxygen equilibrium curve. Since the mixed venous blood point on the oxygen equilibrium was only slightly displaced under these conditions, the average slope of the oxygen equilibrium curve was remarkably reduced, whence the reduction of β_b. Within di Prampero's model, this means a reduction of G_Q with a consequent increase in R_Q in subjects with elevated R_p as a consequence of reduced muscle oxidative capacity. Within Wagner's model, this means changing the convective curve and elevating the $\dot{Q}aO_{2max}$ point and the P_aO_2 point in subjects with a flatter diffusive line as a consequence of reduced muscle oxidative capacity. Indeed Cerretelli's experiment, although taken as a demonstration of the muscular limitation of $\dot{Q}aO_{2max}$, provided a most brilliant confirmation of the predominant role of cardiovascular oxygen transport in limiting $\dot{V}O_{2max}$! (Ferretti 2003)

The apparent divergence of the two multifactorial models of $\dot{V}O_{2max}$ limitation in hypoxia depends only on the fact that Wagner keeps looking at the respiratory system distally to P_aO_2, di Prampero tried to integrate the effects of R_V and R_L, which in hypoxia, contrary to normoxia, become limiting steps. Within Wagner's

model, hypoxia implies a displacement downwards and leftwards of the convective curve, which lacks its flat part at high $P_{\bar{v}}O_2$, because it covers only the steep part of the oxygen equilibrium curve (Fig. 4.8). With regard to the diffusive line, its slope appears reduced because of the decreased mitochondrial oxidative capacity, despite the increased capillary density. Using data from Operation Everest II, Wagner (1996b) demonstrated the linearity of the oxygen equilibrium curve in hypoxia in the $P_aO_2 - P_{\bar{v}}O_2$ pressure range. If we admit a linear oxygen equilibrium curve, and thus of an invariant β_b, the oxygen conductance equation takes a linear solution, so that the effective oxygen pressure gradient in di Prampero's model is given by P_IO_2 instead of P_aO_2. Thus, we obtain the following equation:

$$F_Q = \frac{\dot{V}O_{2max}}{\dot{Q}aO_{2max}} \cdot \frac{P_aO_2}{P_IO_2} \tag{4.29}$$

If we solve Eq. (4.29) using the data of Operation Everest II reported by Wagner (1996b), we get $F_Q = 0.19$, a value that is very close to the theoretical value of 0.20

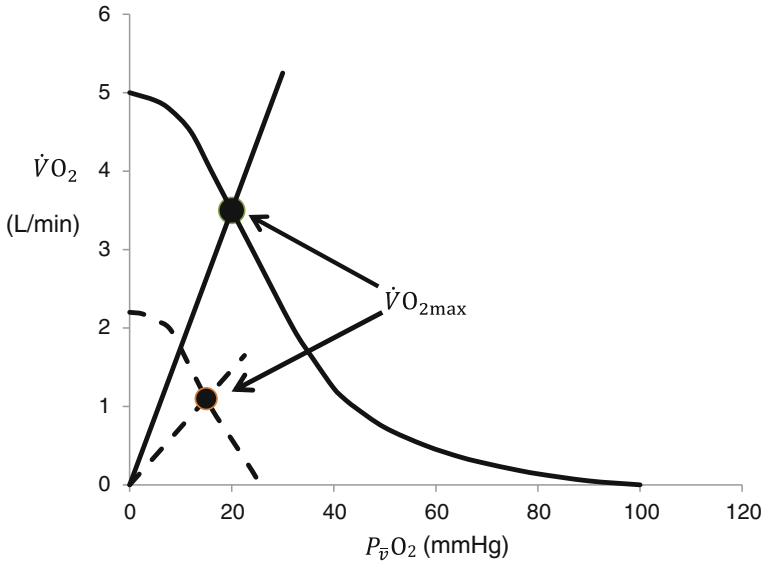


Fig. 4.8 Graphical representation of Wagner's model in extreme hypoxia. Oxygen uptake ($\dot{V}O_2$) is plotted as a function of mixed venous oxygen pressure ($P_{\bar{v}}O_2$). Continuous lines represent the convective curve and the diffusion line, as from Fig. 4.5. Dashed lines refer to the convective curve and the diffusion line in hypoxia. Concerning the convective curve in hypoxia, it lacks the flattening part at high $P_{\bar{v}}O_2$ values, because we operate exclusively of the steep part of the oxygen equilibrium curve. The diffusion line has lower slope in hypoxia than in normoxia, indicating the decrease of Wagner's constant K_W in hypoxia. In normoxia, arterial oxygen partial pressure was assumed equal to 100 mmHg, and $P_{\bar{v}}O_2$ was assumed equal to 20 mmHg. The data of Operation Everest II (Wagner 1996b) were used for the construction of the convective curve and of the diffusion line in hypoxia. After Ferretti (2014)

obtained by Ferretti and di Prampero (1995) in their simulation. On the other hand, we would obtain

$$F_{\mathrm{p}} = \left(1 - \frac{\dot{V}\,\mathrm{O}_{2\mathrm{max}}}{\dot{Q}\,a\mathrm{O}_{2\mathrm{max}}}\right) \cdot \frac{P_a\mathrm{O}_2}{P_I\mathrm{O}_2} \tag{4.30}$$

whence, using the same data, $F_{\mathrm{p}} = 0.22$. Wagner (1996b) pointed out the predominance of the peripheral diffusing component in setting $\dot{V}\,\mathrm{O}_{2\mathrm{max}}$ variations as a consequence of acute manoeuvres in extreme hypoxia. This viewpoint is shared by this analysis within di Prampero's model.

Of Maximal Oxygen Consumption at the End of Bed Rest

Physical training and prolonged bed rest are the most common tools that can be used to induce functional adaptive variations along the entire respiratory system, leading to simultaneous changes in more than one in-series resistance to oxygen flow in the oxygen cascade, and thus in $\dot{V}\,\mathrm{O}_{2\mathrm{max}}$. A huge number of papers on the effects of training on $\dot{V}\,\mathrm{O}_{2\mathrm{max}}$, its determinants and generally speaking human performance in health and disease can be retrieved in the physiological literature (for review, see e.g. Blomqvist and Saltin 1983; Booth et al. 2012; Bouchard et al. 2011; Cerretelli and di Prampero 1987; Coyle 1995; Gibala et al. 2012; Hagberg 1987; Hoppeler 1986; Hoppeler et al. 2008; Howald 1982; Rogers and Evans 1993; Rowell 1974; Saltin 1977). Unfortunately, no standardization of exercise training protocols can be reckoned in the literature: training intensity and duration, exercise modes, modality of power administration are so different, that transversal analyses across the literature are virtually impossible. Conversely, bed rest without countermeasures is an excellent, well-controlled adaptive condition in which the entire respiratory system undergoes functional adaptations entailing a change in $\dot{V}\,\mathrm{O}_{2\mathrm{max}}$. Therefore, the present analysis of the factors that limit $\dot{V}\,\mathrm{O}_{2\mathrm{max}}$ after overall adaptive changes in the respiratory system relies specifically on studies concerning prolonged bed rest without countermeasures. Moreover, in this experimental model, only the duration of the bed rest period varies among studies, allowing a precise evaluation of the time courses of the functional modifications induced by bed rest.

$\dot{V}\,\mathrm{O}_{2\mathrm{max}}$ decreases after bed rest (Bringard et al. 2010; Capelli et al. 2006; Convertino et al. 1982; Ferretti et al. 1997a; Greenleaf et al. 1989; Kashihara et al. 1994; Saltin et al. 1968; Stremel et al. 1976; Trappe et al. 2006), even of very short duration (Smorawinski et al. 2001). The size of the $\dot{V}\,\mathrm{O}_{2\mathrm{max}}$ decrease is larger the longer is the bed rest duration, being fast in the first days, and progressively slower as bed rest proceeds. This means that the change in $\dot{V}\,\mathrm{O}_{2\mathrm{max}}$ in upright posture at the end of bed rest, as a function of bed rest duration, is nonlinear, tending to an asymptote (Capelli et al. 2006). It is kept implicit that these statements apply to

$\dot{V}\,O_{2max}$ measurements in upright posture shortly after the end of the bed rest period. In fact, this is not so during bed rest (or space flight), or in supine posture after bed rest, since very small changes, if any, in $\dot{V}\,O_{2max}$ were found in these conditions (Bringard et al. 2010; Greenleaf et al. 1989; Levine et al. 1996; Trappe et al. 2006).

The time course of $\dot{V}\,O_{2max}$ changes in upright posture at the end of head-down tilt bed rest without countermeasures is shown in Fig. 4.9, on the assumption of an exponential $\dot{V}\,O_{2max}$ decay. Linearization of the same relationship, after its expression in logarithmic form (Ferretti and Capelli 2009), allows clear identification of two components in the $\dot{V}\,O_{2max}$ decline with bed rest. The algebraic formulation of the $\dot{V}\,O_{2max}$ decline with bed rest would then take the following form:

$$\dot{V}\,O_{2max,t} - \dot{V}\,O_{2max,a} = (\dot{V}\,O_{2max,0} - \dot{V}\,O_{2max,a})\left(e^{-k_1 \cdot t}\right)\left(e^{-k_2 \cdot t}\right) \tag{4.31}$$

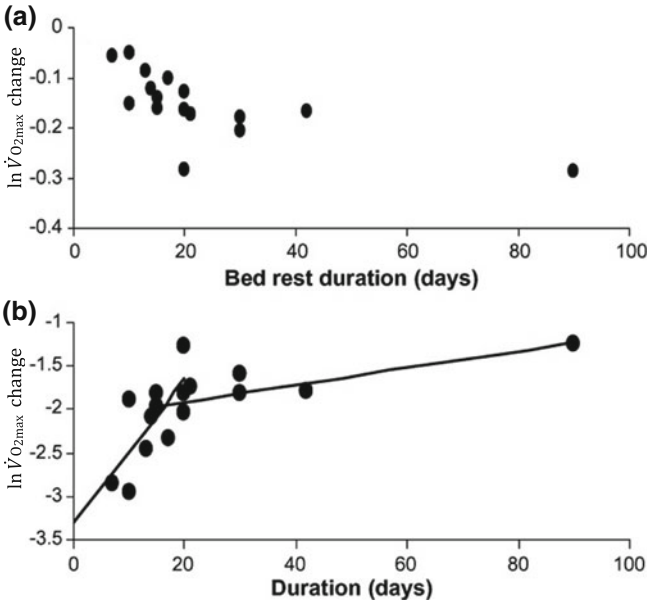


Fig. 4.9 *Top panel* The change in maximal oxygen consumption ($\dot{V}\,O_{2max}$) in upright posture, at the end of bed rest or space flight, is expressed as the absolute change in $\dot{V}\,O_{2max}$ with respect to the corresponding pre-bed rest value and plotted as a function of bed rest duration. *Bottom panel* Same as on top, except that the change in $\dot{V}\,O_{2max}$ is expressed in logarithmic form. The lines are regression lines calculated for bed rests lasting less than 20 days and longer than 20 days, respectively. The slopes of the two lines indicate the velocity constant of the rapid (0.083 day^{-1}) and the slow (0.0098 day^{-1}) components of the $\dot{V}\,O_{2max}$ decrease. The corresponding time constants are 8.4 and 70.7 days, respectively. From Ferretti and Capelli 2009

where $\dot{V}\,O_{2max,\,0}$, $\dot{V}\,O_{2max,\,a}$ and $\dot{V}\,O_{2max,\,t}$ are the $\dot{V}\,O_{2max}$ values before bed rest, at the asymptote of the $\dot{V}\,O_{2max}$ decrease and at time t during bed rest, respectively, and k_1 and k_2 are the velocity constants of the two components of the $\dot{V}\,O_{2max}$ decrease during bed rest (slope of the straight lines of the bottom panel of Fig. 4.9), for which values of 0.083 day^{-1} and 0.0098 day^{-1} were obtained, respectively. The corresponding time constants were equal to 8.4 and 70.7 days, respectively.

According to Ferretti (2014), Fig. 4.9 shows that the distal part of respiratory system, from arterial blood to the mitochondria, may consist of two capacitances of different size connected in series. When an adaptive change takes place on the overall system, the effects on the smaller capacitance initially prevail, imposing a rapid change in $\dot{V}\,O_{2max}$ already in the first days, leading to an asymptote within short, one month in this case. This makes the effects on the second, larger capacitance more important (and detectable), whence a further, though slower, $\dot{V}\,O_{2max}$ decline. The fast component of the $\dot{V}\,O_{2max}$ decrease after bed rest was attributed to changes in R_Q and thus to the reduction of $\dot{Q}\,aO_{2max}$, whereas the slow component was related to changes in R_p and thus to muscle hypotrophy. Concerning R_Q, note that the decrease of $\dot{Q}_{max}$ in upright posture after the end of bed rest appears to be complete after a bed rest duration of 15 days only. Concerning R_p, the apparent time constant of the decrease of lower-limb muscle cross-sectional area during bed rest, as reckoned from different sources in the literature, corresponds well to that of the slower component of the $\dot{V}\,O_{2max}$ decrease (Capelli et al. 2006). Obviously enough, the effects of muscle mass reduction on $\dot{V}\,O_{2max}$ intervene since the first days in bed, but since they are slow and relatively small, they are not visible in short-term bed rest, being overcome by the more rapid cardiovascular changes.

Another factor possibly affecting the magnitude of the $\dot{V}\,O_{2max}$ decline after bed rest is the day after reambulation at which the test was carried out. In most of the studies used for the construction of Fig. 4.9, $\dot{V}\,O_{2max}$ was measured at least three days after the end of bed rest, at a time when recovery of cardiovascular function was already taking place (Spaak et al. 2005), so that the amplitude of the rapid component of the $\dot{V}\,O_{2max}$ decline might have been underestimated, especially when the bed rest duration was short. Only exceptions were the studies by Bringard et al. (2010) and Lee et al. (2007, 2009), with measurements carried out on the day of reambulation. The results from these studies, for which the bed rest duration was 35 and 30 days, respectively, compared well with those from other studies, perhaps because there was already a significant impact of the slow component of the $\dot{V}\,O_{2max}$ decline, the recovery of which is expected to be slower than that of the rapid cardiovascular component.

Similar results in upright posture were reported, upon return from a 17-day space flight, by Levine et al. (1996), who conversely found no changes in $\dot{V}\,O_{2max}$ on the same subjects in space. They attributed the $\dot{V}\,O_{2max}$ decline observed in upright posture upon return to the effects of sudden blood volume redistribution after gravity resumption, which are enhanced in Astronauts who underwent cardiovascular adaptation to microgravity. I would add that this is the case also after bed rest.

The data of Levine et al. (1996), however, were obtained at the end of a space flight, the duration of which was barely too short to evidence the effects of the slower component of the $\dot{V}O_{2max}$ decline, related to muscle hypotrophy. This component in fact was already visible, after the same time, in the study by Trappe et al. (2006) in space and in supine posture after bed rest. Bringard et al. (2010) found a 44 % reduction of stroke volume at maximal exercise in upright posture after 35-day bed rest as compared to the value before bed rest with no modification in maximal heart rate: the consequence was a 45 % decrease in maximal $\dot{Q}$. This results, associated with a 13 % increase in CaO_2 due to higher haemoglobin concentration, originated a 38 % decrease in $\dot{Q}aO_{2max}$. In the same study, no changes in maximal $\dot{Q}$ were observed in supine posture after bed rest, so that there was a slight, though non-significant, increase in $\dot{Q}aO_{2max}$. So, it turned out that after bed rest, $\dot{Q}aO_{2max}$ was 56 % lower and R_Q 78 % higher, upright than supine: an acute postural change from supine to upright entailed a $\dot{V}O_{2max}$ decrease only due to changes in R_Q. Similar results were obtained after Levine et al. (1996), when comparing the $\dot{V}O_{2max}$ data in flight with those obtained upright shortly after landing from space flight.

Figure 4.10 reports a representation of di Prampero's model for the case of prolonged bed rest, using the data of Bringard et al. (2010). The continuous line represents the theoretical F_Q value of 0.7 as from di Prampero's model. The open symbols lying on it refer to the acute manoeuvre of moving from supine to upright, before and after 35-day bed rest. The full dots lying above it refer to the overall effect of bed rest, in supine—lower left point—and upright—upper right point—posture. The quantity of the upward shift of open symbols with respect to the filled points is the same for both postures, indicating that the factor that caused the $\dot{V}O_{2max}$ decrease supine after bed rest acted by the same extent also in the upright posture. This means that this factor is independent of the acute postural change. According to Bringard et al. (2010), the upward shift of open symbols represents the effects of a change in R_p consequent to the development of muscle hypotrophy.

In the context of Wagner's model, the increase in R_p due to muscle hypotrophy translates into a decrease in the slope of the diffusion line, whereas the cardiovascular effect is represented by the downward shift of the $\dot{Q}aO_2$ point, with consequent change in the slope of the convective curve (Fig. 4.11). The results of this analysis provide full quantitative justification to the concept of the dual component of the $\dot{V}O_{2max}$ decrease after bed rest. In more general terms, I feel confident in stating that whenever there is an overall adaptive phenomenon that changes the size of the resistances along the entire oxygen cascade, the time course of the ensuing $\dot{V}O_{2max}$ changes is characterized by more than one exponential. If changes are in opposite directions, they may compensate each other; if compensation is complete, no effect on $\dot{V}O_{2max}$ would be visible. If changes are homodirectional, they add the one to the other, and the final effect on $\dot{V}O_{2max}$ would depend on the ensuing fractional

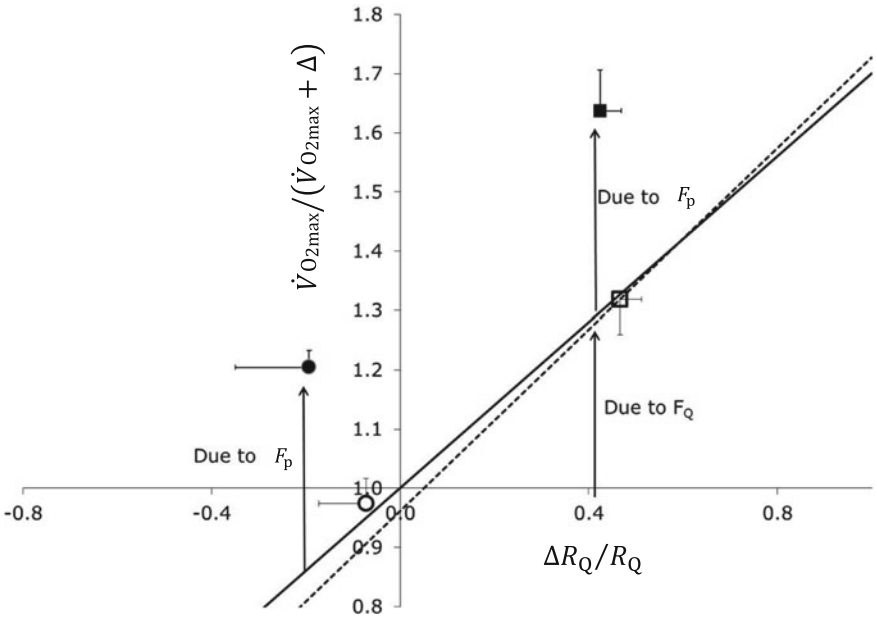


Fig. 4.10 The ratio between maximal oxygen consumption ($\dot{V}O_{2max}$) before and after a given manoeuvre [$\dot{V}O_{2max}/(\dot{V}O_{2max}+\Delta)$, *y*-axis] is plotted as a function of the relative change in the cardiovascular resistance to oxygen flow ($\Delta R_Q/R_Q$, x-axis). The continuous line, with a slope of 0.7, is the theoretical line obtained by di Prampero and Ferretti (1990) after an analysis of the literature. The open symbols concern the effects of postural changes from supine to upright before (open dot) and after (open square) bed rest. The dashed line is experimental and represents the regression equation calculated on the data of Bringard et al. (2010) after bed rest (y = 0.76x + 0.96). The slope of the experimental line did not differ significantly from that of the theoretical line. The y-intercept of the experimental line was not significantly different from 1. The filled symbols, located well above the experimental line, refer to the effects of bed rest in supine (filled dot) and upright (filled square). Error bars indicate standard error. The arrows highlight the effect on $\dot{V}O_{2max}$ due to cardiovascular (F_Q) and peripheral (F_p) $\dot{V}O_{2max}$ limitation. From Ferretti (2014)

limitation of $\dot{V}O_{2max}$ imposed by the various in-series resistances, or on the point on a Cartesian plane where the modified convective curve and diffusion line intersect.

Of the Central Governor Hypothesis

The models of $\dot{V}O_{2max}$ limitation accounted for in this chapter are the two mechanistic models that were generated in the context of the oxygen cascade theory and of the multifactorial approach to the subject of the factors that limit $\dot{V}O_{2max}$. They currently are the only $\dot{V}O_{2max}$ limitation models that can be analysed within the context of the general theory of the energetics of muscular exercise. As such, they

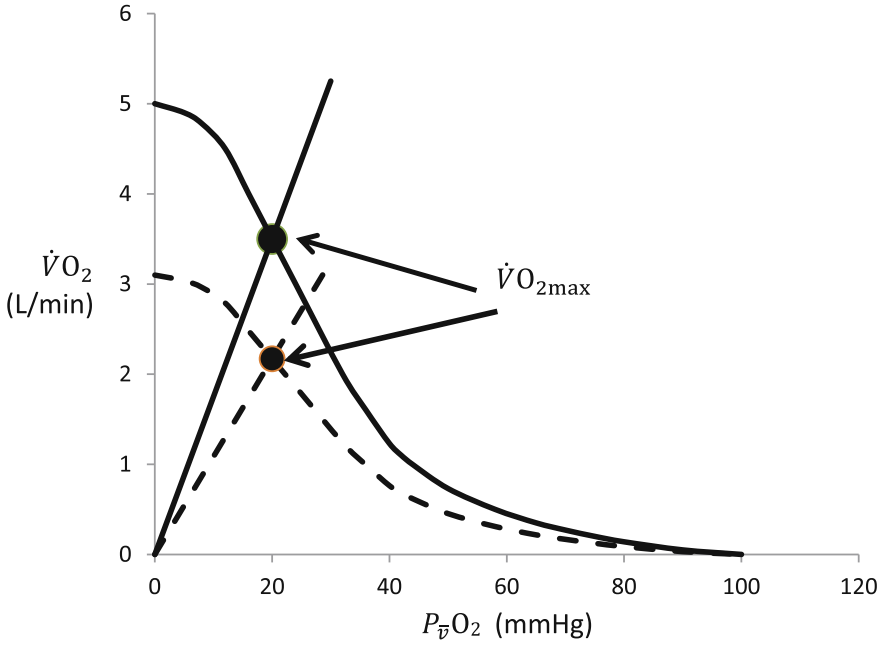


Fig. 4.11 Graphical representation of the effects of bed rest on maximal oxygen consumption in the context of Wagner's model. Oxygen uptake ($\dot{V}O_2$) is plotted as a function of mixed venous oxygen pressure ($P_{\bar{v}}O_2$). Continuous lines are the convective curve and the diffusion line, as from Fig. 4.5, assumed to represent the control condition before bed rest. Dashed lines refer to the convective curve and the diffusion line after bed rest in upright posture calculated after the data of Ferretti et al. (1997a, b). Concerning the convective curves, the one after bed rest is flatter than the one before bed rest, because of the dramatic decrease in arterial oxygen flow after bed rest. The diffusion line after bed rest indicates the decrease of Wagner's constant K_W, due to the development of muscle hypotrophy. Arterial oxygen partial pressure was assumed unchanged and equal to 100 mmHg. The $P_{\bar{v}}O_2$ in the control condition was assumed equal to 20 mmHg

account for most of the physiological observations carried out so far at maximal exercise and they have resisted remarkably well experimental testing. They currently represent the core of the contemporary debate on this issue. Nevertheless, in recent years, a different approach to the subject of $\dot{V}O_{2max}$ limitation has also gained momentum, which I would define the psychological model of $\dot{V}O_{2max}$ limitation: the central governor hypothesis (Noakes 1998; Noakes et al. 2001). In the form it is usually formulated, it states that the central nervous system (central governor) controls the cardiovascular system during maximal exercise in such a way as to hinder its ability to fully exploit its capacity in order to prevent the insurgence of heart ischaemia. Thus, according to the central governor hypothesis, $\dot{V}O_{2max}$ is only a consequence of the amount of work that the heart is allowed to

perform by the central nervous system. The direct consequence of this statement is that $\dot{V}O_{2max}$ would have to do neither with the ability of the respiratory system to transport oxygen to the contracting muscle mass nor with the capacity of muscle fibres to consume oxygen and sustain aerobic metabolism.

This hypothesis has the charm of simplicity, as compared to the multifactorial models, and gained appeal by selling itself as an example of modernity, for its attempt at placing the brain as the controller of the entire organism at maximal exercise. In fact, its lack of quantitative analysis of the structural and functional mechanisms that underlie changes in $\dot{V}O_{2max}$ makes it difficult to perform an experimental testing of the central governor hypothesis, so that its epistemological value is undermined. For these reasons, several authors denied its scientific characteristics and rejected it simply on the subsequently presumed inability of experimental falsification of this hypothesis. Nevertheless, after some years, a way to submit the central governor hypothesis to experimental testing was figured out, demonstrating its scientific characteristics, but at the same time leading to its clear confutation (Brink-Elfegoun et al. 2007). These authors in fact showed that it was possible to increase the work of the heart beyond the limits attained at maximal exercise, without any further increase in $\dot{V}O_{2max}$. These results were in contrast to the central governor hypothesis, as long as it predicts that $\dot{V}O_{2max}$ would increase whenever the central governor (the brain) allows an increase in heart functional variables. A similar experiment was carried out a few years later (Elliott et al. 2015), with similar results. Curiously enough, and in spite of the evidence, these authors refused to admit refutation of the central governor hypothesis, although they recognized the experimental evidence as a matter of fact, providing one of the most impressive examples of dogmatism in physiological science.

Of Measuring $\dot{V}O_{2max}$

The classical protocol for $\dot{V}O_{2max}$ measurement is the incremental discontinuous steady-state protocol, by which $\dot{V}O_{2max}$ is identified as the plateau attained by the relationship between "steady-state" oxygen consumption ($\dot{V}O_2$) and power ($\dot{w}$) (Fig. 4.1). The $\dot{w}$ at which the plateau is attained was defined as the maximal mechanical aerobic power ($\dot{w}_{max}$). In fact, if we abstract from phase III as classically was the case (see below for a discussion of this issue), $\dot{w}_{max}$ would correspond to the minimal $\dot{w}$ requiring a $\dot{V}O_2$ equal to $\dot{V}O_{2max}$. The performance of the classical protocol, whose standardized procedure is described in details in the Åstrand textbook (Åstrand et al. 2003), requires the execution of exercise steps of progressively increasing intensity lasting between 4 and 6 min. The $\dot{V}O_2$ is measured during the last minute of each step. The duration of the steps may be reduced as the expected maximal power is approached. This may be predicted from heart rate

measurements. Successive steps are separated by resting recovery periods, lasting some 5–6 min, during which the peak lactate concentration can be measured for each step. Incidentally, this allows construction of lactate—power curves, on which the so-called lactate threshold may also be identified.

The classical protocol was thought to allow a direct measurement of the actual $\dot{w}_{max}$, which is unequivocally identified as the $\dot{w}$ at the crossing between the $\dot{V}O_{2max}$ plateau and the line describing the $\dot{V}O_2$ versus $\dot{w}$ relationship (Åstrand et al. 2003; di Prampero 1981; Howley et al. 1995; Taylor et al. 1955). The $\dot{V}O_{2max}$ plateau, however, is not observable in all tests. The incidence of the $\dot{V}O_{2max}$ plateau depends on the modality of exercise administration (Gordon et al. 2012). In the absence of a clear $\dot{V}O_{2max}$ plateau, subsidiary criteria for the establishment of $\dot{V}O_{2max}$ were proposed. These include: (i) a lack of increase in heart rate between successive workloads; (ii) a respiratory exchange ratio value ≥1.1; (iii) blood lactate concentration higher than 10 mM at maximal exercise; and (iv) a rate of perceived exertion on the Borg scale of at least 19/20 (Åstrand et al. 2003). When at least two of these subsidiary criteria are met at the end of the test, the identification of $\dot{V}O_{2max}$ is ensured (Howley et al. 1995). In the absence of a plateau, if at least two of the subsidiary criteria hold, the $\dot{w}$ corresponding to the highest measured $\dot{V}O_{2max}$ can be retained as the $\dot{w}_{max}$ of the test. In holding with these criteria, I note that when a $\dot{V}O_{2max}$ test is followed by a constant-power exercise of supramaximal intensity, no further increase in $\dot{V}O_{2max}$ is observed (Hawkins et al. 2007).

In addition to the classical protocol, a variety of procedures, either continuous or discontinuous, were proposed in the last decades to measure $\dot{V}O_{2max}$. After the introduction of commercial breath-by-breath metabolic carts and the development of electro-magnetically braked cycle ergometers, the **continuous ramp protocols** (Buchfuhrer et al. 1983) have achieved worldwide diffusion, progressively replacing the classical discontinuous protocol, because they have much shorter duration and lower cost than the classical protocol, being normally completed within 12 min. This makes ramp protocols convenient also in current sport medicine practice.

Ramp protocols and the classical discontinuous protocol yield the same values of $\dot{V}O_{2max}$; moreover, the $\dot{V}O_{2max}$ attained at the end of ramp protocols is independent of the ramp characteristics (Adami et al. 2013; Amann et al. 2004; Duncan et al. 1997; Maksud and Coutts 1971; Morton et al. 1997; Zhang et al. 1991). Yet ramp protocols generate higher peak mechanical powers ($\dot{w}_{peak}$) at the end of the tests, the greater is the mean slope of the ramp (Adami et al. 2013; Morton et al. 1997). This means that the $\dot{w}_{peak}$ attained in a ramp test depends on the protocol characteristics, being unrelated to $\dot{V}O_{2max}$. So, it does not correspond to the $\dot{w}_{max}$.

The concept of a strict relation between $\dot{V}O_{2max}$ and $\dot{w}_{max}$ was undermined also by the identification of the slow component of the $\dot{V}O_2$ kinetics (see Chap. 3). The slow component, implying a continuous increase of $\dot{V}O_2$ until exhaustion,

precludes the attainment of a steady state at high intensity exercise. Therefore, the linearity of the $\dot{V}O_2$ versus $\dot{w}$ relationship along the entire power range, a crucial element for the identification of $\dot{w}_{max}$ in Fig. 4.1, was questioned. The slow component may indeed become visible within the first 5 min of exercise. In this time window, however, the effects of the slow component may be counteracted by an opposite effect due to the slowing of primary component of the $\dot{V}O_2$ kinetics at elevated powers, with associated early lactate accumulation (di Prampero and Ferretti 1999). Although these two effects may cancel out, so that the points on an individual $\dot{V}O_2$ versus power relationship, which we may obtain from a classical protocol, may well be aligned on a given straight line along the entire power range, this alignment may be accidental. In fact, in contrast to this concept, Zoladz et al. (1995), who used a continuous protocol which amplifies the role of the slow component, showed an upward shift of the $\dot{V}O_2$ values at the highest powers before the attainment of the peak power, thus obtaining a nonlinear $\dot{V}O_2$ versus power relationship, at variance with what is usually found with the classical protocol.

As already discussed in Chap. 3, if we accept exponential models of the $\dot{V}O_2$ kinetics, we can identify at each $\dot{w}$ the asymptote of the primary component (phase II amplitude), actually present at all powers between rest and maximal exercise. To this asymptote, we may then add, at intense exercise only, at least above the critical power, a phase III amplitude, whose steady state might be attained at $\dot{V}O_2$ levels higher than the maximum, and therefore invisible experimentally. If we admit that, as hypothesized in Chap. 3, phase II and phase III do not refer to the same phenomena, only the former would represent the metabolic power sustaining muscle contraction in aerobic conditions. In this case, the classical steady-state $\dot{V}O_2$, directly proportional to the applied mechanical power, would correspond to the steady state of phase II only. This redefines the meaning of Fig. 4.1 and of $\dot{w}_{max}$, which becomes the highest power at which the contracting muscle mass can deliver metabolic power from aerobic sources with a mechanical efficiency around 0.25. This is not, of course, the highest power attained during a $\dot{V}O_{2max}$ test, which depends on the protocol characteristics, whereas the rate of energy expenditure corresponding to $\dot{w}_{max}$ may be less than $\dot{V}O_{2max}$, being closer to it the larger is the active muscle mass. If this is so, the classical protocol would not provide a direct measure of $\dot{w}_{max}$; it would rather provide the best possible estimate of it. Note also that, as discussed in Chap. 5, there is a strong link between $\dot{w}_{max}$ and critical power, which are bound to vary together and by the same absolute amount. The concept of $\dot{w}_{max}$ still remains a crucial concept in exercise physiology, even if its meaning has changed as a consequence of the identification of the slow component.

To sum up, if one is to measure $\dot{V}O_{2max}$, he can rely on any type of ramp protocol. Conversely, if one is to measure also $\dot{w}_{max}$, ramp protocols are inadequate, and the classical discontinuous protocols are questioned, but still remain the most useful tool for this aim.

Conclusions

There is growing consensus around the concept of multifactorial $\dot{V}O_{2max}$ limitation. In this context, two sets of equations were created, defining mechanistic models, both capable of explaining several aspects of $\dot{V}O_{2max}$ limitation, often the same. These models competed for years, although they were pointing to the same direction, being formulations of the same concepts in different terms. A statement like "cardiovascular oxygen transport provides 70 % of the overall limitation to $\dot{V}O_{2max}$" implies that the crossing of the diffusion line with the convective curve of Fig. 4.7 necessarily occurs only at one precise point on a Cartesian plane, the point on the convective curve where the ratio between $\dot{V}O_{2max}$ and $\dot{Q}aO_{2max}$ is equal to 0.7.

In hypoxia, where also the lungs become limiting, di Prampero tried to include R_V and R_L in the analysis. The consequence was a diminution of F_Q from 0.7 in normoxia to 0.2 at a P_IO_2 of 90 mmHg (Ferretti and di Prampero 1995), so that F_Q became much lower than the $\dot{V}O_{2max}/\dot{Q}a\dot{V}O_{2max}$ ratio. This is not necessarily a holistic expansion of di Prampero's model: the model remains the same, but Ferretti and di Prampero (1995) tried a speculative analysis which Wagner (1996a) refrained from doing, and perhaps with a good reason, at least to my mind: the inability of accounting for the effects of $\dot{V}_A/\dot{Q}$ heterogeneity on R_L and F_L. The attempt by Ferretti and di Prampero (1995) to circumvent the problem by creating a lumped conductance term for the alveolar–arterial step, which was assumed proportional to D_L, was an oversimplification.

The classical concept of cardiovascular $\dot{V}O_{2max}$ limitation is reinforced by the multifactorial models, showing that cardiovascular oxygen transport—represented in the form of either systemic or muscle oxygen delivery—provides most of the limitation to oxygen flow at maximal exercise, at least in normoxia. However, the same models show that the role of peripheral oxygen diffusion and utilization as limiting factors is such that it cannot be neglected. The role of peripheral factors is greater the smaller is the active muscle mass. In hypoxia, the progressive intervention of lung oxygen flow as a limiting factor restricts the role played by cardiovascular and muscular factors. Moreover, the balance between them is changed in favour of a greater role of peripheral factors. As a consequence, F_Q in hypoxia turns out drastically reduced.

References

Adami A, Sivieri A, Moia C, Perini R, Ferretti G (2013) Effects of step duration in incremental ramp protocols on peak power and maximal oxygen consumption. Eur J Appl Physiol 113:2647–2653

Amann M, Subudhi A, Foster C (2004) Influence of testing protocol on ventilatory thresholds and cycling performance. Med Sci Sports Exerc 36:613–622

Andersen P, Henriksson J (1977) Capillary supply of the quadriceps skeletal muscle of man: adaptive response to exercise. J Physiol 270:677–690

Andersen P, Saltin B (1985) Maximal perfusion of skeletal muscle in man. J Physiol 366:233–249

Åstrand PO, Rodahl K, Dahl HA, Strømme SB (2003) Textbook of work physiology. Physiological bases of exercise, 4th ed. Human Kinetics, Champaign

Åstrand PO, Saltin B (1961) Maximal oxygen uptake and heart rate in various types of muscular activity. J Appl Physiol 16:977–981

Benoit H, Busso T, Castells J, Denis C, Geyssant A (1995) Influence of hypoxic ventilatory response on arterial O_2 saturation during maximal exercise in acute hypoxia. Eur J Appl Physiol 72:101–105

Berg HE, Dudley GA, Hather B, Tesch PA (1993) Work capacity and metabolic and morphologic characteristics of the human quadriceps muscle in response to unloading. Clin Physiol 13:337–347

Bergh U, Kanstrup IL, Ekblom B (1976) Maximal oxygen uptake during exercise with various combinations of arm and leg work. J Appl Physiol 41:191–196

Blomqvist CG, Saltin B (1983) Cardiovascular adaptations to physical training. Annu Rev Physiol 45:169–189

Booth FW (1982) Effect of limb immobilization on skeletal muscle. J Appl Physiol 52:1113–1118

Booth FW, Roberts CK, Laye MJ (2012) Lack of exercise is a major cause of chronic diseases. Compr Physiol 2:1143–1211

Bouchard C, Rankinen T, Timmons JA (2011) Genomics and genetics in the biology of adaptation to exercise. Compr Physiol 1:1603–1648

Bringard A, Pogliaghi S, Adami A, De Roia G, Lador F, Lucini D, Pizzinelli P, Capelli C, Ferretti G (2010) Cardiovascular determinants of maximal oxygen consumption in upright and supine posture at the end of prolonged bed rest in humans. Respir Physiol Neurobiol 172:53–62

Brink-Elfegoun T, Kaijser L, Gustafsson T, Ekblom B (2007) Maximal oxygen uptake is not limited by a central nervous system governor. J Appl Physiol 102:781–786

Brodal P, Ingjer F, Hermansen L (1977) Capillary supply of skeletal muscle fibers in untrained and endurance-trained men. Am J Physiol Heart Circ Physiol 232:H705–H712

Buchfuhrer MJ, Hansen JE, Robinson TE, Sue DY, Wasserman K, Whipp BJ (1983) Optimizing the exercise protocol for cardio-pulmonary assessment. J Appl Physiol 55:1558–1564

Buick FJ, Gledhill N, Froese AB, Spriet LL, Meyers EC (1980) Effect of induced erythrocythemia on aerobic work capacity. J Appl Physiol 48:636–642

Calbet JA, Gonzalez-Alonso J, Helge JW, Søndergaard H, Munch-Andersen T, Boushel R, Saltin B (2007) Cardiac output and leg and arm blood flow during incremental exercise to exhaustion on the cycle ergometer. J Appl Physiol 103:969–978

Calbet JAL, Jensen-Urstad M, Van Hall G, Holmberg HC, Rosdahl H, Saltin B (2004) Maximal muscular vascular conductances during whole body upright exercise in humans. J Physiol 558:319–331

Calbet JAL, Rådegran G, Boushel R, Saltin (2009) On the mechanisms that limit oxygen uptake during exercise in acute and chronic hypoxia: role of muscle mass. J Physiol 587:477–490

Capelli C, Antonutto G, Azabji-Kenfack M, Cautero M, Lador F, Moia C, Tam E, Ferretti G (2006) Factors determining the time course of $\dot{V}O_{2max}$ decay during bedrest: implications for $\dot{V}O_{2max}$ limitation. Eur J Appl Physiol 98:152–160

Cardus J, Marrades RM, Roca J, Barbera JA, Diaz O, Mascians JR, Rodriguez-Roisin R, Wagner PD (1998) Effect of FIO_2 on leg $\dot{V}O_2$ during cycle ergometry in sedentary subjects. Med Sci Sports Exerc 30:697–703

Celsing F, Svedenhag J, Pihlstedt P, Ekblom B (1987) Effects of anaemia and stepwise-induced polycythaemia on maximal aerobic power in individuals with high and low haemoglobin concentrations. Acta Physiol Scand 129:47–54

Cerretelli P (1976) Limiting factors to oxygen transport on Mount Everest. J Appl Physiol 40:658–667

Cerretelli P (1980) Gas exchange at high altitude. In: West JB (ed) Pulmonary gas exchange, vol. II. Academic Press, New York, pp 97–147
Cerretelli P, di Prampero PE (1987) Gas exchange in exercise. In: Farhi LE, Tenney SM (eds) Handbook of physiology. The respiratory system III. vol 4: gas exchange. The American Physiological Society, Bethesda, pp 297–339
Cerretelli P, Hoppeler H (1996) Morphologic and metabolic response to chronic hypoxia. In: Fregly MJ, Blatteis CM (eds) Handbook of physiology. Environmental physiology, sect. 4, vol. II. Oxford University Press, New York, pp 1155–1181
Clausen JP (1977) Effect of physical training on cardiovascular adjustments to exercise in man. Physiol Rev 57:779–815
Convertino VA, Hung J, Goldwater DJ, Debusk RF (1982) Cardiovascular responses to exercise in middle age men after 10 days of bed-rest. Circulation 65:134–140
Costill DL, Daniels J, Evans W, Fink W, Krahenbuhl G, Saltin B (1976) Skeletal muscle enzymes and fiber composition in male and female track athletes. J Appl Physiol 40:149–154
Coyle EF (1995) Integration of the physiological factors determining endurance performance ability. Exerc Sport Sci Rev 23:25–63
Davies CTM, Sargeant AJ (1974) Effects of training on the physiological responses of one- and two-leg work. J Appl Physiol 38:377–381
Dempsey JA, Hanson PG, Henderson KS (1984) Exercise-induced arterial hypoxaemia in healthy human subjects at sea level. J Physiol 355:161–175
Dempsey JA, Wagner PD (1999) Exercise-induced arterial hypoxemia. J Appl Physiol 87:1997–2006
di Prampero PE (1981) Energetics of muscular exercise. Rev Physiol Biochem Pharmacol 89:143–222
di Prampero PE (1985) Metabolic and circulatory limitations to $\dot{V}O_{2max}$ at the whole animal level. J Exp Biol 115:319–331
di Prampero PE (2003) Factors limiting maximal performance in humans. Eur J Appl Physiol 90:420–429
di Prampero PE, Ferretti G (1990) Factors limiting maximal oxygen consumption in humans. Respir Physiol 80:113–128
di Prampero PE, Ferretti G (1999) The energetics of anaerobic muscle metabolism: a reappraisal of older and recent concepts. Respir Physiol Neurobiol 118:103–115
Downey AE, Chenoweth LM, Townsend DK, Ranum JD, Ferguson CS, Harms CA (2007) Effects of inspiratory muscle training on exercise responses in normoxia and hypoxia. Respir Physiol Neurobiol 156:137–146
Duncan GE, Howley ET, Johnson BN (1997) Applicability of $\dot{V}O_{2max}$ criteria: discontinuous versus continuous protocols. Med Sci Sports Exerc 29:273–278
Ekblom B (1969) The effect of physical training on oxygen transport system in man. Acta Physiol Scand Suppl 328:1–45
Ekblom B (1986) Factors determining maximal aerobic power. Acta Physiol Scand Suppl 556:15–19
Ekblom B, Åstrand PO, Saltin B, Stenberg J, Wallström B (1968) Effect of training on circulatory response to exercise. J Appl Physiol 24:518–528
Ekblom B, Huot R (1972) Response to submaximal and maximal exercise at different levels of carboxyhemoglobin. Acta Physiol Scand 86:474–482
Ekblom B, Huot R, Stein EM, Thorstensson AT (1975) Effect of changes in arterial oxygen content on circulation and physical performance. J Appl Physiol 39:71–75
Ekblom B, Wilson G, Åstrand PO (1976) Central circulation during exercise after venesection and reinfusion of red blood cells. J Appl Physiol 40:379–383
Elliott AD, Skowno J, Prabhu M, Noakes TD, Ansley L (2015) Evidence of cardiac functional reserve upon exhaustion during incremental exercise to determine $\dot{V}O_{2max}$. Br J Sports Med 49:128–132

Esposito F, Ferretti G (1997) The effects of breathing He–O_2 mixtures on maximal oxygen consumption in normoxic and hypoxic men. J Physiol 503:215–221

Esposito F, Limonta E, Alberti G, Veicsteinas A, Ferretti G (2010) Effect of respiratory muscle training on maximum aerobic power in normoxia and hypoxia. Respir Physiol Neurobiol 170:268–272

Ferretti G (1990) On maximal oxygen consumption in hypoxic humans. Experientia 46:1188–1194

Ferretti G (2003) Limiting factors to oxygen transport on Mount Everest 30 years after: a critique of Paolo Cerretelli's contribution to the study of altitude physiology. Eur J Appl Physiol 90:344–350

Ferretti G (2014) Maximal oxygen consumption in healthy humans: theories and facts. Eur J Appl Physiol 114:2007–2036

Ferretti G, Antonutto G, Denis C, Hoppeler H, Minetti AE, Narici MV, Desplanches D (1997a) The interplay of central and peripheral factors in limiting maximal O_2 consumption in man after prolonged bed rest. J Physiol 501:677–686

Ferretti G, Capelli C (2009) Maximal O_2 consumption: effects of gravity withdrawal and resumption. Respir Physiol Neurobiol 169:S50–S54

Ferretti G, di Prampero PE (1995) Factors limiting maximal O_2 consumption: effects of acute changes in ventilation. Respir Physiol 99:259–271

Ferretti G, Moia C, Thomet J, Kayser B (1997b) The decrease of maximal oxygen consumption during hypoxia in man: a mirror image of the oxygen equilibrium curve. J Physiol 498:231–237

Gavin TP, Derchak PA, Stager JM (1998) Ventilation's role in the decline in $\dot{V}O_{2max}$ and SaO_2 in acute hypoxic exercise. Med Sci Sport Exerc 30:195–199

Gayeski TE, Honig CR (1986) O_2 gradients from sarcolemma to cell interior in red muscle at maximal. Am J Physiol Heart Circ Physiol 251:H789–H799

Gibala MJ, Little JP, Macdonald MJ, Hawley JA (2012) Physiological adaptations to low-volume, high-intensity interval training in health and disease. J Physiol 590:1077–1084

Giesbrecht GG, Puddy A, Ahmed M, Younes M, Anthonisen NR (1991) Exercise endurance and arterial desaturation in normobaric hypoxia with increased chemosensitivity. J Appl Physiol 70:1770–1774

Gollnick PD, Armstrong RB, Saltin B, Saubert CW IV, Sembrowich L, Shephard RE (1973) Effect of training on enzyme activity and fiber composition of human skeletal muscle. J Appl Physiol 34:107–111

Gollnick PD, Armstrong RB, Saubert CW IV, Piehl K, Saltin B (1972) Enzyme activity and fiber composition in skeletal muscle of trained and untrained men. J Appl Physiol 33:312–319

Gordon D, Mehter M, Gernigon M, Caddy O, Keiller D, Barnes R (2012) The effects of exercise modality on the incidence of plateau at $\dot{V}O_{2max}$. Clin Physiol Funct Imaging 32:394–399

Greenleaf JE, Bernauer EM, Ertl AC, Trowbridge TS, Wade CE (1989) Work capacity during 30 days of bed rest with isometric and isotonic exercise. J Appl Physiol 67:1820–1826

Hagberg JM (1987) Effect of training on the decline of $\dot{V}O_{2max}$ with aging. Fed Proc 46:1830–1833

Hawkins MN, Raven PB, Snell PG, Stray-Gundersen J, Levine BD (2007) Maximal oxygen uptake as a parametric measure of cardiorespiratory capacity. Med Sci Sports Exerc 39:103–107

Henriksson J (1977) Training induced adaptation of skeletal muscle and metabolism during submaximal exercise. J Physiol 270:661–675

Herbst R (1928) Der Gasstoffwechsel als Mass der körperlichen Leistungsfähigkeit. I. Mitteilung: die Bestimmung des Sauerstoffaufnahmevermögens bein Gesunden. Deut Arch Klin Med 162:33–50

Hikida RS, Gollnick PD, Dudley GA, Convertino VA, Buchanan P (1989) Structural and metabolic characteristics of human skeletal muscle following 30 days of simulated microgravity. Aviat Space Environ Med 60:664–670

Hill AV, Lupton H (1923) Muscular exercise, lactic acid, and the supply and utilization of oxygen. Q J Med 16:135–171

Holloszy JO, Coyle EF (1984) Adaptations of skeletal muscle to endurance exercise and their metabolic consequences. J Appl Physiol 56:831–838

Hoppeler H (1986) Exercise-induced ultrastructural changes in skeletal muscle. Int J Sports Med 7:187–204

Hoppeler H, Howald H, Conley K, Lindstedt SL, Claassen H, Vock P, Weibel ER (1985) Endurance training in humans: aerobic capacity and structure of skeletal muscle. J Appl Physiol 59:320–327

Hoppeler H, Kleinert E, Schlegel C, Claassen H, Howald H, Kayar SR, Cerretelli P (1990) Morphological adaptations of human skeletal muscle to chronic hypoxia. Int J Sports Med 11 (suppl 1):S3–S9

Hoppeler H, Klossner S, Vogt M (2008) Training in hypoxia and its effects on skeletal muscle tissue. 18. Scand J Med Sci Sports 18(Suppl 1):38–49

Howald H (1982) Training-induced morphological and functional changes in skeletal muscle. Int J Sports Med 3:1–12

Howald H, Hoppeler H, Claassen H, Mathieu O, Straub R (1985) Influences of endurance training on the ultrastructural composition of the different muscle fibre types in humans. Pflügers Arch 403:369–376

Howley ET, Bassett DR, Welch HG (1995) Criteria for maximal oxygen uptake: review and commentary. Med Sci Sports Exerc 27:1292–1301

Ingjer F (1979) Effects of endurance training on muscle fiber ATP-ase activity, capillary supply and mitochondrial content in man. J Physiol 294:419–432

Jones JH, Lindstedt SL (1993) Limits to maximal performance. Annu Rev Physiol 55:547–569

Kaijser L (1970) Limiting factors for aerobic muscle performance. Acta Physiol Scand Suppl 346:1–96

Kashihara H, Haruna Y, Suzuki Y, Kawakubo K, Takenaka K, Bonde-Petersen F, Gunji A (1994) Effects of mild supine exercise during 20 days bed rest on maximal oxygen uptake rate in young humans. Acta Physiol Scand Suppl 616:19–26

Kayser B, Marconi C, Amatya T, Basnyat B, Colombini A, Broers B, Cerretelli P (1994) The metabolic and ventilatory response to exercise in Tibetans born at low altitude. Respir Physiol 98:15–26

Koistinen P, Takala T, Martikkala V, Leppaluoto J (1995) Aerobic fitness influences the response of maximal oxygen uptake and lactate threshold in acute hypobaric hypoxia. Int J Sports Med 16:78–81

Krip B, Gledhill N, Jamnik V, Warburton D (1997) Effect of alterations in blood volume on cardiac function during maximal exercise. Med Sci Sports Exerc 29:1469–1476

Lacour JR, Flandrois R (1977) Le rôle du métabolisme aérobie dans l'exercice intense de longue durée. J Physiol Paris 73:89–130

Lee SM, Schneider SM, Boda WL, Watenpaugh DE, Macias BR, Meyer RS, Hargens AR (2007) Supine LBNP exercise maintains exercise capacity in male twins during 30-d bed rest. Med Sci Sports Exerc 39:1315–1326

Lee SM, Schneider SM, Boda WL, Watenpaugh DE, Macias BR, Meyer RS, Hargens AR (2009) LBNP exercise protects aerobic capacity and sprint speed of female twins during 30 days of bed rest. J Appl Physiol 106:919–928

Levine BD (2008) $\dot{V}O_{2max}$: what do we know, and what do we still need to know? J Physiol 586:25–34

Levine BD, Lane LD, Watenpaugh DE, Gaffney FA, Buckey JC, Blomqvist CG (1996) Maximal exercise performance after adaptation to microgravity. J Appl Physiol 81:686–694

Lindstedt SL, Wells DJ, Jones JR, Hoppeler H, Thronson HA (1988) Limitations to aerobic performance in mammals: interaction of structure and demand. Int J Sports Med 9:210–217

Maksud MG, Coutts KD (1971) Comparison of a continuous and discontinuous graded treadmill test for maximal oxygen uptake. Med Sci Sports 3:63–65

Marconi C, Marzorati M, Grassi B, Basnyat B, Colombini A, Kayser B, Cerretelli P (2004) Second generation Tibetan lowlanders acclimatize to high altitude more quickly than Caucasians. J Physiol 556:661–671

Mitchell JH, Blomqvist CG (1971) Maximal oxygen uptake. New Engl J Med 284:1018–1022

Morton RH, Green S, Bishop D, Jenkins DG (1997) Ramp and constant power trials produce equivalent critical power estimates. Med Sci Sports Exerc 29:833–836

Noakes TD (1998) Maximal oxygen uptake: 'classical' versus 'contemporary' viewpoints: a rebuttal. Med Sci Sports Exerc 30:1381–1398

Noakes TD, Peltonen JE, Rusko HK (2001) Evidence that a central governor regulates exercise performance during acute hypoxia and hyperoxia. J Exp Biol 204:3225–3234

Oelz O, Howald H, di Prampero PE, Hoppeler H, Claassen H, Jenni R, Bühlmann A, Ferretti G, Brückner JC, Veicsteinas A, Gussoni M, Cerretelli P (1986) Physiological profile of world class high altitude climbers. J Appl Physiol 60:1734–1742

Ogawa T, Calbet JAL, Honda Y, Fuji N, Nishiyasu T (2010) The effects of breathing a helium–oxygen gas mixture on maximal pulmonary ventilation and maximal oxygen consumption during exercise in acute moderate hypobaric hypoxia. Eur J Appl Physiol 110:853–861

Ogawa T, Hayashi K, Ichinose M, Nishiyasu T (2007) Relationship between rest ventilatory chemosensitivity and maximal oxygen uptake in moderate hypobaric hypoxia. J Appl Physiol 103:1221–1226

Piiper J, Meyer M, Scheid P (1984) Dual role of diffusion in tissue gas exchange: blood-tissue equilibration and diffusion shunt. Respir Physiol 56:131–144

Piiper J, Scheid P (1981) Model for capillary-alveolar equilibration with special reference to O_2 uptake in hypoxia. Respir Physiol 46:193–208

Pirnay F, Dujardin J, Deroanne R, Petit JM (1971) Muscular exercise during intoxication by carbon monoxide. J Appl Physiol 31:573–575

Powers SK, Lawler J, Dempsey JA, Dodd S, Landry G (1989) Effects of incomplete pulmonary gas exchange on VO_{2max}. J Appl Physiol 66:2491–2495

Rådegran G, Blomstrand E, Saltin B (1999) Peak muscle perfusion and oxygen uptake in humans: importance of precise estimates of muscle mass. J Appl Physiol 87:2375–2380

Richardson RS, Kennedy B, Knight DR, Wagner PD (1995a) High muscle blood flows are not attenuated by recruitment of additional muscle mass. Am J Physiol Heart Circ Physiol 269:H1545–H1552

Richardson RS, Knight DR, Poole DC, Kurdak SS, Hogan MC, Grassi B, Wagner PD (1995b) Determinants of maximal exercise $\dot{V}O_2$ during single leg knee-extensor exercise in humans. Am J Physiol Heart Circ Physiol 268:H1453–H1461

Richardson RS, Newcomer SC, Noyszewski EA (2001) Skeletal muscle intracellular PO_2 assessed by myoglobin desaturation: response to graded exercise. J Appl Physiol 91:2679–2685

Roach RC, Koskolou MD, Calbet JA, Saltin B (1999) Arterial O_2 content and tension in regulation of cardiac output and leg blood flow during exercise in humans. Am J Physiol Heart Circ Physiol 276:H438–H445

Roca J, Hogan MC, Story D, Bebout DE, Haab P, Gonzalez R, Ueno O, Wagner PD (1989) Evidence for tissue diffusion limitation of $\dot{V}O_{2max}$ in normal humans. J Appl Physiol 67:291–299

Rogers MA, Evans WJ (1993) Changes in skeletal muscle with aging: effects of exercise training. Exerc Sport Sci Rev 21:65–102

Rowell LB (1974) Human cardiovascular adjustments to exercise and thermal stress. Physiol Rev 54:75–159

Rowell LB, Saltin B, Kiens B, Christensen NJ (1986) Is peak quadriceps blood flow in humans even higher during exercise with hypoxemia? Am J Physiol Heart Circ Physiol 251:H1038–H1044

Russell G, Gore CJ, Ashenden MJ, Parisotto R, Hahn AG (2002) Effects of prolonged low doses of recombinant human erythropoietin during submaximal and maximal exercise. Eur J Appl Physiol 86:442–449

Saltin B (1977) The interplay between peripheral and central factors in the adaptive response to exercise and training. Ann N Y Acad Sci 301:224–231
Saltin B, Blomqvist CG, Mitchell RC, Johnson RL, Wildenthal K, Chapman CB (1968) Response to exercise after bed rest and after training. Circulation 38(suppl. 7):1–78
Saltin B, Nazar K, Costill DL, Stein E, Jansson E, Essén B, Gollnick PD (1976) The nature of the training response: peripheral and central adaptations to one-legged exercise. Acta Physiol Scand 96:289–305
Saltin B, Rowell LB (1980) Functional adaptations to physical activity and inactivity. Fed Proc 39:1506–1513
Saltin B, Strange S (1992) Maximal oxygen uptake: "old" and "new" arguments for a cardiovascular limitation. Med Sci Sports Exerc 24:30–37
Schaffartzik W, Barton ED, Poole DC, Tsukimoto K, Hogan MC, Bebout DE, Wagner PD (1993) Effect of reduced hemoglobin concentration on leg oxygen uptake during maximal exercise in humans. J Appl Physiol 75:491–498
Scheuer J, Tipton CM (1977) Cardiovascular adaptations to physical training. Annu Rev Physiol 39:221–251
Secher N, Ruberg-Larsen H, Binkhorst RA, Bonde-Petersen F (1974) Maximal oxygen uptake during arm cranking and combined arm plus leg exercise. J Appl Physiol 36:515–518
Shephard RJ (1969) A non-linear solution of the oxygen conductance equation : applications to performance at sea level and at an altitude of 7,350 ft. Int Z angew Physiol 27:212–225
Smorawinski J, Nazar K, Kaciuba-Uscilko H, Kaminska E, Cybulski G, Kodrzycka A, Bicz B, Greenleaf JE (2001) Effects of 3-day bed rest on physiological responses to graded exercise in athletes and sedentary men. J Appl Physiol 91:249–257
Spaak J, Montmerle S, Sundblad P, Linnarsson D (2005) Long-term bed rest-induced reductions in stroke volume during rest and exercise: cardiac dysfunction vs. volume depletion. J Appl Physiol 98:648–654
Spriet LL, Gledhill N, Froese AB, Wilkes DL (1986) Effect of graded erythrocythemia on cardiovascular and metabolic responses to exercise. J Appl Physiol 61:1942–1948
Stamford BA (1988) Exercise and the elderly. Exerc Sport Sci Rev 16:341–379
Stremel RW, Convertino VA, Bernauer EM, Greenleaf JE (1976) Cardiorespiratory deconditioning with static and dynamic leg exercise during bed rest. J Appl Physiol 41:905–909
Sutton JR (1992) Limitations to maximal oxygen uptake. Sports Med 13:127–133
Taylor CR (1987) Structural and functional limits to oxidative metabolism: insights from scaling. Annu Rev Physiol 49:135–146
Taylor CR, Weibel ER (1981) Design of the mammalian respiratory system. I. Problem and strategy. Respir Physiol 44:1–10
Taylor HL, Buskirk E, Henschel A (1955) Maximal oxygen uptake as an objective measure of cardiorespiratory performance. J Appl Physiol 8:73–80
Tesch PA (1985) Exercise performance and beta-blockade. Sports Med 2:389–412
Tesch PA, Karlsson J (1985) Muscle fiber types and size in trained and untrained muscles of elite athletes. J Appl Physiol 59:1716–1720
Thomsen JJ, Rentsch RL, Robach P, Calbet JAL, Boushel R, Rasmussen P, Juel C, Lundby C (2007) Prolonged administration of recombinant human erythropoietin increases submaximal performance more than maximal aerobic power. Eur J Appl Physiol 101:481–486
Trappe T, Trappe S, Lee G, Widrick J, Fitts R, Costill D (2006) Cardiorespiratory responses to physical work during and following 17 days of bed rest and spaceflight. J Appl Physiol 100:951–957
Turner DL, Hoppeler H, Noti C, Gurtner HP, Gerber H, Schena F, Kayser B, Ferretti G (1993) Limitations to VO_{2max} in humans after blood retransfusion. Respir Physiol 92:329–341
Vogel JA, Gleser MA (1972) Effect of carbon monoxide on oxygen transport during exercise. J Appl Physiol 32(234–239):287
Wagner PD (1992) Gas exchange and peripheral diffusion limitation. Med Sci Sports Exerc 24:54–58
Wagner PD (1993) Algebraic analysis of the determinants of $\dot{V}O_{2max}$. Respir Physiol 93:221–237

Wagner PD (1995) Muscle O_2 transport and O_2 dependent control of metabolism. Med Sci Sports Exerc 27:47–53

Wagner PD (1996a) Determinants of maximal oxygen transport and utilization. Annu Rev Physiol 58:21–50

Wagner PD (1996b) A theoretical analysis of factors determining $\dot{V}O_{2max}$ at sea level and altitude. Respir Physiol 106:329–343

Wagner PD (2012) Muscle intracellular oxygenation during exercise: optimization for oxygen transport, metabolism, and adaptive change. Eur J Appl Physiol 112:1–8

Wagner PD, Erickson BK, Seaman J, Kubo K, Hiraga A, Kai M, Yamaya Y (1996) Effects of altered FIO_2 on maximum $\dot{V}O_2$ in the horse. Respir Physiol 105:123–134

Wagner PD, Gillespie JR, Landgren GL, Fedde MR, Jones BW, DeBowes RM, Pieschl RL, Erickson HH (1989) Mechanism of exercise-induced hypoxemia in horses. J Appl Physiol 66:1227–1233

Wehrlin JP, Hallén J (2006) Linear decrease in $\dot{V}O_{2max}$ and performance with increasing altitude in endurance athletes. Eur J Appl Physiol 96:404–412

Weibel ER (1987) Scaling of structural and functional variables in the respiratory system. Annu Rev Physiol 49:147–159

Weibel ER, Taylor CR, Hoppeler H (1992) Variations in function and design: testing symmorphosis in the respiratory system. Respir Physiol 87:325–348

West JB (1983) Climbing Mt. Everest without oxygen: an analysis of maximal exercise during extreme hypoxia. Respir Physiol 52:265–279

West JB, Lahiri S, Maret KH, Peters RM, Pizzo CJ (1983) Barometric pressures at extreme altitudes on Mt. Everest: physiological significance. J Appl Physiol 54:1188–1194

Woodson RD, Wills RE, Lenfant C (1978) Effect of acute and established anemia on O_2 transport at rest, submaximal and maximal work. J Appl Physiol 44:36–43

Zhang YY, Johnson MC 2nd, Chow N, Wasserman K (1991) Effect of exercise testing protocol on parameters of aerobic function. Med Sci Sports Exerc 23:625–630

Zoladz JA, Rademaker ACHJ, Sargeant AJ (1995) Non-linear relationship between O_2 uptake and power output at high intensities of exercise in humans. J Physiol 488:211–217

Zumstein A, Mathieu O, Howald H, Hoppeler H (1983) Morphometric analysis of the capillary supply in skeletal muscles of trained and untrained subjects. Its limitations in muscle biopsies. Pflügers Arch. 397:277–283

Chapter 5
Critical Power

Abstract The critical power ($\dot{w}_{cr}$) is the highest power that can be sustained relying exclusively on aerobic metabolism, although unevenly distributed among muscle fibres, and thus, it is the highest power for which oxygen consumption is, not only in theory, the sole source of metabolic energy. As such, the $\dot{w}_{cr}$ concept is fundamental in exercise physiology for its strict relation to the concept of metabolic steady state and for its association to the maximal lactate steady state. The $\dot{w}_{cr}$ corresponds to the y-axis asymptote of the hyperbolic relationship between sustained power and time to exhaustion. The curvature of the hyperbole defines a constant corresponding to the amount of mechanical work that can be sustained above the $\dot{w}_{cr}$ (energy store component). The energy store component does not correspond to the anaerobic capacity, but to the amount of work that can be carried out at powers higher than the $\dot{w}_{cr}$, the energy sustaining it deriving from both aerobic and anaerobic sources. After a survey of the descriptive physiology of $\dot{w}_{cr}$, the case of intermittent exercise is discussed, as is the relationship between $\dot{w}_{cr}$ and the maximal aerobic power. Finally, the three-parameter model of $\dot{w}_{cr}$, taken as an example of generalization, is considered, evidencing the relation between its y-axis intercept and the maximal instantaneous anaerobic alactic power. The determination of $\dot{w}_{cr}$ is a key issue in exercise testing. Procedures for simplifying its determination have been proposed.

Contents

G. Ferretti, *Energetics of Muscular Exercise*,
DOI 10.1007/978-3-319-05636-4_5

Introduction

The concept of **critical power** ($\dot{w}_{cr}$) is fundamental in exercise physiology for its strict relation to the concept of metabolic steady state. The $\dot{w}_{cr}$ was firstly defined by Monod and Scherrer (1965) as "the maximum power that can be kept up for a very long time without fatigue". This qualitative definition came nevertheless from the quantitative analysis of a graph, in which they plotted the total work done, determined during several fatiguing exercise bouts of variable intensity, as a function of the exhaustion time. They gave a hyperbolic solution to this plot, where $\dot{w}_{cr}$ corresponds to the dependent variable's asymptote (Fig. 5.1), while the curvature of the hyperbole [the product of x times $(y - \dot{w}_{cr})$] defines a constant corresponding to the amount of mechanical work that can be sustained above $\dot{w}_{cr}$, which was called the "**energy store**" **component** (W'). This relationship can be linearized by replacing time with its reciprocal as independent variable, in which case the $\dot{w}_{cr}$ is the y-axis intercept and W' is the line's slope.

Monod and Scherrer (1965) considered $\dot{w}_{cr}$ dependent, at least in part, on muscle blood flow and hence oxygen delivery. Moritani et al. (1981) associated $\dot{w}_{cr}$ with the lactate threshold. Although it has become clear that $\dot{w}_{cr}$ is a higher power than that corresponding to the lactate threshold, at least in non-athletic individuals (Poole et al. 1988, 1990), this may be the case in endurance athletes (Jones and Poole 2009), who are characterized by an elevated fraction of type I slow aerobic fibres in locomotory muscles as compared to the former. Subsequent studies have related W' to overall anaerobic capacity and $\dot{w}_{cr}$ to the power sustained in evenly aerobic conditions, with all muscle fibres acting as normoaerobic fibres. This made these two constants conceptually independent of each other (Hill 1993; Miura et al. 2000; Poole et al. 1990; Vanhatalo and Jones 2009). This concept is criticized in the paragraph on the physiological meaning of W'.

The present definition of $\dot{w}_{cr}$ includes an oversimplification. Considering $\dot{w}_{cr}$ as the asymptote of hyperbolic power versus time curve implies that, for powers below the $\dot{w}_{cr}$, power can be sustained for an infinite time. Obviously, this is not so. Below the $\dot{w}_{cr}$, the maximal duration is limited by the amount of substrates for aerobic exercise, which is finite. Thus, there must exist another hyperbolic power versus time relationship, whose y-axis asymptote may be the resting metabolic rate, or even the basal metabolic rate, and whose curvature is proportional to the amount of substrates for aerobic metabolism that are stored in the body, consisting of glycogen and lipids. This amount, however, is so huge that power versus time relationship at powers below the $\dot{w}_{cr}$ must be very flat, almost undistinguishable from a horizontal line. Saltin (1973) treated it as linear. Thus, from a practical viewpoint, the present definition of $\dot{w}_{cr}$ can be considered, on first approximation, acceptable, at least for exercise durations shorter than 6 h, which is approximately the best time of the 100-km run for top athletes (for an analysis of ultra-marathon running performance, see Hoffman 2010).

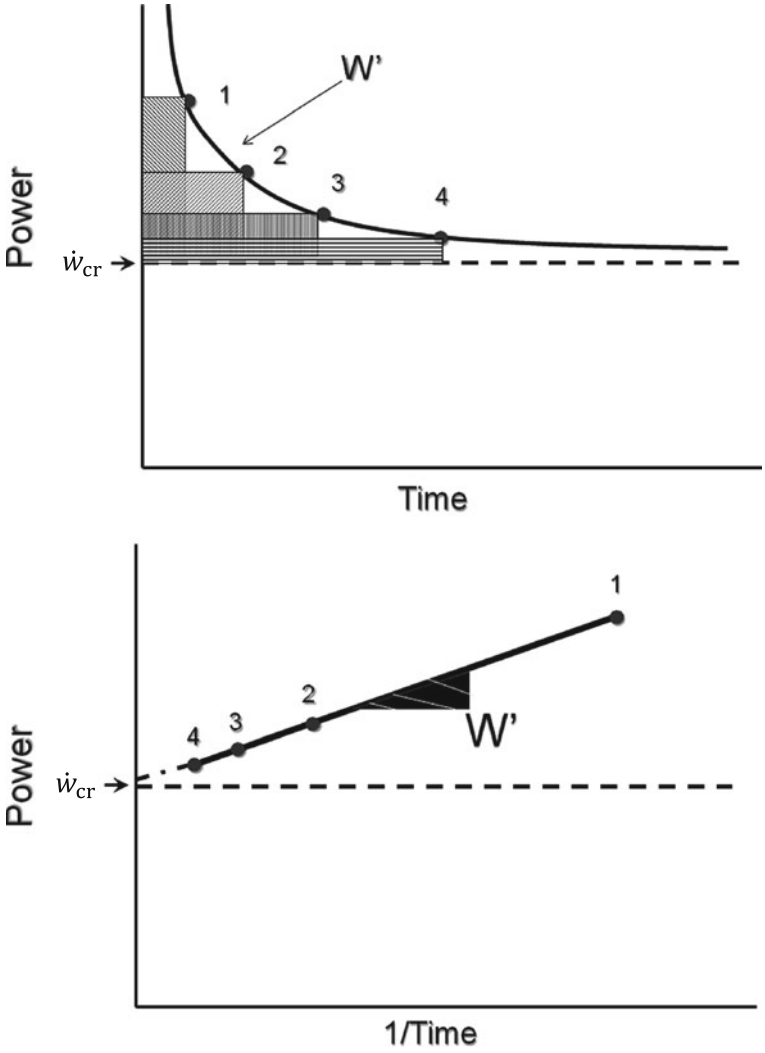


Fig. 5.1 *Top panel* Schematic qualitative representation showing the power versus time relationship for high-intensity exercise. Points 1–4 indicate the time to exhaustion for independent tests at the designated power. The critical power ($\dot{w}_{cr}$) is the y-axis asymptote of the hyperbola. *Bottom panel* Schematic qualitative representation showing the linearized version of the power versus time relationship, obtained by replacing time by its reciprocal. Points 1–4 indicate the time to exhaustion for independent tests at the designated power, as in the top panel. The $\dot{w}_{cr}$ is the y-axis intercept of the line. In both graphs, *W'* is the mechanical work above $\dot{w}_{cr}$: it corresponds to the hyperbola's curvature in the *top panel* and to the line's slope in the bottom graph. Modified after Jones et al. (2010)

The Physiological Meaning of the Energy Store Component

The energy store component W' has received various interpretations, the meaning of which has been questioned under several respects. To date, the consensus about the concept of W' is still weak and is undermined by the different meaning that is given to the concept of aerobic metabolism. The present discussion of W' is carried out in the wide context of the general theory of the energetics of muscular exercise, developed by Margaria and his successors (see Chap. 1).

Mechanically speaking, there is little doubt that W' (expressed in J) corresponds to the mechanical work that can be performed above the $\dot{w}_{cr}$. Being a constant characterizing the power versus time relationship, its value is independent of the applied mechanical power. A corollary of the association, made by Moritani et al. (1981), between $\dot{w}_{cr}$ and the lactate threshold, is that $\dot{w}_{cr}$ is the highest sustainable rate of aerobic metabolism, at which the maximal lactate steady state occurs (Poole et al. 1988; Pringle and Jones 2002). As a consequence, W' was interpreted as the work that can be sustained relying on anaerobic lactic metabolism. This interpretation is affected by the notion that the lactate threshold defines the boundary between aerobic and anaerobic metabolism, which is a physiologically incorrect concept (di Prampero and Ferretti 1999), and thus, it must be rejected.

Jones et al. (2010) have corrected this interpretation by adding a small aerobic contribution from myoglobin- and (venous) haemoglobin-bound oxygen stores, but this does not appear as a substantial modification of the above concept that W' corresponds to the anaerobic capacity. Nevertheless, the same authors acknowledged that the physiological underpinnings of $\dot{w}_{cr}$ and W' have been the subject of some controversy, for their difficulty in being assessed. They relate this to the ambiguous meaning of **fatigue**, which is an elegant way of admitting that the situation is confused. Based on various findings, part of which are summarized below, Jones et al. (2010) stated that "*W' may not represent a fixed "anaerobic" substrate store, but rather a mechanical work capacity that can be used while* [*PCr*] *and pH project toward a nadir value, which occurs near* $\dot{V}O_{2max}$ *and ultimately exhaustion*". This alternate definition of the meaning of W', however, does not bring this concept outside the domain of anaerobic capacity, although in the same paper, these authors admit that interpreting W' as the anaerobic capacity is an oversimplification.

If we accept the notion that $\dot{w}_{cr}$ has some relation to the maximal lactate steady state, it might represent the highest power at which metabolic power is delivered in fully aerobic conditions. In this case, after the attainment of a steady state for oxygen consumption, the general equation of the energetics of muscular exercise would take the simplified form of Eq. (2.2) (see Chap. 2). Under these conditions, aerobic metabolism may be either evenly distributed, in which case all muscle fibres oxidize pyruvate via the Krebs cycle, or oddly distributed, in which case hypoaerobic type II fibres reduce part of the accumulated pyruvate into lactate: this in turn is taken up by adjacent hyperaerobic type I fibres and converted back to pyruvate, which is then fully oxidized via the Krebs cycle. The condition of uneven

aerobic metabolism requires an increase in muscle and blood lactate concentrations. This increase takes place during the exercise transient (early lactate, see Chap. 3 and Cerretelli et al. 1979) and leads to stable lactate concentrations with time at a higher level than the resting one. The only difference between an even and an odd aerobic metabolism is that in the former case, the entire oxidation process from glycogen to CO_2 takes place within a single muscle fibre, whereas in the latter case, the same process requires the intervention of two adjacent fibres, one working in hypoaerobic condition and accumulating lactate, and the other working in hyperaerobic condition and oxidizing lactate. Both cases are fully compatible with Eq. (2.2). An increase in lactate concentration above a given level does not define the transition from aerobic to anaerobic metabolism. Oxygen consumption still increases at powers higher than $\dot{w}_{cr}$, and the maximal oxygen consumption is higher than the oxygen consumption incurring at the $\dot{w}_{cr}$.

The above reasoning includes the demonstration that W' does not represent anaerobic capacity, even with the addition of a small aerobic component from oxygen stores. The energy balance in the range of powers comprised between $\dot{w}_{cr}$ and the maximal aerobic power ($\dot{w}_{max}$), which defines the intense exercise domain, consists of a mixture of energy derived from aerobic and from anaerobic sources. Oxygen consumption does still increase, because it has not achieved the uppermost limit that mitochondrial oxidative capacity is able to attain and/or because it can be sustained by a further increase in systemic oxygen delivery. In other terms, neither the peripheral resistance nor the cardiovascular resistance to oxygen flow has yet attained their minimal value at the $\dot{w}_{cr}$.

At the same time, the number of muscle fibres operating in hypoaerobic condition goes up as the mechanical power increases, as does their rate of lactate production, until a power is attained at which the lactate produced by hypoaerobic power exceeds the capacity of hyperaerobic fibres to remove it. Also these fibres in fact increase the rate at which they oxidize glycogen, and thus have fewer margins to face a higher rate of lactate production by hypoaerobic fibres. Once this condition has been attained, lactate concentration keeps increasing with time at a rate which is higher the higher the mechanical power, and anaerobic lactic power (see Chap. 6) becomes positive.

This line of reasoning applies only to the fraction of mechanical power above the $\dot{w}_{cr}$, which even at $\dot{w}_{max}$ represents a relatively small amount with respect to the total applied mechanical power. Within the power range between $\dot{w}_{cr}$ and $\dot{w}_{max}$, we may also account for the "slow component" of muscle phosphocreatine decrease (Rossiter et al. 2002). If we assume that this is associated with the activation of anaerobic alactic metabolism, we can state that during intense exercise, above $\dot{w}_{cr}$ but below $\dot{w}_{max}$, all the three main energy metabolisms are simultaneously active also at exercise times longer than the 4–5 min that classically define the duration of the exercise transient. Note that this is the same power range in which the slow component of the oxygen uptake kinetics (Chap. 3) becomes visible. If we finally consider that, at the net of the oxygen deficit, all the power between rest and $\dot{w}_{cr}$ is sustained by aerobic metabolism, oxygen consumption represents anyway and by far the largest contributor to the overall metabolic rate also at powers comprised between $\dot{w}_{cr}$ and $\dot{w}_{max}$.

Descriptive Physiology of Critical Power and Energy Store Component

For reasons that are outlined below, pertaining to the strict relations between $\dot{w}_{cr}$ and $\dot{w}_{max}$, all chronic adaptive phenomena and all acute manoeuvres that act on $\dot{V}\,O_{2max}$, and thus on $\dot{w}_{max}$, act also on $\dot{w}_{cr}$. Not all conditions, however, have been investigated in terms of effects on $\dot{w}_{cr}$. In any case, and coherently with the principles pointed out here above, it has been demonstrated that both continuous (Heubert et al. 2003; Jenkins and Quigley 1992) and high-intensity interval training (Gaesser and Wilson 1988; Jenkins and Quigley 1993; Kendall et al. 2009; Poole et al. 1990; Vanhatalo et al. 2008) increase $\dot{w}_{cr}$. Moreover, strength training was shown to increase the time to exhaustion during high-intensity exercise by an effect on W' without changes of $\dot{w}_{cr}$ (Sawyer et al. 2014). It seems logical to expect a decrease in $\dot{w}_{cr}$ after prolonged bed rest, especially during upright exercise, but I am unaware of any study specifically addressing this issue. Conversely, there is some evidence that $\dot{w}_{cr}$ goes down in hypoxia (Dekerle et al. 2012; Moritani et al. 1981; Parker-Simpson et al. 2014; Valli et al. 2011). Possibly for its effects on muscle blood flow, and thus on the rate of lactate accumulation, prior high-intensity exercise displaces $\dot{w}_{cr}$ closer to $\dot{w}_{max}$ and reduces W' (Ferguson et al. 2007, 2010; Miura et al. 2009; Vanhatalo and Jones 2009).

Interesting is the case of hyperoxia. If the degree of hyperoxia is sufficiently strong, so that the concentration of free oxygen in blood becomes significant, hyperoxia increases $\dot{w}_{cr}$, thus reducing the rate at which lactate concentration goes up and muscle phosphocreatine goes down at a given power. Since hyperoxia does not increase $\dot{V}\,O_{2max}$, and thus $\dot{w}_{max}$, this reduces the difference between $\dot{w}_{max}$ and $\dot{w}_{cr}$, so that the size of the energy store component W' inevitably decreases, as demonstrated by Vanhatalo et al. (2010). More generally speaking, I would tend to state that whenever the difference between $\dot{w}_{max}$ and $\dot{w}_{cr}$ is reduced—implying an increase of the $\dot{w}_{cr}/\dot{w}_{max}$ ratio—the size of W' decreases; conversely, whenever the difference between $\dot{w}_{max}$ and $\dot{w}_{cr}$ is enhanced, the size of W' increases. The $\dot{w}_{cr}/\dot{w}_{max}$ ratio is increased also when there is an identical absolute increase in $\dot{w}_{max}$ and $\dot{w}_{cr}$. This occurs for instance during exercise training (Heubert et al. 2003; Jenkins and Quigley 1992): also in this condition, the increase in $\dot{w}_{cr}$ is accompanied by a decrease in W' (Vanhatalo et al. 2008).

Interventions specifically acting on substrate stores can be predicted to have an effect on W', which is positive if substrate stores are enlarged, negative in the opposite case. Coherently with this prediction, glycogen depletion reduces W' (Miura et al. 2000), whereas creatine supplementation increases it (Kendall et al. 2009; Smith et al. 1998).

All these results are coherent with the energetic meaning of $\dot{w}_{cr}$ and W' outlined previously. They thus provide strong experimental support to the concepts that (i) $\dot{w}_{cr}$ represents the upper limit of unevenly distributed aerobic metabolism as

summarized by Eq. (2.2), and (ii) the energetics of W' consists of the simultaneous intervention of aerobic, anaerobic lactic and eventually also anaerobic alactic metabolism.

Energetic Consequences of the Hyperbolic Critical Power Model

The hyperbolic model of $\dot{w}_{cr}$ originally conceived by Monod and Scherrer (1965) and represented in Fig. 5.1 can be algebraically represented in the following form:

$$(\dot{w} - \dot{w}_{cr})t_{lim} = W' \tag{5.1}$$

where t_{lim} is the maximal time over which a given $\dot{w}$ above the $\dot{w}_{cr}$ can be sustained. Equation (5.1) tells that t_{lim} is inversely proportional and W' is directly proportional to the $\dot{w} - \dot{w}_{cr}$ difference. Equation (5.1) therefore provides a solid theoretical explanation of the experimental results reported in the preceding paragraph and allows precise predictions of how the power versus time relationship evolves when chronic adaptive changes or acute manoeuvres alter W' and/or $\dot{w}_{cr}$.

The total amount of mechanical work (W) carried out during a square wave exercise lasting a time equal to t_{lim} is given by:

$$W = \dot{w} \cdot t_{lim} \tag{5.2}$$

whence, after combining Eqs. (5.1) and (5.2) and rearranging, we obtain:

$$W = W' + \dot{w}_{cr} \cdot t_{lim} \tag{5.3}$$

Equation (5.3) can be expressed in terms of metabolic energy as follows:

$$E = \frac{W'}{\eta} + \frac{\dot{w}_{cr}}{\eta} \cdot t_{lim} \tag{5.4}$$

where η is the mechanical efficiency of exercise. Since the lactate concentration at the steady state of an exercise carried out at $\dot{w} = \dot{w}_{cr}$ does not vary with time, the ratio $\dot{w}_{cr}/\eta$ corresponds to the net (measured value minus resting value) steady-state oxygen consumption at the $\dot{w}_{cr}$, which I propose to call the critical oxygen consumption ($\dot{V}O_{2cr}$), and Eq. (5.4) can be rewritten as follows:

$$E = \frac{W'}{\eta} + \dot{V}O_{2cr} \cdot t_{lim} \tag{5.5}$$

where the ratio W'/η, according to the general equation of the energetics of muscular exercise, is equal to:

$$\frac{W'}{\eta} = \left[\left(\dot{V}\,O_2 - \dot{V}\,O_{2cr}\right) + \beta\dot{L}a\right]t_{lim} \tag{5.6}$$

where $\dot{L}a$ is the rate at which lactate concentration in blood increases (slope of a lactate versus time line) after the first 5 min of exercise, and β is a proportionality constant indicating the amount of energy corresponding to a mole of lactate accumulated in blood (energy equivalent of blood lactate accumulation, see Chap. 6). Combining Eqs. (5.5) and (5.6) yields:

$$E = \left(\dot{V}\,O_2 + \beta\,\dot{L}a\right)t_{lim} \tag{5.7}$$

In Eq. (5.7), $\dot{V}\,O_2$ is the net oxygen consumption, to be expressed in watts when energy is expressed in joules (note that 1 L of oxygen STPD provides about 20.9 kJ of energy). $\dot{V}\,O_2$ corresponds to the asymptote of the primary component of the oxygen consumption kinetics (steady state of phase II) and includes the energy derived from anaerobic sources during contraction of the oxygen deficit (O_{2def}), which is given by.

$$O_{2def} = \dot{V}\,O_2\,\tau \tag{5.8}$$

Because of Eq. (3.4), Eq. (5.8) can be rewritten as follows:

$$O_{2def} = \dot{V}\,O_2 \cdot (\lambda \cdot [La]_e + \tau_0) \tag{5.9}$$

where the lactate concentration $[La]_e$ represents early lactate, λ is the constant indicating how much τ increases per unit increase of lactate in blood during the exercise transient (di Prampero and Ferretti 1999), and τ_0 is the time constant of the obligatory component of the oxygen deficit, i.e. the time constant that would incur in the absence of early lactate accumulation. The τ_0 values range between 23 and 30 s (see Chap. 3), which corresponds well to the time constant of muscle phosphocreatine depletion upon exercise onset (Binzoni et al. 1992; di Prampero et al. 2003; Francescato et al. 2008, 2013; Rossiter et al. 1999, 2002). Therefore, during exercise at any power $\dot{w}$ higher than $\dot{w}_{cr}$, the amount of energy derived from the anaerobic lactic component (E_{La}) of the metabolic energy expenditure is equal to:

$$E_{La} = \beta\,\dot{L}a \cdot t_{lim} + O_{2def} - \dot{V}\,O_2 \cdot \tau_0 \tag{5.10}$$

On the other hand, the anaerobic alactic component (E_{PC}) of the metabolic energy expenditure is equal to:

$$E_{PC} = \dot{V}\,O_2 \cdot \tau_0 \tag{5.11}$$

It is noteworthy that Eqs. (5.10) and (5.11) do not account for the slow component of both phosphocreatine and $\dot{V}\,O_2$, which is known to occur at powers

higher than $\dot{w}_{cr}$. Further analysis to include the slow component in these equations requires, however, a precise knowledge of its effects on η and an assumption on its time course, which are both hazardous items preventing me from implementing them. While abstaining from doing so, I am nonetheless aware that Eqs. (5.10) and (5.11) may be oversimplifications entailing some underestimate of the anaerobic components of the energy balance during exercise above the $\dot{w}_{cr}$. Whatever the case, it remains a matter of fact that, for an exercise carried out for a time equal to t_{lim}, the quantity of metabolic energy represented by E_{La} and E_{PC} is by far lower than that derived from aerobic metabolism.

The Critical Power Model in Intermittent Exercise

A continuous exercise carried out until t_{lim} can also be subdivided into n fractions of shorter duration, separated by recovery intervals of perhaps, but not necessarily, equivalent duration (intermittent exercise). In this case, for a given power during the exercise phase $\dot{w}_e > \dot{w}_{cr}$, one might in principle expect equivalent t_{lim} for continuous as for intermittent exercise. However, the energy balance is more complex in the latter than in the former exercise mode, due to repeated cycles of oxygen-deficit contraction followed by oxygen debt payment. If the times of exercise (t_e) and recovery (t_r) are sufficiently short, the refilling of anaerobic energy stores may be incomplete in the recovery phase, so that the exercise would be interrupted at depletion of anaerobic alactic capacity. If this is the case, and if recovery is indeed carried out at rest (i.e. with a power during the recovery phase, $\dot{w}_r$, of 0 W), then the t_{lim} obtained for intermittent exercise as the product of n times t_e would be shorter than that for continuous exercise at the same intensity.

These principles are at the basis of the application of the critical power model for intermittent exercise proposed by Morton and Billat (2004). In fact, their application has more general value than reported above, because it admits not only $\dot{w}_e > \dot{w}_{cr}$, but also $\dot{w}_{cr} > \dot{w}_r \geq 0$ W, in which case the oscillations between $\dot{w}_e$ and $\dot{w}_r$ are reduced in amplitude. These inequalities may also be seen as constraints, and so Morton and Billat (2004) did, as long as they considered the power above $\dot{w}_{cr}$ as anaerobic, although it is a mixture of aerobic and anaerobic metabolism. Indeed, the only actual constraint is to have two different power values during exercise and recovery, the former being higher than the latter, in a condition allowing computation of an accurate energy balance. I nevertheless agree with them that only taking $\dot{w}_e > \dot{w}_{cr}$ would allow the establishment of a $\dot{w}_e$ versus t_{lim} relationship for intermittent exercise.

The metabolic energy, aerobic and anaerobic, above $\dot{w}_{cr}$ at each $\dot{w}_e$ interval is delivered at a rate that is equal to the ratio between the $\dot{w}_e - \dot{w}_{cr}$ difference and the mechanical efficiency η. Its amount in each time fraction spent at $\dot{w}_e$ corresponds to:

$$E_e = \frac{\dot{w}_e - \dot{w}_{cr}}{\eta} t_e \tag{5.12}$$

where subfix e indicates any period at $\dot{w}_e$ into which t_{lim} is subdivided, with $t_{lim} = n\ t_e$. During each recovery interval, however, anaerobic capacity is partially refilled at a rate that depends on (i) the difference between $\dot{E}_e$ and $\dot{E}_r$, (ii) the time constant of the oxygen debt payment during the recovery phase, (iii) the rate of blood lactate accumulation during each $\dot{w}_e$ interval and (iv) the rate of blood lactate removal during each $\dot{w}_r$ interval, which in turn is a function of $\dot{w}_r$ (Gisolfi et al. 1966). The combination of the effects of the ensemble of these factors determines the rate of depletion of anaerobic energy sources, which dictates the changes in t_{lim} ($=n\ t_e$) with respect to the value obtained during continuous exercise.

Morton and Billat (2004) assumed a faster rate of anaerobic energy sources depletion during intermittent exercise with any given $\dot{w}_e$ and $\dot{w}_r$ combination than one would compute on the basis of the analysis proposed here above, as a consequence of their assertion that all the power above $\dot{w}_{cr}$ is derived from anaerobic metabolism. In the preceding paragraph, I tried to demonstrate that this assertion is not correct. There is, however, a further aspect to consider, namely that anaerobic lactic capacity may be up to twice larger during intermittent than during continuous exercise at the same power, as indicated by the classical results of Osnes and Hermansen (1972): this being the case, for the same rate of anaerobic energy sources depletion t_{lim} would become correspondingly longer. A theoretical analysis of the effects of intermittent exercise on the $\dot{w}_e$ versus t_{lim} relationship is depicted in Fig. 5.2. Morton and Billat (2004) obtained a 18 % decrease in $\dot{w}_{cr}$ (in fact its equivalent during running, i.e. critical velocity) and a 16 % increase in anaerobic work (in fact mechanical work above the $\dot{w}_{cr}$) during intermittent running than during continuous running at the same exercising speed, although their results are to be taken with caution in view of the limited number of observation.

The Relationship Between $\dot{V}O_{2max}$, Critical Power and Maximal Aerobic Power

As pointed out in Chap. 4, ramp protocols have attained worldwide diffusion in the performance of exercise testing and the measurement of maximal oxygen consumption ($\dot{V}O_{2max}$). A mechanical analysis of ramp protocols helps shedding light on the relationship between $\dot{w}_{cr}$ and $\dot{w}_{max}$. To this aim, it is important to remind that the highest power attained at the end of a ramp protocol (peak power, $\dot{w}_{peak}$) **is not** the $\dot{w}_{max}$, is higher than $\dot{w}_{max}$ and is higher the greater the ramp slope.

On one side, Whipp (1994) analysed the links between $\dot{w}_{peak}$ and $\dot{w}_{max}$. His model, concerning discrete ramps with steps of varying duration, implies an inverse

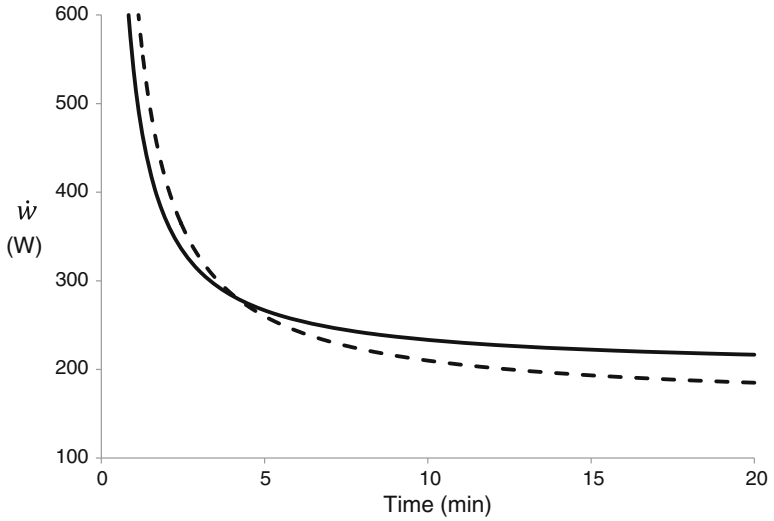


Fig. 5.2 Theoretical analysis of the effects of intermittent exercise on the power ($\dot{w}$) versus time relationship. The continuous curve refers to continuous exercise and the dashed curve to intermittent exercise. The critical power was 200 and 160 W, respectively, after assuming a critical power decrease in intermittent exercise equal to that reported by Morton and Billat (2004). The curvature increase was assumed to be larger (+50 %) than reported by these authors, to account for a higher apparent anaerobic capacity in intermittent exercise

relationship between $\dot{w}_{peak}$ and step duration, described by the following translated equilateral hyperbola:

$$T_S \cdot \left(\dot{w}_{peak} - b\right) = a \tag{5.13}$$

where T_S is the step duration, constant b is equivalent to $\dot{w}_{max}$ and constant a to the anaerobic work, i.e. the amount of mechanical work carried out relying on anaerobic energy sources. Solving Eq. (5.13) for $\dot{w}_{peak}$ yields:

$$\dot{w}_{peak} = \frac{a}{T_S} + b \tag{5.14}$$

Equation (5.14) describes a linear relationship between $\dot{w}_{peak}$ and $1/T_S$, with slope equal to a and y-intercept equal to b, for which Adami et al. (2013) obtained a = 2.61 kJ and b = 264 W: the latter value corresponded well to the experimental $\dot{w}_{max}$ that the same authors determined during a classical $\dot{V}O_{2max}$ protocol (267 W).

On the other side, Morton (1994, 2011) assumed that the $\dot{w}$ in a ramp test increases continuously with time (t) at a constant rate. Consequently, he implied a linear relationship between $\dot{w}$ and t whose angular coefficient is the ramp slope (S). In this case, the total mechanical work performed during a ramp is equal to the area

of the triangle under the $\dot{w}$ versus t line (see Fig. 5.3). On this basis, Morton (1994) developed an algebraic system which led to the following equation:

$$T = \frac{\dot{w}_{cr}}{S} + \sqrt{\frac{2W'}{S}} \tag{5.15}$$

where T is the time to exhaustion and W' is the work carried out above $\dot{w}_{cr}$ in a ramp test. If we then multiply Eq. (5.15) by S, we get:

$$S \cdot T = \dot{w}_{peak} = \dot{w}_{cr} + \sqrt{2W'S} \tag{5.16}$$

Equation (5.16) predicts that, if we plot $\dot{w}_{peak}$ as a function of $\sqrt{S}$, we obtain linear relationships with slope equal to $\sqrt{2W'}$ and y-intercept equal to $\dot{w}_{cr}$. Adami et al. (2013) constructed such a plot (Fig. 5.4) and obtained $\dot{w}_{cr} = 198$ watt, i.e. 74.2 % of the $\dot{w}_{max}$ determined on the same subjects, and $W' = 16.8$ kJ. Similar values for W' were obtained also by Morton et al. (1997). It is of note that, according to Adami et al. (2013), W' was seven times greater than constant a of Whipp's model, despite being calculated from the same experimental results. This discrepancy confirms that, whereas a refers indeed to the energy from anaerobic

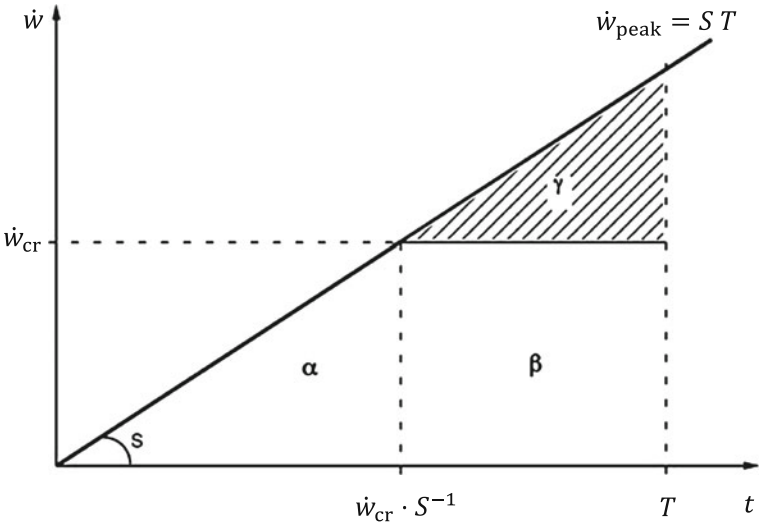


Fig. 5.3 Geometric representation of the work done during a ramp test. The *straight bold line* represents the increment of power ($\dot{w}$) as a function of time (t). The angular coefficient of this line coincides with the ramp slope (S). $\dot{w}_{cr}$ indicates the critical power and T the time to exhaustion. The *area of triangle* α is equal to $1/2\dot{w}_{cr}^2 S^{-1}$. The *area of rectangle* β is equal to $\dot{w}_{cr}(T - \dot{w}_{cr}S^{-1})$. The *area of triangle* γ is equal to $1/2(\dot{w}_{peak} - \dot{w}_{cr})(T - \dot{w}_{cr}S^{-1})$. Morton (2011) identified the area of triangle γ (striped area in this figure) as the anaerobic work capacity. The sum of areas α + β + γ corresponds to the total mechanical work performed ($1/2\dot{w}_{peak}T$). Modified after Adami et al. (2013)

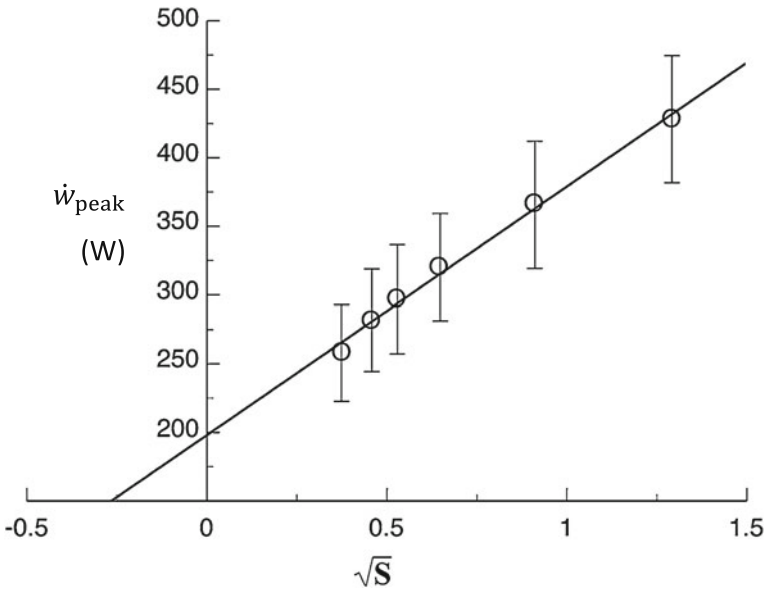


Fig. 5.4 An experimental analysis of Morton's model of ramp tests, whereby peak power ($\dot{w}_{peak}$) is plotted as a function of the square root of the mean ramp slope (S). Data are presented as mean ± SD. The regression line was calculated on the ensemble of the individual data, from Adami et al. (2013)

sources sustaining supramaximal powers, W', which includes a, is the energy (aerobic and anaerobic) sustaining all the work carried out above $\dot{w}_{cr}$, as previously discussed.

In both models, $\dot{w}_{max}$ varies only with the mean ramp slope, whereas $\dot{w}_{cr}$ (in Morton's model) and $\dot{w}_{max}$ (in Whipp's model) are constants. As a consequence, for any given ramp, Eqs. (5.14) and (5.16) must produce equivalent results, i.e. they must yield the same $\dot{w}_{peak}$ value. This allows combination of these two equations, to obtain, after rearrangement (Adami et al. 2013):

$$\sqrt{2W'S} = \frac{a}{T_S} + (\dot{w}_{max} - \dot{w}_{cr}). \tag{5.17}$$

Equation (5.17) tells that $\sqrt{2W'S}$ is a linear function of $1/T_S$, with y-intercept equal to $(\dot{w}_{max} - \dot{w}_{cr})$ and slope equal to a. Thus, (i) the difference between $\dot{w}_{max}$ and $\dot{w}_{cr}$ is a constant, independent of anaerobic capacity, step duration and ramp slope; (ii) $\dot{w}_{max}$ and $\dot{w}_{cr}$ are linked by precise quantitative relations and can vary only by the same absolute amount; and (iii) the ratio between $\dot{w}_{cr}$ and $\dot{w}_{max}$ gets higher the higher is $\dot{w}_{max}$.

Equation (5.17) provides the theoretical basis explaining several observations about $\dot{w}_{cr}$. The fact that the $\dot{w}_{cr}/\dot{w}_{max}$ ratio (i) is higher in athletes with elevated $\dot{V}O_{2max}$ (Heubert et al. 2005) than in subjects with low $\dot{V}O_{2max}$ (Adami et al. 2013),

(ii) increases with aerobic training (Heubert et al. 2003; Jenkins and Quigley 1992) and high-intensity interval training (Gaesser and Wilson 1988) and (iii) decreases in hypoxia (Dekerle et al. 2012; Valli et al. 2011) is fully coherent with Eq. (5.17). Finally, Eq. (5.17) implies that $\dot{w}_{max}$ has a radically different meaning from $\dot{w}_{peak}$. It defines the maximal $\dot{w}$ that can be attained by the contracting muscle mass thanks to the convertion of chemical energy into mechanical work by aerobic metabolism. A theoretical corollary of this definition is the linearity of the $\dot{V}O_2$ versus $\dot{w}$ relationship along the entire $\dot{w}$ range, provided the phase II asymptote for oxygen consumption (see Chap. 3) is taken as representative of the necessary aerobic power to sustain muscle contraction at powers above $\dot{w}_{cr}$.

Simultaneous Determination of Critical Power and Maximal Aerobic Power

The procedure for the determination of $\dot{w}_{cr}$ and of the relationship between $\dot{w}$ and t_{lim} is complex, cumbersome and long. It requires performance of several constant-load exercises at powers higher than $\dot{w}_{cr}$ up to exhaustion. The need of allowing adequate recovery periods between successive tests implies that a $\dot{w}_{cr}$ determination cannot be completed within one experimental day (Hill 2004; Jenkins and Quigley 1992; Moritani et al. 1981; Morton et al. 1997). These constraints have limited its application to routine exercise testing.

Equation (5.17) provides a nice tool for determining the absolute difference between $\dot{w}_{max}$ and $\dot{w}_{cr}$ after ramp tests. Although also this procedure requires the performance of multiple tests, the duration of each test is however shorter than that of exhaustive continuous exercises at powers higher than $\dot{w}_{cr}$. Thus, estimating $\dot{w}_{max}$ and $\dot{w}_{cr}$ after ramp tests by a procedure including Eq. (5.17) would represent a significant step forward in the procedures for exercise testing.

The use of ramp tests for the estimate of $\dot{w}_{max}$ and $\dot{w}_{cr}$ requires an assumption concerning W' and the knowledge of precise values of S and T_S, which in fact are predetermined for each ramp. In ordinary conditions, W' can be estimated after Adami et al. (2013). With three discrete ramp tests up to exhaustion, an equivalent of Fig. 5.4 can be constructed. This figure allows computations of the characteristic parameters of Eq. (5.17) by linear regression analysis. Of the three ramps that are necessary to construct Fig. 5.4, one should be carried on with a modified procedure, foreseeing the measurement of oxygen uptake ($\dot{V}O_2$). This ramp should consist of a few $\dot{w}$ below $\dot{w}_{cr}$, carried out until steady state, followed by a steep ramp: the ramp would provide the $\dot{V}O_{2max}$ value of the subject, and the steady-state light steps would allow construction of the submaximal $\dot{V}O_2$ versus $\dot{w}$ line. Extrapolation then of this line up to $\dot{V}O_{2max}$ would provide an estimate of the $\dot{w}_{max}$ value. Since Eq. (5.17) provides a value for the absolute difference between $\dot{w}_{max}$ and $\dot{w}_{cr}$, this last would then easily be obtained. The implicit assumption, of course, is that, according to the energetic principles discussed in Chap. 3, the extra $\dot{V}O_2$ related to

the appearance of the slow component is not included in the rate of aerobic metabolism that is necessary to sustain the energy transformation during muscle contraction.

The Three-Parameter Model of Critical Power

The three-parameter model for $\dot{w}_{cr}$ (Morton 1996) is a generalization of the basic $\dot{w}_{cr}$ model discussed so far, which we may also call the two-parameter model. Only one difference exists between the two mathematical developments: in the basic $\dot{w}_{cr}$ model, the x-axis asymptote of the $\dot{w}$ versus t_{lim} relationship is constrained to 0, whereas in the three-parameter model, it is let to vary and thus to take different values from 0. In this form, the x-axis asymptote (k_t) is considered as a third parameter of the critical power model, which needs to be determined.

In this new context, the solution for W' of Eq. (5.1), which represents a particular case of the three-parameter model for $k_t = 0$ s, takes the following general form:

$$(\dot{w} - \dot{w}_{cr})(t_{lim} - k_t) = W' \tag{5.18}$$

From an analytical viewpoint, this means that the hyperbola describing the relationship between $\dot{w}$ and t_{lim} is translated not only on the y-axis, but also on the x-axis (see Fig. 5.5). Of course k_t, which is a negative time, has no practical use. However, a leftward x-axis translation means that there is a finite positive y-axis intercept, corresponding to the power attained when $t_{lim} = 0$ s, i.e. the maximum instantaneous power ($\dot{w}_0$). From the physiological viewpoint, determination of constant k_t is a tool allowing computation of $\dot{w}_0$.

In theory, $\dot{w}_0$ is the power which can be developed starting from rest when the rate of anaerobic energy store depletion is infinite. In practice, the closest concept to $\dot{w}_0$ is that of maximal instantaneous anaerobic alactic power, related to the maximal rate of ATP splitting (see Chap. 6), which may be sustained for a few milliseconds. Since the maximal anaerobic power decreases when the amount of anaerobic alactic energy stores is decreased, the three-parameter model carries along three corollaries: (i) a decrease in anaerobic energy stores implies a decrease not only in W', but also in k_t, so that the $\dot{w}$ versus t_{lim} relationship not only takes a different curvature, but is also displaced leftward; (ii) $\dot{w}_{cr}$ is independent of k_t; and (iii) when anaerobic alactic energy stores are fully depleted, energy liberation is impossible at powers higher than $\dot{w}_{cr}$.

The three-parameter model can be applied to the analysis of ramp exercise. In fact, Eq. (5.15) is simply a solution of the following more general equation

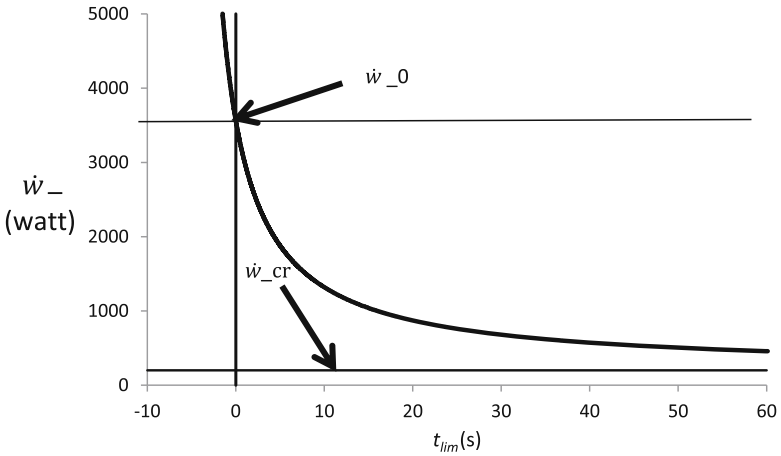


Fig. 5.5 Graphical representation of the three-parameter model of critical power. The relationship between power ($\dot{w}$) and time to exhaustion (t_{lim}) for high-intensity exercise is reported for the time window 1 to 60 s. The critical power ($\dot{w}_{cr}$) and the energy store component obtained by Adami et al. (2013) were used. The x-axis asymptote is equal to −6 s. *Arrows* indicate $\dot{w}_{cr}$ and the power for t_{lim} = 0 s. The latter corresponds to the maximal instantaneous anaerobic power

$$T = \frac{\dot{w}_{cr}}{S} + \sqrt{\left(k_t^2 + \frac{2W'}{S}\right)} + k_t \tag{5.19}$$

for the special case in which k_t = 0 s. If we then multiply Eq. (5.19) by S, we get:

$$S \cdot T = \dot{w}_{peak} = \dot{w}_{cr} + \sqrt{\left(S^2 k_t^2 + 2W'S\right)} + Sk_t \tag{5.20}$$

As a consequence, combination of Eqs. (5.14) (Whipp's model) and (5.20) yields:

$$\sqrt{\left(S^2 k_t^2 + 2W'S\right)} + Sk_t = \frac{a}{T_S} + \left(\dot{w}_{max} - \dot{w}_{cr}\right) \tag{5.21}$$

The left-hand branches of Eqs. (5.17) and (5.21) are both equal to the difference between $\dot{w}_{peak}$ and $\dot{w}_{cr}$, which is a linear function of $\frac{1}{T_S}$. If both $\dot{w}_{cr}$ models were correct, the basic model being just a particular case of the three-parameter model, they should yield, for any value of S, the same $\dot{w}_{peak}$ values. This would be so only if the values taken by constants k_t and W' remain invariant, or if they vary in such a way as to compensate one for the other. Neither is the case: the three-parameter model implies only a horizontal shift of the hyperbola describing the $\dot{w}$ versus t_{lim} relationship, without changes in its curvature, as long as anaerobic alactic energy stores are not reduced. As a consequence, moving from the two- to the three-parameter

model implies variations of k_t without changes in W', so that the two models cannot predict the same $\dot{w}_{peak}$ values. As long as we operate on the flat part of the hyperbola, e.g. for $t_{lim} > 5$ min, the differences between the two models are negligible, but the resulting $\dot{w}_{peak}$ values diverge progressively as t_{lim} decreases below 5 min, well into the supramaximal exercise domain. The largest difference is observed at $t_{lim} = 0$ min: the corresponding power, $\dot{w}_0$, is equal to ∞ in the two-parameter model, but takes a finite value, close to the maximal instantaneous anaerobic alactic power, in the three-parameter model. Measured values of maximal power during explosive exercise, for which $t_{lim} < 2$ min, are compatible with the latter, not with the former $\dot{w}_{cr}$ model.

When we move to the analysis of ramp exercise, a consequence of what precedes is that the relationship reported in Fig. 5.4 would change, if we use the three-parameter model. In fact, letting k_t vary implies a shift of the y-intercept by an amount equivalent to Sk_t. Moreover, since k_t has a relation to a, also the slope changes. Thus, since S varies among different ramps, each point in Fig. 5.4 would lie on a different relationship, with different slope and y-intercept. Thus, when looking into the overall physiological relationship reported in Fig. 5.4, a curve would be obtained. The relationship shown in Fig. 5.4 was constructed inside the two-parameter model of $\dot{w}_{cr}$. Despite representing a special case, wherein a linear rather than nonlinear relationship is imposed by introducing the constraint of $k_t = 0$ s, it nevertheless provides acceptable estimates of $\dot{w}_{max} - \dot{w}_{cr}$, as long as it does not include powers implying large differences between the two models. Nevertheless, no quantitative analyses after experimental data obtained during ramp exercise could be done so far, due to the difficulty of attributing specific, different a values for each ramp within the frame of Whipp's model.

Conclusions

The $\dot{w}_{cr}$, i.e. the y-axis asymptote of the power–time relationship, is the highest power that can be sustained relying exclusively on aerobic metabolism, although unevenly distributed among muscle fibres, and thus, it is the highest power for which $\dot{V}O_2$ is in practice, not only in theory, the sole source of energy. At all powers above $\dot{w}_{cr}$, there is a continuous increase in blood lactate concentration, even though $\dot{V}O_2$ does still increase with power. As a consequence, the slow component appears until the time of exhaustion is attained. There is a direct link between $\dot{w}_{cr}$ and $\dot{w}_{max}$, but $\dot{w}_{cr}$ is independent of anaerobic capacity. The determination of $\dot{w}_{cr}$ is a key issue in exercise testing. Procedures for simplifying its determination have been proposed.

The three-parameter model of $\dot{w}_{cr}$ is an excellent theoretical tool, which includes and summarizes the mechanics of all exercise modes up to exhaustion. It provides estimates that better correspond to the peak power values that are measured during explosive exercise in the supramaximal domain. It describes all powers higher than

$\dot{w}_{cr}$ under the cover of a unique equation, namely Eq. (5.18). This equation, however, has limited practical value in applied sport science, for its complexity (three instead of two constants) and for the experimental irrelevance of some of them.

References

Adami A, Sivieri A, Moia C, Perini R, Ferretti G (2013) Effects of step duration in incremental ramp protocols on peak power and maximal oxygen consumption. Eur J Appl Physiol 113:2647–2653

Binzoni T, Ferretti G, Schenker K, Cerretelli P (1992) Phosphocreatine hydrolysis by ^{31}P-NMR at the onset of constant-load exercise in humans. J Appl Physiol 73:1643–1649

Cerretelli P, Pendergast DR, Paganelli WC, Rennie DW (1979) Effects of specific muscle training on $\dot{V}O_2$-on response and early blood lactate. J Appl Physiol 47:761–769

Dekerle J, Mucci P, Carter H (2012) Influence of moderate hypoxia on tolerance to high-intensity exercise. Eur J Appl Physiol 112:327–335

di Prampero PE, Ferretti G (1999) The energetics of anaerobic muscle metabolism: a reappraisal of older and recent concepts. Respir Physiol Neurobiol 118:103–115

di Prampero PE, Francescato MP, Cettolo V (2003) Energetics of muscle exercise at work onset: the steady-state approach. Pflügers Arch 445:741–746

Ferguson C, Rossiter HB, Whipp BJ, Cathcart AJ, Murgatroyd SR, Ward SA (2010) Effect of recovery duration from prior exhaustive exercise on the parameters of the power-duration relationship. J Appl Physiol 108:866–874

Ferguson C, Whipp BJ, Cathcart AJ, Rossiter HB, Turner AP, Ward SA (2007) Effects of prior very-heavy intensity exercise on indices of aerobic function and high-intensity exercise tolerance. J Appl Physiol 103:812–822

Francescato MP, Cettolo V, di Prampero PE (2008) Influence of phosphagen concentration on phosphocreatine breakdown kinetics. Data from human gastrocnemius muscle. J Appl Physiol 105:158–164

Francescato MP, Cettolo V, di Prampero PE (2013) Oxygen uptake kinetics at work onset: role of cardiac output and of phosphocreatine breakdown. Respir Physiol Neurobiol 185:287–295

Gaesser GA, Wilson LA (1988) Effects of continuous and interval training on the parameters of the power-endurance time relationship for high-intensity exercise. Int J Sports Med 9:417–421

Gisolfi F, Robinson S, Turrell ES (1966) Effects of aerobic work performed during recovery from exhausting work. J Appl Physiol 21:1767–1772

Heubert RAP, Billat VL, Chasseaing P, Bocquet V, Morton RH, Koralsztein JP, di Prampero PE (2005) Effects of a previous sprint on the parameters of the work-time to exhaustion relationship in high intensity cycling. Int J Sport Med 26:583–592

Heubert R, Bocquet V, Koralsztein JP, Billat VL (2003) Effets de 4 semaines d'entraînement sur le temps limite à $\dot{V}O_{2max}$. Can J Appl Physiol 28: 717–736

Hill DW (1993) The critical power concept. Sports Med 16:237–254

Hill DW (2004) The relationship between power and time to fatigue in cycle ergometer exercise. Int J Sports Med 25:357–361

Hoffman MD (2010) Performance trend in 161-km ultramarathons. Int J Sports Med 31:31–37

Jenkins DG, Quigley BM (1992) Endurance training enhances critical power. Med Sci Sports Exerc 24:1283–1289

Jenkins DG, Quigley BM (1993) The influence of high-intensity exercise training on the W_{lim}–T_{lim} relationship. Med Sci Sports Exerc 25:275–282

Jones AM, Poole DC (2009) Physiological demands of endurance exercise. In: Maughan RJ (ed) Olympic textbook of science in sport. Blackwell, Chichester, pp 43–55

Jones AM, Vanhatalo A, Burnley M, Morton RH, Poole DC (2010) Critical power: implications for the determination of $\dot{V}O_{2max}$ and exercise tolerance. Med Sci Sports Exerc 42:1876–1890
Kendall KL, Smith AE, Graef JL, Fukuda DH, Moon JR, Beck TW, Cramer JT, Stout JR (2009) Effects of four weeks of high-intensity interval training and creatine supplementation on critical power and anaerobic working capacity in college-aged men. J Strength Cond Res 23:1663–1669
Miura A, Sato H, Sato H, Whipp BJ, Fukuba Y (2000) The effect of glycogen depletion on the curvature constant parameter of the power–duration curve for cycle ergometry. Ergonomics 43:133–141
Miura A, Shiragiku C, Hirotoshi Y, Kitano A, Endo MY, Barstow TJ, Morton RH, Fukuba Y (2009) The effect of prior heavy exercise on the parameters of the power-duration curve for cycle ergometry. Appl Physiol Nutr Metab 34:1001–1007
Monod H, Scherrer J (1965) The work capacity of a synergic muscular group. Ergonomics 8:329–338
Moritani T, Nagata A, deVries HA, Muro M (1981) Critical power as a measure of physical work capacity and anaerobic threshold. Ergonomics 24:339–350
Morton RH (1994) Critical power test for ramp exercise. Eur J Appl Physiol 69:435–438
Morton RH (1996) A 3-parameter critical power model. Ergonomics 39:611–619
Morton RH (2011) Why peak power is higher at the end of steeper ramps: an explanation based on the "critical power" concept. J Sport Sci 29:307–309
Morton RH, Billat LV (2004) The critical power model for intermittent exercise. Eur J Appl Physiol 91:303–307
Morton RH, Green S, Bishop D, Jenkins DG (1997) Ramp and constant power trials produce equivalent critical power estimates. Med Sci Sports Exerc 29:833–836
Osnes JB, Hermansen L (1972) Acid base balance after maximal exercise of short duration. J Appl Physiol 32:59–63
Parker Simpson L, Jones AM, Skiba PF, Vanhatalo A, Wilkerson D (2014) Influence of hypoxia on the power-duration relationship during high-intensity exercise. Int J Sports Med, e-pub ahead of print. doi:10.1055/s-0034-1389943
Poole DC, Ward SA, Gardner GW, Whipp BJ (1988) Metabolic and respiratory profile of the upper limit for prolonged exercise in man. Ergonomics 31:1265–1279
Poole DC, Ward SA, Whipp BJ (1990) The effects of training on the metabolic and respiratory profile of high-intensity cycle ergometer exercise. Eur J Appl Physiol 59:421–429
Pringle JSM, Jones AM (2002) Maximal lactate steady state, critical power and EMG during cycling. Eur J Appl Physiol 88:214–226
Rossiter HB, Ward SA, Doyle VL, Howe FA, Griffiths JA, Whipp BJ (1999) Inferences from pulmonary O_2 uptake with respect to intramuscular [phosphocreatine] kinetics during moderate exercise in humans. J Physiol 518:921–932
Rossiter HB, Ward SA, Kowalchuk JM, Howe FA, Griffiths JR, Whipp BJ (2002) Dynamic asymmetry of phosphocreatine concentration and O_2 uptake between the on- and off-transients of moderate- and high-intensity exercise in humans. J Physiol 541:991–1002
Saltin B (1973) Oxygen transport by the circulatory system during exercise in man. In: Keul J (ed) Limiting factors of physical performance. Thieme, Stuttgart, pp 235–252
Sawyer BJ, Stokes DG, Womack CJ, Morton RH, Weltman A, Gaesser GA (2014) Strength training increases endurance time to exhaustion during high-intensity exercise despite no change in critical power. J Strength Cond Res 28:601–609
Smith JC, Stephens DP, Hall EL, Jackson AW, Earnest CP (1998) Effect of oral creatine ingestion on parameters of the work rate–time relationship and time to exhaustion in high-intensity cycling. Eur J Appl Physiol 77:360–365
Valli G, Cogo A, Passino C, Bonardi D, Morici G, Fasano V, Agnesi M, Bernardi L, Ferrazza AM, Ward SA, Palange P (2011) Exercise intolerance at high altitude (5050 m): critical power and W′. Respir Physiol Neurobiol 177:333–341
Vanhatalo A, Doust JH, Burnley M (2008) A 3-min all-out cycling test is sensitive to a change in critical power. Med Sci Sports Exerc 40:1693–1699

Vanhatalo A, Fulford J, DiMenna FJ, Jones AM (2010) Influence of hyperoxia on muscle metabolic responses and the power–duration relationship during severe-intensity exercise in humans: a ^{31}P magnetic resonance spectroscopy study. Exp Physiol 95:528–540

Vanhatalo A, Jones AM (2009) Influence of prior sprint exercise on the parameters of the "all-out critical power test" in men. Exp Physiol 94:255–263

Whipp BJ (1994) The bioenergetic and gas exchange basis of exercise testing. Clin Chest Med 15:173–192

Chapter 6
Supramaximal Exercise

Abstract Powers higher than the maximal aerobic power can be attained relying on anaerobic lactic and alactic metabolisms as energy source. These metabolisms are analysed separately in this Chapter, where the power and capacity of both have been quantified. Anaerobic lactic metabolism has been treated first, although it is still a controversial issue on quantitative grounds, because several authors denied the possibility of performing a correct estimate of the metabolic energy corresponding to a mole of lactate accumulation in blood. Thus, its analysis is preceded by a preliminary discussion of the principles and assumption behind the concept of energetic meaning of blood lactate accumulation is based. Then, anaerobic alactic metabolism is discussed, for which a distinction between average and instantaneous powers is introduced: the former reflects the rate of ATP resynthesis from the Lohmann's reaction and the latter refers to the maximal rate of ATP hydrolysis and concerns the ATP already available at the contraction site. This analysis shows that the maximal power generated by anaerobic alactic metabolism is extremely high, up to some 20 times higher than the maximal aerobic power for the instantaneous methods. The price to pay for this is an extremely low capacity, so that exercise can be sustained at maximal power only for a very short time, of the order of a few seconds for average power, some milliseconds for instantaneous power. Such an organization of energetic metabolism, with a wide range of powers and capacities for the ensemble of the metabolic pathways, allows animals, humans included, to face the multiple needs that a prey–predator system imposes. In general terms, animals have evolved in such a way that power is highest when capacity is lowest, and vice versa.

Contents

G. Ferretti, *Energetics of Muscular Exercise*,
DOI 10.1007/978-3-319-05636-4_6

Introduction

The maximal aerobic power ($\dot{w}_{max}$) is not the highest power that a human can develop. Powers higher than the $\dot{w}_{max}$ can be attained relying only on anaerobic metabolism as an energy source. In this case, the general equation of the energetics of muscular exercise takes the following form:

$$\dot{E} \propto \overleftarrow{\dot{A}TP} = \overrightarrow{\dot{A}TP} = c\dot{V}O_{2max} + b\dot{L}a + a\dot{P}C \tag{6.1}$$

where the two terms $b\dot{L}a$ and $a\dot{P}C$ indicate the amount of ATP that is generated from anaerobic lactic metabolism and anaerobic alactic metabolism, respectively. These are analysed separately in this chapter. Of both, the power and capacity are quantified. From a more general perspective, the aim of this chapter was indeed to discuss the energetics of explosive supramaximal exercise.

I will treat anaerobic lactic metabolism first, of which some hints have already been given in previous chapters, especially as far as the genesis of early lactate accumulation during exercise transients is concerned. Several aspects of anaerobic alactic metabolism were also treated previously, as long as this is the main contributor to the obligatory component of the oxygen deficit. Anaerobic lactic metabolism as an energy source is, however, still a controversial issue on quantitative grounds, because several authors denied the possibility of performing a correct estimate of the metabolic energy corresponding to a mole of lactate accumulation in blood. As a consequence, the study of the energetics of anaerobic supramaximal exercise underwent decay in recent years, so that our current knowledge still relies mostly on the classical results obtained by the School of Margaria between the sixties and the eighties of last century. A preliminary discussion of the principles on which the energetic meaning of blood lactate accumulation is based is therefore necessary.

The Meaning of Blood Lactate in Supramaximal Exercise

Let us take as an axiom the concept that maximal oxygen consumption represents the uppermost limit of aerobic metabolism. As a necessary consequence, the metabolic power above $\dot{w}_{max}$ can derive only from anaerobic energy sources. Apart

from the contraction of the obligatory component of the oxygen deficit, which occurs also in the early stages of a supramaximal exercise, reliance is mostly made on anaerobic lactic metabolism. On this basis, on the assumption that the overall metabolic power is directly proportional to the applied mechanical power also during supramaximal exercise, Margaria et al. (1963b) predicted that the rate at which lactic acid is produced, and thus accumulates in blood (and I would add in muscle), is a constant whose value depends on the size of the applied supramaximal power. Experimental validation of this prediction implies linear relationships between blood lactate concentration ($[La]_b$) and exercise time during constant-power supramaximal exercise, with higher slopes the higher is the applied mechanical power. In order to establish these relationships, Margaria et al. (1963b) performed supramaximal exercises of varying intensities while running on a treadmill at various inclines. At each speed and incline, the subjects repeated several trials of progressively increasing duration up to exhaustion. At the end of each trial, the subjects rested and $[La]_b$ was measured throughout the recovery period. This led to the demonstration of the predicted linear relationships between $[La]_b$ and time, and to the demonstration that, as put 50 years ago, the rate at which lactic acid is *produced* (in g kg^{-1} min^{-1})—actually accumulated, and on average, as more correctly pointed out by di Prampero and Ferretti (1999)—increases linearly with the corresponding metabolic power (in kcal kg^{-1} min^{-1}) (Fig. 6.1). The intercept on the *x*-axis of this line was considered indicative of the metabolic power below which no net lactate production occurs (an oversimplification indeed). The slope of the line was taken as a measure of the amount of energy released in vivo by the production of 1 mmol of lactic acid: it amounted to 222 cal g^{-1} or 84 kJ mol^{-1}. Moreover, assuming that (i) the peak concentration of lactic acid between the 5th and the 8th min of recovery is the same in all body fluids (attainment of equilibrium in lactate concentration) and (ii) the water fractions of the blood and of the whole body are 0.8 and 0.6 respectively, Margaria et al. (1963a, b) deemed possible to estimate the amount of lactic acid produced per kg of body mass.

Those results, however, were affected by numerous assumptions, some of which were undemonstrated in those times. Moreover, Margaria et al. (1963b) had the inadvertence of speaking of lactate production rather than lactate accumulation. Therefore, despite the consistency of the evidence that was being progressively accumulated, a stirred debate developed around the concept of energy equivalent of blood lactate accumulation and the energetic significance of lactic acid production. In particular, the concept of equilibrium in lactate distribution was contested by the Scandinavian school of exercise physiology. According to di Prampero and Ferretti (1999), this precluded a widespread practical use of these concepts in vivo, thus finally hindering the progress of our knowledge in the field. I strongly maintain that the **energy equivalent of blood lactate accumulation**, even though with some cautions and less emphasis than in the past, is and remains a key concept, of extreme utility in the analysis of whole-body energy expenditure during supramaximal exercise (di Prampero 1981).

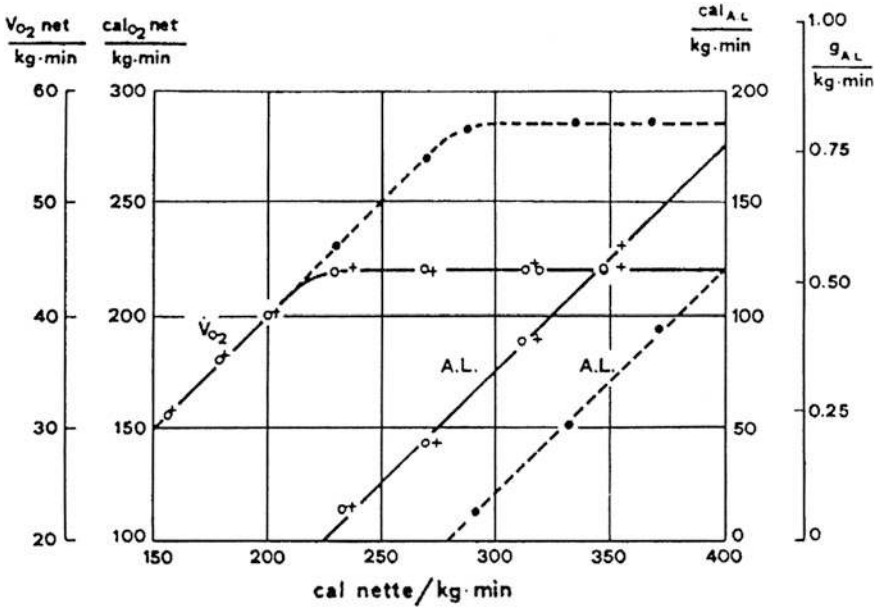


Fig. 6.1 Lactate increase in the body, expressed in g kg^{-1} min^{-1} (*right ordinate*) and net steady-state oxygen consumption per unit of body mass (*left ordinate*) as a function of power, expressed in cal kg^{-1} min^{-1}. *Full lines* refer to non-athletes, *dashed lines* to athletes. The *full line* for lactate intercepts the *x*-axis at a power equal to 220 cal kg^{-1} min^{-1}, approximately the same value at which the corresponding oxygen consumption line reaches its maximum. According to Margaria et al. (1963b), below this power no lactate was produced and the power was sustained by aerobic metabolism. The lactate line for athletes is displaced to the right. This indicates higher aerobic power and maximal oxygen consumption. The slope of the two lactate lines is the same. Its value indicates an energy "production" of 222 cal g^{-1} of lactate formed. From Margaria et al. (1963b)

On the Distribution of Lactate

Margaria et al. (1963b) calculated the rate of lactate *production* per unit of body mass, on the assumption that the peak $[La]_b$ attained between min 5 and 8 of resting recovery after the end of an exercise bout represented the attainment of an equilibrium in lactate concentration in blood and interstitial fluids. This concentration was also assumed to be equal in all body compartments. The latter assumption was demonstrated to be incorrect, as long as (i) lactate anions at equilibrium are mostly located in the extracellular phase (Roos 1975), so that (ii) lactate concentration gradients between intracellular and interstitial fluids exist, and (iii) a passive equilibrium in lactate concentration is not possible. The further characterization of lactate exchange in terms of lactate–proton co-transport shed new light on the equilibria of lactate dynamics (Bonen 2001; Juel 1997, 1998; Juel and Halestrap 1999), even at the subcellular level (Hashimoto and Brooks 2008). Under these circumstances, it is uneasy to calculate the precise amount of lactate that is

produced per unit of body mass without a preliminary knowledge of the lactate concentrations in intracellular and interstitial fluids and of their respective fractions. We must also consider that lactate, as it is produced, is also removed, so that the peak $[La]_b$ at min 5–8 during recovery is probably less than it would be, where the distribution and mixing of lactate in the body instantaneous. It is easy to state today that the estimate of the energy equivalent of lactate accumulation made by Margaria et al. (1963b) was rough. However, this does not mean that the concept that blood lactate accumulation has an energetic meaning is to be rejected.

Let us assume that peak $[La]_b$ reflects indeed the attainment of the equilibrium in lactate distribution in the extracellular compartments. This equilibrium should be independent of the absolute lactate concentrations in blood, and in interstitial and intracellular fluids, each of which can be assimilated to a capacitance that needs to be "discharged". Thus, after that equilibrium has been attained, two possibilities are given: (i) these capacitances differ in size or in resistance, so that the process of lactate removal is characterized by different time constants, in which case two exponentials are necessary to characterize the function describing lactate removal from the body, or (ii) these two capacitances have the same size and resistance, so that the process of lactate removal from the two body fluids is characterized by equal time constants, in which case a mono-exponential fully describes the entire phenomenon. The body of evidence in favour of the latter hypothesis is important though ancient (Åstrand 1960; di Prampero et al. 1978a, b; Gisolfi et al. 1966; Hermansen and Stensvold 1972; Margaria et al. 1933, 1963b).

A two-compartment model of a different kind, in which one compartment consists of the previously active muscle mass and the other compartment includes the remainder of the volume of blood lactate distribution, was also conceived. This has generated a double-exponential model of lactate removal (Oyono-Enguelle et al. 1993; Zouloumian and Freund 1981), so that some studies have analysed lactate removal after exercise according to this model as well (Freund et al. 1986; Oyono-Enguelle et al. 1990; Taoutaou et al. 1996). This model explains some features of lactate removal immediately after the end of exercise; the first exponential, however, is by far faster than the second, so that the asymptote is quickly attained: therefore, once the equilibrium of lactate concentration in the body has been attained, the first exponential has already reached its asymptote and the further decrease of lactate reflects has the time constant of the second exponential. In other terms, it is as if these two compartments have merged, so that the kinetics of lactate disappearance after recovery min 8 becomes compatible with the classical mono-exponential model.

An elegant quantitative discussion of lactate distribution at equilibrium was carried out by di Prampero (1981). He calculated the ratio of blood to whole-body lactate concentrations at equilibrium, which he demonstrated to be a constant whose value depends on the characteristics of lactate transport across biological membranes, but is independent of the lactate concentrations in the various compartments. Once the equilibrium has been achieved, this constant is invariant with time. Therefore, it could be used for computation of whole-body lactate concentration at the very end of exercise, after determination of the corresponding blood lactate

concentration, by back-extrapolation to recovery time 0 of the exponential equation describing the lactate washout from blood during recovery. On this basis, although with a significant degree of approximation, di Prampero et al. (1978b) were able to estimate that the production of 1 mol of lactate during supramaximal exercise can provide about 100 kJ of metabolic energy. Considering the numerous approximations involved, this figure is remarkably close to that obtained by Margaria et al. (1963b).

The Energetics of Supramaximal Exercise

During supramaximal exercise, oxygen consumption may attain its maximum ($\dot{V}\,O_{2max}$) in less than 1 min. After this time, we can reasonably assume that the energetic contribution from anaerobic alactic energy sources (Lohmann reaction) desists (di Prampero and Ferretti 1999). So the metabolic power after the initial period is the sum of two terms, one being $\dot{V}\,O_{2max}$, the second being related to anaerobic lactic metabolism. As a consequence, the general equation takes the following form:

$$\dot{E} \propto \overleftarrow{\dot{A}TP} = \overrightarrow{\dot{A}TP} = c\,\dot{V}\,O_{2max} + b\,\dot{L}a \tag{6.2}$$

If we express $\dot{E}$ in oxygen equivalents, Eq. (6.2) can be rewritten as follows:

$$\dot{E} = \dot{V}\,O_{2max} + \beta\,\dot{L}a \tag{6.3}$$

where β is the **energy equivalent of blood lactate accumulation**, i.e. the amount of energy generated by the accumulation of 1 mol of lactate in blood, and $\dot{L}a$ is the rate of blood lactate accumulation. Expressing then Eq. (6.3) relative to $\dot{V}\,O_{2max}$ yields

$$\frac{\dot{E}}{\dot{V}\,O_{2max}} = 1 + \frac{\beta\,\dot{L}a}{\dot{V}\,O_{2max}} \tag{6.4}$$

Equation (6.4) allows a comparison of subjects differing in maximal aerobic power and thus working at different levels of supramaximal exercise with different exercise modes. From the data of Margaria et al. (1971a) during treadmill running and Pendergast et al. (1977) during swimming, it was possible to calculate β for both exercise modes. The results, reported in Fig. 6.2, indicate that the energy equivalent of blood lactate accumulation was strikingly similar (3.0 and 2.7 ml O_2 kg^{-1} mM^{-1} for running and swimming, respectively). These values were essentially confirmed by the analysis of further data obtained under a variety of conditions on humans (Cerretelli et al. 1979; di Prampero et al. 1978b; Margaria et al. 1972), dogs (Cerretelli et al. 1964) and isolated–perfused dog gastrocnemii (Cerretelli et al. 1969). More recently, Capelli and di Prampero (1995) measured the

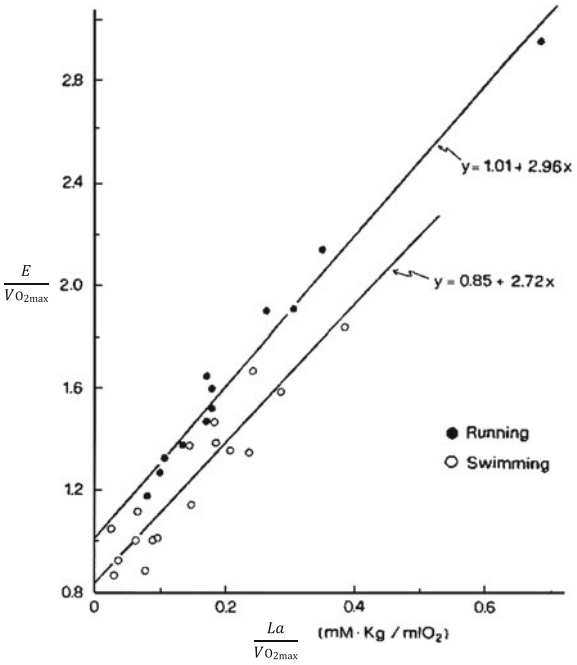


Fig. 6.2 Overall metabolic power ($\dot{E}$) as a function of the rate of blood lactate accumulation ($\dot{L}a$), both expressed relative to the maximal oxygen consumption ($\dot{V}o_{2max}$), in running [*full dots*, from Margaria et al. (1971a)] and swimming [*open dots*, from di Prampero et al. (1978b)]. Constant β is obtained from the slopes of the two regression lines

rate of blood lactate accumulation during supramaximal track cycling in a condition in which $\dot{E}$ was known. This allowed application of Eq. (6.4), from which β during cycling resulted equal to that for running and swimming. It is nowadays admitted that β is a constant whose value is under any circumstances comprised between 2.7 and 3.3 ml O_2 kg^{-1} mM^{-1} (di Prampero and Ferretti 1999).

It is noteworthy that β is not the energetic equivalent of lactate *formation* in the working muscles and does not yield any direct information on the stoichiometric relation between lactate formation and ATP resynthesis. It is nevertheless a constant allowing determination of the energy release in the body whenever $[La]_b$ increases in blood. As an example, take the case of ramp exercise carried out until exhaustion, which is commonly used in exercise testing. During ramp exercise, the highest work loads are supramaximal, and the more the steeper is the ramp. Thus, part of the ramp is performed at powers above the maximal aerobic power, which are sustained by anaerobic lactic metabolism. If the mechanical efficiency of exercise is known, as is the case for exercise on the cycle ergometer, it would be possible to obtain a good estimate of $\dot{E}$ from each value of mechanical power. Solution of Eq. (6.4) for $\dot{L}a$ yields

$$\dot{L}a = \frac{\dot{E} - \dot{V}\,O_{2max}}{\beta} \tag{6.5}$$

which allows estimating, after assuming a value for β, $\dot{L}a$ whenever $\dot{E} > \dot{V}O_{2max}$, e.g. at each step during the final, supramaximal part of a steep ramp test for $\dot{V}O_{2max}$ determination.

The Maximal Lactic Power

Since $[La]_b$ increases linearly with the exercise intensity, one may predict that it attains a maximum when the energy release from anaerobic lactic metabolism requires the highest possible rate of chemical reactions in the glycolytic pathway. This prediction was demonstrated to be correct during strenuous exercise on the treadmill (Margaria et al. 1964). In fact, subjects ran at 18 km h^{-1} at slopes up to 25 %, thus performing exercises requiring a metabolic power larger than twice the maximal aerobic power. The results showed that $\dot{L}a$ attains an invariant maximal value which does not increase by further increasing the exercise intensity (Fig. 6.3). Moreover, the time after which $[La]_b$ starts increasing was found to be shorter the higher is the exercise intensity (displacement on the left of the *x*-axis intercept of the linear relations in Fig. 6.3). Margaria et al. (1964) proposed that the energy sources for the time that precedes the increase in $[La]_b$ were derived from anaerobic alactic metabolism, due to the contraction of the alactic oxygen deficit.

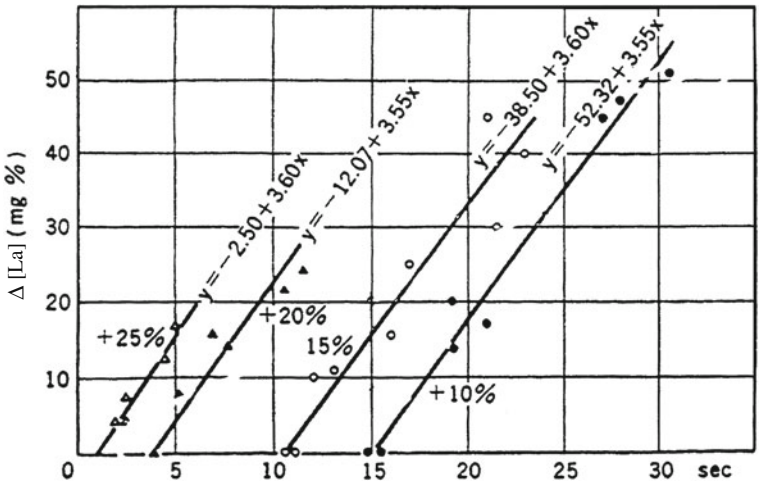


Fig. 6.3 Lactate increase in blood ($\Delta[La]_b$) as a function of exercise duration. The *four lines* refer to four different supramaximal workloads, which were obtained by changing the incline of a treadmill while running at an invariant speed of 18 km h^{-1}. The slope of the lines is equal to the rate of blood lactate accumulation. Since it is unchanged when the incline is increased (the regression equations are reported on the figure), the slope is equal to the maximal rate of lactate accumulation in blood, which is equivalent to the maximal rate of energy release from anaerobic lactic metabolism, or maximal lactic power. From Margaria et al. (1964)

Quantification from these experiments of the **maximal lactic power** was made possible by the knowledge of β, calculated as described above. On this basis, di Prampero and Ferretti (1999) obtained a value equivalent to some 75 ml O_2 kg^{-1} min^{-1}. This value, which applied to non-athletic young male subjects, corresponded to about 1.5 times the mean $\dot{V}O_{2max}$ for this type of population.

The complexity of the protocol for the determination of the maximal lactic power is such to restrict a wide use of this test, even for research purposes. So, the studies on the maximal lactic power are extremely scanty. We know that it is higher in power athletes than in non-athletes (Hermansen 1971) and that it is reduced after altitude acclimatization (Grassi et al. 1995). Some relation to the muscle fibre composition of lower limbs must exist, so that it would be easy to predict a low maximal lactic power in endurance athletes, possibly less than their maximal aerobic power. The loss of muscle mass with ageing allows predicting its decrease at older ages. Sport practice demonstrates that it can be trained—interval training was introduced to this purpose indeed—but no study of the effects of specific training on the maximal lactic power was ever carried out.

The Maximal Lactic Capacity

Knowledge of β, of the overall energy requirement of the exercise, and of the time constant of $\dot{V}O_2$ kinetics, which determines the contraction of the alactic oxygen deficit (23 s, Binzoni et al. 1992), allows computation, after measurement of peak $[La]_b$ at exhaustion and of $\dot{V}O_{2max}$, of the amount of energy that can be derived from the full utilization of anaerobic lactic energy stores, or **maximal lactic capacity**. This ranges, for continuous supramaximal exercise, between 45 and 55 ml O_2 kg^{-1} (di Prampero and Ferretti 1999), corresponding to a peak $[La]_b$ at exhaustion between 14 and 17 mM. It is greater the larger is the active muscle mass, higher in power athletes and lower in marathon runners than in non-athletic subjects (Komi et al. 1977; Nummela et al. 1996; Tam et al. 2012). It may be as twice as high during intermittent exercise (Osnes and Hermansen 1972) and is decreased in chronic hypoxia (Cerretelli 1967; Cerretelli and Binzoni 1990).

Lactate accumulation in muscle is obviously associated with a simultaneous increase in H^+ concentration in the active muscle mass, which may well limit maximal lactic capacity. This depends also on the buffer characteristics of muscle fibres and blood, and on the rate at which lactate can be removed from muscles. If this is so, then the higher lactic capacity during intermittent exercise is a consequence of the effects of recovery periods—no matter whether active or resting—on H^+ concentration in muscle fibres. In fact H^+ inhibit glycolysis, stopping the glycolytic energy flow when given lactate concentrations are attained: these would correspond, at the end of continuous exhausting exercise, to the $[La]_b$ values reported above. The slight decrease in muscle lactate during the recovery phase of intermittent exercise allows further lactate production in the successive supramaximal bout, whence the attainment of higher $[La]_b$ values, and so of a larger

lactic capacity, in intermittent than in continuous exercise, thus explaining the results of Osnes and Hermansen (1972). In sport practice, this reasoning provides the physiological explanation of how and why during interval training sessions athletes can tolerate numerous extremely high power repetitions, otherwise incompatible with the findings at the end of supramaximal continuous constant-load exercise in the laboratory.

The maximal lactic capacity is unchanged in acute hypoxia, but progressively decreases in chronic hypoxia (Cerretelli 1967). The reduction of maximal lactic capacity in chronic hypoxia, an intriguing aspect of altitude acclimatization, is reversible after return to sea level (Cerretelli and Binzoni 1990) and is unaffected by bicarbonate loading (Kayser et al. 1993). These findings are not due to changes in the activity of glycolytic enzymes, which is unaffected by chronic hypoxia (Cerretelli and Hoppeler 1996). The ensemble of these results was considered contradictory, so that this phenomenon was called **the lactate paradox**. Although the maximal $[La]_b$ is lower the higher is the altitude at which acclimatization has occurred, the ability of muscle fibres to produce lactate seems unaffected by the acclimatization process: what appears to be reduced is the net flux of lactate from the contracting muscle mass to the blood (Brooks et al. 1998). This led to the hypothesis that the lactate paradox might follow a fall of lactate transport outside muscle fibres, perhaps due to reduced activity of the lactate–proton co-transporter. If the acclimatization process is prolonged beyond 6 weeks, maximal lactic capacity progressively recovers, until the differences between acute and chronic hypoxia disappear (Lundby et al. 2000), suggesting that the lactate paradox may be a transient phenomenon. In fact the rate of lactate outflow from muscle fibres to blood increases with time at altitude, which implies also an increase in the rate of lactate removal from blood by lactate metabolizing organs, such as liver, brain, kidneys and heart, and eventually also non-contracting muscles. If the hypothesis of a reduced activity of the lactate–proton co-transporter in chronic hypoxia is correct, then the recovery of the maximal lactic capacity after the 6 week at altitude implies up-regulation of co-transporter synthesis (van Hall et al. 2001). Such modification requires alterations of the regulation of protein synthesis, and thus necessarily has a slow kinetics. If this is so, then there would be dissociation between co-transporter inhibition and increased co-transporter synthesis, which would explain the lactate paradox as a transitory phenomenon. However, the lactate paradox was observed also in populations living permanently at altitude, which undergo lifelong hypoxic stimulation: if the lactate paradox was transitory, these populations would not be affected by it. Clearly enough, our understanding of the lactate paradox is still incomplete.

The P/La Ratio

Constant β is an epiphenomenon of the actual phenomenon that is the amount of energy released by anaerobic lactic metabolism through ATP resynthesis, the latter being the actual source of energy for muscular contraction. Thus, knowledge of the

amount of ATP resynthesized from the accumulation of 1 mol of lactate in the contracting muscle mass is a key element for our understanding of the energetics of muscular exercise. This is the **P/La ratio**, i.e. constant b in Eq. (6.2), which is related to β through another constant γ, the dimension of which is moles of ATP resynthesized per J of energy released (reciprocal of the amount of energy that is necessary to resynthesize one mole of ATP). Computation of the P/La ratio from the measurement of blood lactate accumulation in humans is impossible because we do not know the value of γ. The P/La ratio was calculated from data obtained in isolated–perfused dog gastrocnemii with blood flow occlusion under supramaximal stimulation (di Prampero et al. 1978a). Under these conditions, the amount of energy derived from muscle oxygen stores is negligible, so that the general equation reduces to

$$\dot{E} \propto \overleftarrow{\dot{\mathrm{ATP}}} = \overrightarrow{\dot{\mathrm{ATP}}} = b\,\dot{\mathrm{La}} + a\,\dot{\mathrm{PC}} \tag{6.6}$$

Since phosphocreatine concentration, which is invariant at rest, goes down to almost 0 mM at the end of an exhaustive series of supramaximal stimulations (Cerretelli et al. 1969), the energy provided by anaerobic alactic metabolism in the transition from rest to stimulation can be considered constant. As a consequence, the total enthalpy change (ΔH, work plus heat) under those conditions is given by

$$\Delta H = H_{\mathrm{Al}} + X_{\mathrm{La}}[\mathrm{La}]_m \tag{6.7}$$

where H_{Al} is the enthalpy change due to anaerobic alactic metabolism, X_{La} is the enthalpy change due to the formation of 1 mol of lactate at the output of the glycolytic pathway, and $[\mathrm{La}]_m$ is the overall amount of lactate produced (no lactate removal in these circumstances). Equation (6.7) implies a linear relation between ΔH and $[\mathrm{La}]_m$, with slope equal to X_{La} and y-intercept equal to H_{Al}. The linear regression of the relation established by di Prampero et al. (1978a), reported in Fig. 6.4, yielded X_{La} = 76 kJ mol^{-1} and H_{Al} = 1.2 kJ kg^{-1}. Moreover, if the mechanical efficiency of muscular contraction under these conditions was invariant, also the relationship between work (W) and $[\mathrm{La}]_m$ (Fig. 6.4, right ordinate) ought to be linear, with slope indicating the work done per mole of lactate produced, for which a value of 20 kJ mol^{-1} was obtained. The P/La ratio is given by the further ratio of this last value to the W per mole of ATP split ($W^*_{\sim p}$), which was found to range between 16 and 19 kJ mol^{-1} (Cerretelli et al. 1969, 1972; Cerretelli and di Prampero 1988; Ferretti et al. 1987). As a consequence, the P/La ratio ranges between 1.25 and 1.05 mol of phosphate per mole of lactate, which is slightly less than the value of 1.5 predicted from stoichiometry. These values would be compatible with a range of values for the enthalpy change of ATP hydrolysis comprised between 60 and 72 kJ mol^{-1}, which is significantly higher than what one would expect from the value of 50 kJ mol^{-1} that can be calculated assuming a P/La ratio equal to that in vitro.

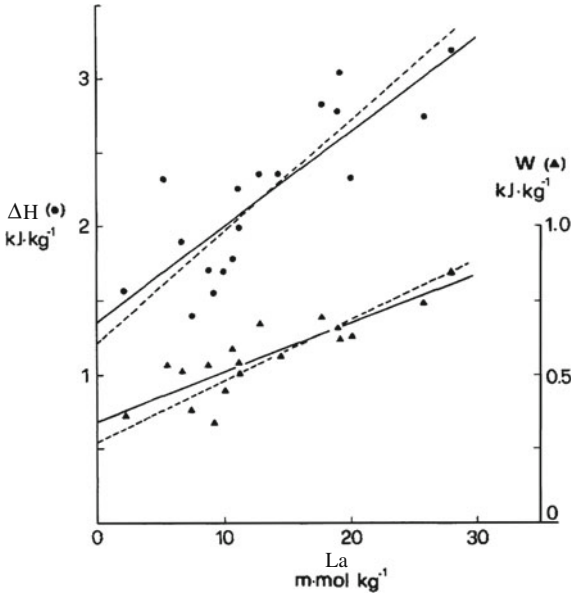


Fig. 6.4 Enthalpy change (ΔH, in kJ kg^{-1}, *left ordinate*, *dots*) and work (W, in kJ kg^{-1}, *right ordinate*, *triangles*) as a function of lactate formed (La, mmol kg^{-1}) during supramaximal stimulation of isolated–perfused dog gastrocnemius in anoxia. The slopes of the lines indicate, respectively, the energy released by (*top lines*) and the work performed by (*bottom lines*) a unit of lactate formed during contraction. *Continuous lines* are regression lines obtained with the classical least-square method; *dashed lines* are regression lines obtained with Brace method. From di Prampero et al. (1978a)

Energetics of All-Out Efforts of Extremely Short Duration

During all-out efforts of extremely short duration, the metabolic power developed by the contracting muscle mass may attain values as high as 200 W per kg of body mass. Such values may be attained, for instance, by power athletes who perform vertical jumps on both legs, for a duration of the push phase of some 0.25 s. Assuming that the mass of the active muscles during such a jump corresponds to 25 % of the overall body mass, this would be tantamount to state that the metabolic power that a muscle may achieve corresponds to some 800 times the resting metabolic rate (1 W kg^{-1}). Such a dramatically fast increase of the rate of energy metabolism of muscle fibres cannot be sustained by either the aerobic or the anaerobic lactic metabolism, the maximal powers of which are by far lower than this and whose kinetics of activation are too slow. Thus, for these types of exercise, the energy for ATP resynthesis can be provided only by anaerobic alactic metabolism through the Lohmann's reaction. If this is so, then the general equation of the energetics of muscular exercise would reduce to

$$\dot{E} \propto \overleftarrow{\dot{\mathrm{A}}\mathrm{TP}} = \overrightarrow{\dot{\mathrm{A}}\mathrm{TP}}_{\max} = a\,\dot{\mathrm{P}}\mathrm{C}_{\max} \tag{6.8}$$

where the suffix max indicates that the process of ATP resynthesis is proceeding at its maximal rate. However, if we push the system to its extremes, we may realize that during very short times, of the order of a few ms, $\overleftarrow{\dot{\mathrm{A}}\mathrm{TP}}_{\max}$ may exceed $\overrightarrow{\dot{\mathrm{A}}\mathrm{TP}}_{\max}$, in which case only the ATP immediately available at the site of the acto-myosin interaction can be used to sustain muscular contraction, since the maximal rate of ATP resynthesis by the Lohmann's reaction is too slow to sustain such a high rate of ATP splitting, and ATP concentration very rapidly falls. So we have

$$\dot{E}_{\max} \propto \overleftarrow{\dot{\mathrm{A}}\mathrm{TP}}_{\max} > \overrightarrow{\dot{\mathrm{A}}\mathrm{TP}}_{\max} = a\,\dot{\mathrm{P}}\mathrm{C}_{\max} \tag{6.9}$$

The ensemble of explosive anaerobic alactic exercises includes all the types of exercise for which Eq. (6.8) applies. Also the anaerobic alactic metabolism is characterized by specific values of maximal power and capacity. With some assumptions, these can be determined in humans from mechanical measurements performed during explosive exercises of known mechanical efficiency and extremely short duration.

The Measurement of Maximal Anaerobic Alactic Power

A direct determination of **maximal anaerobic alactic power** is practically impossible due to the extremely short exercise duration. Equation (6.8) denies the possibility of attaining a steady-state condition. Muscle phosphocreatine concentration keeps decreasing until subject's exhaustion, for no other mechanism can resynthesize ATP, thereby allowing phosphocreatine resynthesis at the required rate and in such short times (less than 10 s in all cases). Thus, we are bound to derive the maximal anaerobic alactic power from the measurement of the maximal mechanical power ($\bar{\dot{w}}$) attained on average during an explosive exercise that leads to exhaustion in less than 10 s and whose mechanical efficiency η is known, and from the subsequent computation of the corresponding metabolic power ($\dot{E}$). In fact, we have

$$\bar{\dot{w}} = \eta\,\alpha\,\dot{\mathrm{P}}\mathrm{C}_{\max} = \eta\,\dot{\mathrm{A}}\mathrm{l}_{\max} \tag{6.10}$$

where $\dot{\mathrm{P}}\mathrm{C}_{\max}$ is the maximal rate of phosphocreatine splitting, $\dot{A}l_{\max}$ is the maximal metabolic anaerobic alactic power, expressed in oxygen equivalents, and α is a constant corresponding to the amount of energy delivered by one mole of phosphate split.

The first among the methods for the determination of $\dot{A}l_{\max}$ was proposed by Margaria et al. (1966) and consists of the determination of the maximal vertical speed attained during an all-out run up a ladder of known slope. In these conditions,

speed attains a peak within 3 s, which is maintained for the next 3–4 s. The maximal mechanical power ($\overline{\dot{w}}$) is directly proportional to the measured vertical speed in the time interval at maximal speed. $\dot{A}l_{max}$ can then be obtained from $\overline{\dot{w}}$, as long as η is known (0.25 for uphill running, Margaria et al. 1963a; Minetti et al. 2002). Similar methods were subsequently devised, using different exercise modes, but with the common characteristics of being all-out efforts of short duration and known η (Bosco et al. 1983; Bar-Or 1987; Ikuta and Ikai 1972; Pirnay and Crielaard 1979).

More complex is the case of the so-called instantaneous methods. In this class, the most common and successful method is still the one proposed by Davies and Rennie (1968), with subsequent modifications (Antonutto et al. 1999; Zamparo et al. 1997). A simplified version of this test was developed by Bosco et al. (1983) for the determination of the time of flight and of the corresponding jump's height only. In short, the time course is assessed of the vertical force exerted on the ground during the push phase of an all-out vertical jump performed on a force platform. Knowing the subject's body mass, we can determine the instantaneous vertical speed from the definite integral of force with respect to time from the start of the push to the start of the flight. Then, from the product of each instantaneous force value times the corresponding velocity value, we obtain the time course of $\dot{w}$. This is the power generated by the entire chain of lower limb extensor muscles (Fig. 6.5). The highest instantaneous $\dot{w}$ value is retained as the maximal anaerobic power or **peak power** ($\widehat{\dot{w}}$). The integral mean of the power versus time curve in the push phase provides the mean anaerobic power ($\overline{\dot{w}}$). The values of $\overline{\dot{w}}$ obtained with the jump method, despite appearing twice higher than those of $\overline{\dot{w}}$ obtained with Margaria's test, are indeed in line with the latter, because in the former case both legs push simultaneously on the force platform, whereas in the latter case, there is the alternate push of a single leg, so that the active muscle mass at each time instant is double with that than with this method. Thus, also on the force platform the measurement of $\overline{\dot{w}}$ corresponds to the maximal rate of ATP resynthesis (Eq. 6.8) rather than of ATP splitting (Eq. 6.9).

An overview of values of maximal anaerobic alactic power is reported in Fig. 6.6. $\widehat{\dot{w}}$ is 3–4 times higher than Margaria's $\overline{\dot{w}}$. The time basis on which $\widehat{\dot{w}}$ is determined is of the order of a few ms: in this case, it is unlike that a significant contribution of the Lohmann's reaction to ATP resynthesis takes place, so we can reasonably state that $\widehat{\dot{w}}$ reflects the maximal rate of hydrolysis of the ATP already available at the acto-myosin interaction site (Ferretti et al. 1987). Since conversely the measurement of $\overline{\dot{w}}$ provides power values that reflect the maximal rate of ATP resynthesis from phosphocreatine, this would imply that the maximal rate of ATP hydrolysis is higher than the maximal rate of ATP resynthesis from the Lohmann's reaction. This explains the need of distinguishing between average methods, which respond to Eq. (6.8), and instantaneous methods, for which Eq. (6.9) applies.

The maximal anaerobic power, whether instantaneous or average, is more elevated in power athletes and lower in endurance athletes than in non-athletic individuals (Chamari et al. 1995; di Prampero et al. 1970; Ferretti et al. 1994).

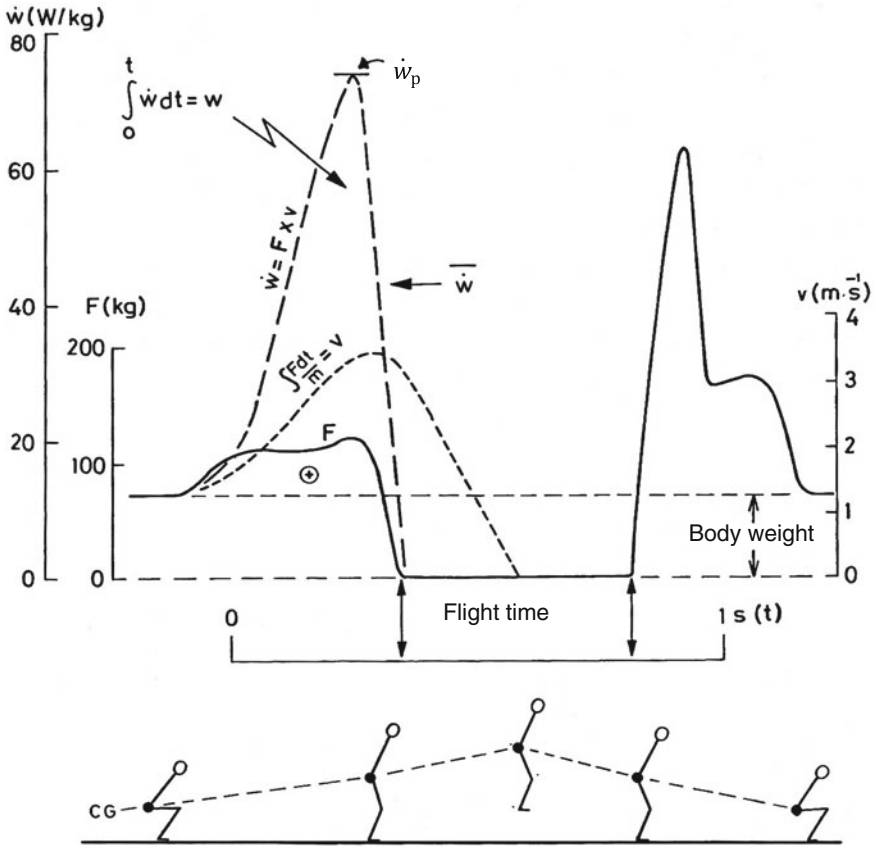


Fig. 6.5 The time courses of instantaneous force (*F*, *continuous line*), velocity (*v*, *dotted line*) and power ($\dot{w}$, *dashed line*) during a maximal vertical jump off both feet without countermovement on a force platform are shown along with the position of the subject's centre of gravity (CG) during the various phases of the jump. The force trace is directly recorded from the platform. Dividing instantaneous force by the body mass yields instantaneous acceleration. Instantaneous *v* is obtained as the time integral of acceleration. The $\dot{w}$ curve is obtained as the product of the force curve times the velocity curve. When the subject stays still on the platform (position 1), the recorded force is equal to the subject's body weight. During the jump push phase (position 2), the force exceeds body weight and an upward vertical acceleration occurs: in this phase, *v* increases and a positive power is developed. During the flight (position 3), the recorded force falls to zero and *v* decreases. *m* stands for mass and *t* for time. The peak power ($\dot{w}_p$) is identified as the highest instantaneous power value on the power curve. The mean power during the push phase is obtained as the integral mean of the power curve. Modified after Ferretti et al. (1987)

It decreases with age (Bonnefoy et al. 1998; Chamari et al. 1995; Ferretti et al. 1994; Grassi et al. 1991) and is lower in women than in men (Batterham and Birch 1996; Murphy et al. 1986). These patterns follow differences in active muscle mass. In chronic hypoxia, both $\hat{\dot{w}}$ and $\overline{\dot{w}}$ are reduced in direct proportion with the decrease

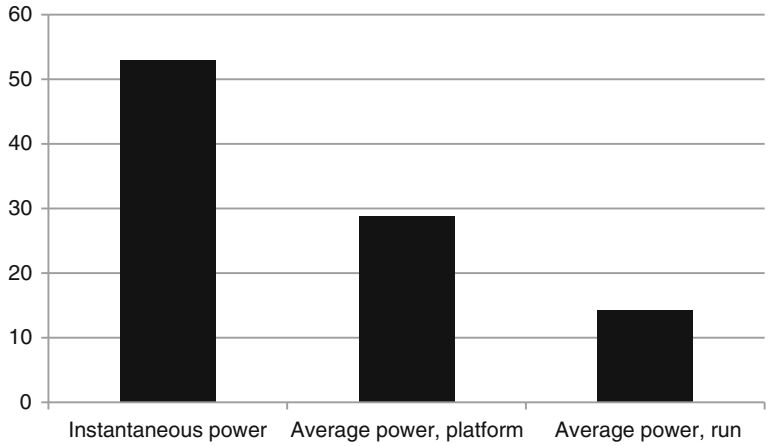


Fig. 6.6 Values of maximal mechanical alactic power in healthy non-athletic humans. Platform data (instantaneous and average) from Ferretti et al. (1987); run data (Margaria's test) from Margaria et al. (1971b)

in muscle cross-sectional area (Ferretti et al. 1990). Different is the case of microgravity exposure: the per cent fall of $\widehat{\dot{w}}$ and $\overline{\dot{w}}$ is larger than that of muscle cross-sectional area, so that the latter is unable to explain the decrease of the former, whether after space flight (Antonutto et al. 1999) or after bed rest (Ferretti et al. 2001), a finding that these authors attributed to asynchrony of motor unit recruitment after microgravity exposure. However, Milesi et al. (2000) suggested the possibility of an inefficient electro-mechanical coupling, whereas Reeves et al. (2002) proposed changes in the architecture of pennate muscles of the lower limbs as a possible explanation. Concerning the maximal rates of ATP splitting and resynthesis, they are both reduced by a decrease in muscle temperature: in this case, one would expect a fall of $\widehat{\dot{w}}$ and $\overline{\dot{w}}$ as demonstrated by Ferretti et al. (1992). To sum up, with the only exception of microgravity, the differences in anaerobic power among human subjects are the result of differences in the speed of ATP splitting and resynthesis times the amount (concentration time muscle mass) of high-energy phosphates in the active muscles. This concept can be formalized by the following equation:

$$\widehat{\dot{w}} = kW^*{}_{\sim p}[\mathrm{ATP}] \tag{6.11}$$

where k is the velocity constant of the reaction and $W^*{}_{\sim p}$ is the work done per unit of phosphate split (19 kJ mol^{-1}). For these reasons, attempts were made at enhancing maximal anaerobic power by increasing the muscle content of high-energy phosphates through creatine supplementation, yet with contradictory results (Bemben et al. 2001; Hoffman et al. 2005; Ziegenfuss et al. 2002) as a consequence of differences in dose among studies and elevated urinary creatine excretion.

Maximal Instantaneous Alactic Power and Aerobic Exercise

The concentration of phosphocreatine and of ATP in muscles is lower the higher is the muscle metabolic rate at the steady state of an aerobic exercise (Binzoni et al. 1992; Karlsson et al. 1972; Molé et al. 1985; Piiper et al. 1968), as a consequence of the contraction of the oxygen deficit. The equilibrium constant of the Lohmann's reaction, however, is such that the equilibrium is displaced towards ATP resynthesis. As a consequence, although there is a negative linear relationship between phosphocreatine concentration and metabolic rate at steady state, the same cannot the case for ATP: the ATP fall is modest at low workloads, to become important only after phosphocreatine concentration has attained remarkably low levels. So, the maximal anaerobic alactic power ought to be lower when increasing the intensity of the exercise baseline on which a power test is superimposed, according to a pattern that recalls that of muscle ATP decrease. In fact, this was found to be the case for $\widehat{w}$ (Ferretti et al. 1987).

A comparison between the data of Ferretti et al. (1987) as a function of steady-state oxygen consumption and the average ATP values obtained in the isolated–perfused dog muscle preparation (Piiper et al. 1968) is reported in Fig. 6.7, in which $\widehat{w}$ and ATP concentration ([ATP]) are expressed relative to the respective resting

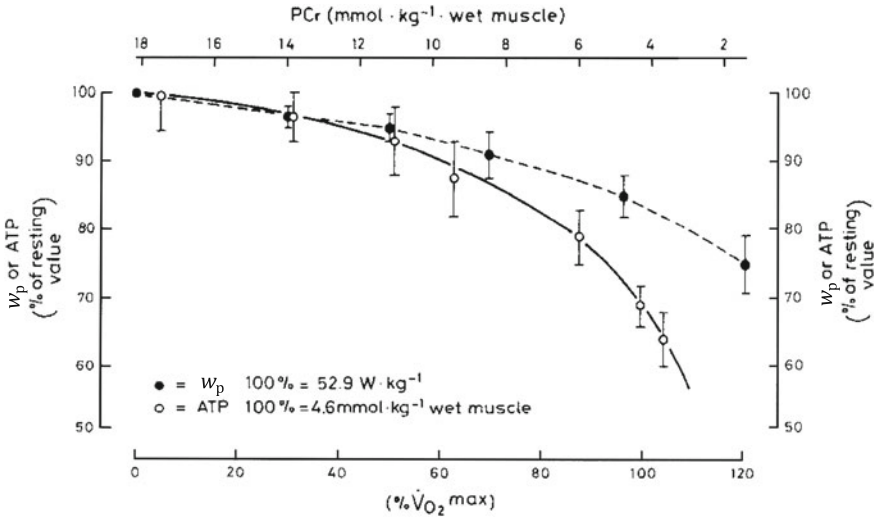


Fig. 6.7 Maximal instantaneous anaerobic power ($\dot{w}_p$, *closed circles* and *dashed line*) and ATP concentration ([ATP]) (*open circles* and *solid line*), both expressed as percent of their resting values, are plotted as a function of the net oxygen consumption of a priming work load, expressed as percent of the maximal oxygen consumption ($\dot{V}o_{2max}$). The phosphocreatine concentration ([PC]) scale, as calculated from Karlsson et al (1972) is also given on top of the figure. From Ferretti et al. (1987)

Table 6.1 Work performed per mole of ATP split ($W^*_{\sim p}$) and velocity constant of ATP splitting (k), after assuming, respectively, k (2.3 s^{-1}) and wp (18.9 kJ mol^{-1}) invariant

Net $\dot{V}o_2$ (% of $\dot{V}o_{2max}$)	$\hat{\dot{w}}$ (W kg^{-1})	[ATP] (mM)	$W^*_{\sim p}$ (kJ mol^{-1})	k (s^{-1})
0	52.9	4.60	18.9	2.30
30	51.3	4.44	19.0	2.32
50	50.4	4.30	19.3	2.35
70	48.1	3.98	19.9	2.42
100	45.1	3.34	22.2	2.71

Data from Ferretti et al. (1987)

$\dot{V}o_2$, Oxygen consumption; $\dot{V}o_{2max}$, Maximal oxygen consumption; $\hat{\dot{w}}$, Maximal instantaneous alactic power; [ATP], ATP concentration

value. According to Eq. (6.10), if constants k and $W^*_{\sim p}$ are invariant, and thus independent of exercise intensity, the two curves of Fig. 6.7 should coincide. This is not so, as during intense exercise relative $\hat{\dot{w}}$ is consistently higher than relative [ATP]. The difference between the two curves becomes evident at powers likely close to the lactate threshold and appears to widen as the workload approaches the maximum. So, Ferretti et al. (1987) linked this discrepancy to the increase of muscle H^+ due to lactate accumulation. The tendency is compatible with an increase of either of the two constants of Eq. (6.11). An increase in $W^*_{\sim p}$ may be advocated, as long as the mechanical efficiency of the contraction occurs in the isolated–perfused dog gastrocnemius during repeated short tetani, simultaneously with lactate accumulation and depletion of the high-energy phosphate stores (di Prampero et al. 1981). Possible solutions of Eq. (6.11) with the data of Fig. 6.7 are shown in Table 6.1.

If Eq. (6.11) holds, the time course of the decrease of $\hat{\dot{w}}$ after the beginning of constant-load exercise should follow the contraction of the obligatory component of the oxygen deficit. Thus, it should be characterized by a mono-exponential kinetics with a time constant of 20–25 s (see Chap. 3). In fact, a value of 20 s could be estimated (Ferretti et al. 1987), in line with that reported for phosphocreatine decrease by Binzoni et al. (1992). After the exercise steady state has been attained, so that phosphocreatine concentration does not change anymore with time, also $\hat{\dot{w}}$ ought to attain a steady level. This should not be the case, however, during intense exercise above the critical power, when lactate does not reach a steady level anymore but keeps increasing with time: following the lactate increase, $\hat{\dot{w}}$ ought to fall continuously to attain a nadir at exhaustion.

Maximal Mean Alactic Power and Aerobic Exercise

The measurement of $\overline{\dot{w}}$ is probably related to the maximal rate of ATP resynthesis from phosphocreatine, as pointed out above. [PC] in contracting muscles decreases linearly with the exerted mechanical power (Binzoni et al. 1992; Piiper et al. 1968),

and thus with the net oxygen consumption ($\dot{V}\,O_2$) of the submaximal priming exercise. Thus, if Margaria's test is performed without discontinuity from the steady state of a preceding light aerobic exercise, there must be a negative linear relationship between $\overline{\dot{w}}$ and $\dot{V}\,O_2$. The data of Margaria et al. (1971b) show that this is the case indeed, the relation being described by the following equation:

$$\overline{\dot{w}} = \overline{\dot{w}}_0 - \delta \dot{V}\,O_2 \tag{6.11}$$

where $\overline{\dot{w}}_0$ is the $\overline{\dot{w}}$ attained starting from a resting condition (y-intercept of the negative relationship between $\overline{\dot{w}}$ and $\dot{V}\,O_2$) and δ is the proportionality constant indicating the loss of $\overline{\dot{w}}$ per unit increase in $\dot{V}\,O_2$. Expressing $\overline{\dot{w}}$ in W kg^{-1} and $\dot{V}\,O_2$ in ml kg^{-1} s^{-1}, we have δ = 3.1 J ml^{-1} and $\overline{\dot{w}}_0$ = 14.2 W kg^{-1} (di Prampero 1981). The value of latter constant corresponds well to the $\overline{\dot{w}}$ obtained by Margaria et al. (1971b) when the test was initiated from rest (see also Table 6.1). Expressing $\overline{\dot{w}}$ and $\dot{V}\,O_2$ in the same units, δ turns out equal to η. Assuming an energy equivalent of $\dot{V}\,O_2$ of 20.9 kJ L^{-1} STPD, as in the case when the respiratory quotient is equal to 0.96, for δ = 3.1 J ml^{-1} we have η = 0.15, a value somewhat lower than the canonical value of 0.25 for exercise (Margaria et al. 1963a; Minetti et al. 2002).

In the experiments of Margaria et al. (1971b), the measurement of $\overline{\dot{w}}$ was superimposed without discontinuity to a priming exercise of the same type, so that part of the energy expended for running up the stairs was of aerobic energy. So we can also write

$$\overline{\dot{w}} = \eta\left(\dot{A}l_{max} + \dot{V}\,O_2\right) \tag{6.12}$$

Since Eqs. (6.11) and (6.12) must have equal solutions, if we express all metabolic powers in the same units (e.g. ml kg^{-1} s^{-1}), so that $\delta = \eta$, we get

$$\eta\left(\dot{A}l_{max} + \dot{V}\,O_2\right) = \overline{\dot{w}}_0 - \eta \dot{V}\,O_2 \tag{6.13}$$

whence

$$\dot{A}l_{max} + \dot{V}\,O_2 = \dot{E}_{Al,\,0} - \dot{V}\,O_2 \tag{6.14}$$

where

$$\dot{E}_{Al,\,0} = \overline{\dot{w}}_0 \eta^{-1} \tag{6.15}$$

Solution of Eq. (6.14) for $\dot{A}l_{max}$ yields

$$\dot{A}l_{max} = \dot{E}_{Al,\,0} - 2\,\dot{V}\,O_2 \tag{6.16}$$

For η comprised between 0.15 and 0.25, as during uphill running, we have $\dot{E}_{Al,\,0}$ ranging from 94.7 to 56.8 W kg^{-1}. This range represents an uppermost limit for

$\dot{A}l_{max}$ as determined with an average method, an extreme of metabolic power release from the Lohmann's reaction during running. Considering then that during vertical jumping on the force platform both legs push simultaneously, this figure is doubled. These figures allow an estimate of the instantaneous metabolic alactic power suggesting that ATP hydrolysis at its maximal rate may provide up to 300 W kg^{-1} of metabolic energy.

Anaerobic Alactic Capacity

As the maximal anaerobic alactic power is extremely high, so the **maximal anaerobic alactic capacity** must be very small. Assuming for simplicity an instantaneous maximal alactic power of 200 W kg^{-1} of body mass, and considering that $\dot{w}_p$ is obtained on a time basis of some 10 ms, we get a maximal anaerobic capacity of about 2 J kg^{-1} (140 J for an ordinary man with a 70 kg body mass). For a resting [ATP] of 5 mM of wet muscle, assuming that the active muscle mass during a vertical jump approximates 26 % of body mass (Ferretti et al. 1987), this would correspond to a quantity of ATP in the active muscles of some 90 mmoles. Considering that 1 mol of ATP yields 19 J of mechanical work (~75 J of energy), the active muscle mass has an immediately available energy store of some 1.7 kJ. This discrepancy means that $\dot{w}_p$ may in principle be maintained for much longer than 10 ms, up to 120 ms.

Let us now consider the case of average anaerobic power. Taking $\dot{A}l_{max} = 56$ W kg^{-1}, as calculated above, and considering that it may be maintained for some 6 s, we obtain a maximal anaerobic capacity of 336 J kg^{-1} (23.5 kJ for an ordinary man with a 70 kg body mass). For a resting [PC] of 20 mM of wet muscle, and assuming that the fraction of body mass represented by the active muscle mass is the same as for a vertical jump (even though there is alternate contraction of the two legs, ATP is consumed in both of them), we end with a quantity of phosphocreatine in the active muscles of some 360 mmoles. Since the stoichiometric ratio of ATP to PC is 1 (constant a of Eq. 6.1), also 1 mol of phosphocreatine yields 19 J of mechanical work (~75 J of energy). Thus, the active muscles have an overall capacity of generating energy from anaerobic alactic sources corresponding to 27 kJ, i.e. more than 15 times the capacity of immediately available ATP. This value is compatible with maximal exercise duration at maximal power of 6.9 s, a very astonishingly close value to what is found in the experimental practice.

Conclusions

The maximal power generated by anaerobic alactic metabolism is extremely high, some 20 times higher than the maximal aerobic power in young healthy non-athletic subjects for the instantaneous power related to the splitting of immediately available

ATP, some 5–6 times higher than the maximal aerobic power when energy is released after ATP resynthesis from phosphocreatine. The price to pay for this is an extremely low capacity, so that exercise can be sustained at maximal power for a very short time, of the order of a few seconds for average power, some milliseconds for instantaneous power. Such an organization of energetic metabolism, with a wide range of powers and capacities for the ensemble of the metabolic pathways, allows animals, humans included, to face the multiple needs that a prey–predator system imposes. In general terms, animals have evolved in such a way that power is highest when capacity is lowest, and vice versa.

The three-parameter critical power model implies a positive, commeasurable *y*-axis intercept corresponding to the power that one would expect when the maximal time over which a given power above the critical power can be sustained (t_{lim}) is equal to 0 s ($\dot{w}_0$). The measurement of $\dot{w}_p$ is what in physiology gets closest to $\dot{w}_0$, and it is tempting to propose that this is so indeed. The fascination of this statement is that, if this is so, it would be possible to introduce aerobic and anaerobic metabolism into a unique equation describing the power versus time relationship in the entire range of potential exercise performance. Wilkie (1980) tried to combine the three main metabolisms in a complex nonlinear equation describing the power versus t_{lim} relationship for exercises lasting less than 10 min. The advancement of knowledge since the publication of his work was such that I frankly recognize nowadays that we deal with a system characterized by several key parameters, namely the critical power, the maximal aerobic power, the maximal lactic power, the maximal average anaerobic alactic power and the maximal instantaneous anaerobic alactic power. All these parameters should be included in a model of the power versus t_{lim} relationship. Apart from the critical power, whose capacity is in theory infinite, in practice limited only by the size of body fat stores, so that it conveniently represents the *y*-axis asymptote of any power versus t_{lim} curve, all other parameters have a finite capacity, which is largest for the maximal aerobic power. Each capacity is a constant, independent of the associated maximal power, defining the curvature of specific power versus time hyperbolas for each of the implicated metabolisms. Establishing such a relation on solid experimental grounds would be the next adventure, in my opinion, in the field of the energetics of muscular exercise.

References

Antonutto G, Capelli C, Girardis M, Zamparo P, di Prampero PE (1999) Effects of microgravity on maximal power of lower limbs during very short efforts in humans. J Appl Physiol 86:85–92

Åstrand I (1960) Aerobic work capacity in men and women with special reference to age. Acta Physiol Scand Suppl 169:1–92

Bar-Or O (1987) The Wingate anaerobic test. An update on methodology, reliability and validity. Med Sports 4:381–394

Batterham AM, Birch KM (1996) Allometry of anaerobic performance: a gender comparison. Can J Appl Physiol 21:48–62

Bemben MG, Bemben DA, Loftiss DD, Knehans AW (2001) Creatine supplementation during resistance training in college football athletes. Med Sci Sports Exerc 33:1667–1673

Binzoni T, Ferretti G, Schenker K, Cerretelli P (1992) Phosphocreatine hydrolysis by ^{3}1P-NMR at the onset of constant-load exercise in humans. J Appl Physiol 73:1643–1649

Bonen A (2001) The expression of lactate transporters (MCT1 and MCT4) in heart and muscle. Eur J Appl Physiol 86:6–11

Bonnefoy M, Kostka T, Arsac LM, Berthouze SE, Lacour JR (1998) Peak anaerobic power in elderly men. Eur J Appl Physiol 77:182–188

Bosco C, Luhtanen P, Komi PV (1983) A simple method for measurement of mechanical power in jumping. Eur J Appl Physiol 50:273–282

Brooks GA, Wolfel EE, Butterfield GE, Cymerman A, Roberts AC, Mazzeo R, Reeves JT (1998) Poor relation between arterial [lactate] and leg net release during exercise at 4,300 m altitude. Am J Physiol Regul Integr Comp Physiol 275:R1192–R1201

Capelli C, di Prampero PE (1995) Blood lactate accumulation in exercising humans. Biochim Clin 19:541–542

Cerretelli P (1967) Lactacid O_2 debt in acute and chronic hypoxia. In: Margaria R (ed) Exercise at altitude. Excerpta Medica, Amsterdam, pp 58–64

Cerretelli P, Binzoni T (1990). Muscular exercise at high altitude. VI. The energetic significance of lactate accumulation in blood at altitude. Int J Sports Med 11(Suppl 1):S27–S30

Cerretelli P, di Prampero PE (1988) High-energy phosphate utilisation for work production and tension maintenance in frog muscle. Pflügers Arch 412:270–276

Cerretelli P, Hoppeler H (1996) Morphologic and metabolic response to chronic hypoxia. In: Fregly MJ, Blatteis CM (eds) Handbook of Physiology. Environmental Physiology, sect 4, vol II. Oxford University Press, New York, pp 1155–1181

Cerretelli P, Piiper J, Mangili F, Ricci B (1964) Aerobic and anaerobic metabolism in exercising dogs. J Appl Physiol 19:29–32

Cerretelli P, di Prampero PE, Piiper J (1969) Energy balance of anaerobic work in the dog gastrocnemius muscle. Am J Physiol 217:581–585

Cerretelli P, di Prampero PE, Ambrosoli G (1972) High-energy phosphate resynthesis from anaerobic glycolysis in frog gastrocnemius muscle. Am J Physiol 222:1021–1026

Cerretelli P, Pendergast DR, Paganelli WC, Rennie DW (1979) Effects of specific muscle training on VO_2-on response and early blood lactate. J Appl Physiol 47:761–769

Chamari K, Ahmaidi S, Fabre C, Massé-Biron J, Préfaut C (1995) Anaerobic and aerobic peak power output and the force-velocity relationship in endurance-trained athletes: effects of aging. Eur J Appl Physiol 71:230–234

Davies CTM, Rennie E (1968) Human power output. Nature 217:770–771

di Prampero PE (1981) Energetics of muscular exercise. Rev Physiol Biochem Pharmacol 89:143–222

di Prampero PE, Ferretti G (1999) The energetics of anaerobic muscle metabolism: a reappraisal of recent and older concepts. Respir Physiol 118:103–115

di Prampero PE, Piñera Limas F, Sassi G (1970) Maximal muscular power (aerobic and anaerobic) in 116 athletes performing at the XIX Olympic Games in Mexico. Ergonomics 13:665–674

di Prampero PE, Meyer M, Cerretelli P, Piiper J (1978a) Energetics of anaerobic glycolysis in dog gastrocnemius. Pflügers Arch 377:1–8

di Prampero PE, Pendergast DR, Wilson DW, Rennie DW (1978b) Blood lactic acid concentration in high-velocity swimming. In: Eriksson B, Furberg B (eds) Swimming medicine IV. University Park Press, Baltimore, pp 249–261

di Prampero PE, Meyer M, Cerretelli P, Piiper J (1981) Energy sources and mechanical efficiency of anaerobic work in dog gastrocnemius. Pflügers Arch 389:257–262

Ferretti G, Gussoni M, di Prampero PE, Cerretelli P (1987) Effects of exercise on maximal instantaneous muscular power of humans. J Appl Physiol 62:2288–2294

Ferretti G, Hauser H, di Prampero PE (1990) Muscular exercise at high altitude. VII. Maximal muscular power before and after exposure to chronic hypoxia. Int J Sports Med 11(suppl 1): S31–S34

Ferretti G, Ishii M, Moia C, Cerretelli P (1992) Effects of temperature on the maximal instantaneous muscle power of humans. Eur J Appl Physiol 64:112–116
Ferretti G, Narici MV, Binzoni T, Gariod L, Le Bas JF, Reutenauer H, Cerretelli P (1994) Determinants of peak muscle power: effects of age and physical conditioning. Eur J Appl Physiol 68:111–115
Ferretti G, Berg HE, Minetti AE, Moia C, Rampichini S, Narici MV (2001) Maximal instantaneous muscular power after prolonged bed rest in humans. J Appl Physiol 90:431–435
Freund H, Oyono-Enguelle S, Heitz A, Marbach J, Ott C, Zouloumian P, Lampert E (1986) Work rate dependent lactate kinetics after exercise in humans. J Appl Physiol 61:932–939
Gisolfi C, Robinson S, Turrell ES (1966) Effects of aerobic work performed during recovery from exhausting work. J Appl Physiol 21:1767–1772
Grassi B, Cerretelli P, Narici MV, Marconi C (1991) Peak anaerobic power in master athletes. Eur J Appl Physiol 62:394–399
Grassi B, Ferretti G, Kayser B, Marzorati M, Colombini A, Marconi C, Cerretelli P (1995) Maximal rate of blood lactate accumulation during exercise at altitude in humans. J Appl Physiol 79:331–339
Hashimoto T, Brooks GA (2008) Mitochondrial lactate oxidation complex and an adaptive role for lactate production. Med Sci Sports Exerc 40:486–494
Hermansen L (1971) Lactate production during exercise. In: Pernow B, Saltin B (eds) Muscle metabolism during exercise. Plenum Press, New York, pp 401–407
Hermansen L, Stensvold I (1972) Production and removal of lactate during exercise in man. Acta Physiol Scand 86:191–201
Hoffman JR, Stout JR, Falvo MJ, Kang J, Ratamess NA (2005) Effect of low-dose, short-duration creatine supplementation on anaerobic exercise performance. J Strength Cond Res 19:260–264
Ikuta K, Ikai M (1972) Study on the development of maximum anaerobic power in man with bicycle ergometer. Res J Phys Ed (Japan) 17:151–157
Juel C (1997) Lactate-proton cotransport in skeletal muscle. Physiol Rev 77:321–358
Juel C (1998) Muscle pH regulation: role of training. Acta Physiol Scand 162:359–366
Juel C, Halestrap AP (1999) Lactate transport in skeletal muscle. Role and regulation of the monocarboxylate transporter. J Physiol 517:633–642
Karlsson J, Nordesjö LO, Jorfeldt L, Saltin B (1972) Muscle lactate, ATP, and CP levels during exercise after physical training. J Appl Physiol 33:199–203
Kayser B, Ferretti G, Grassi B, Binzoni T, Cerretelli P (1993) Maximal lactic capacity at altitude: effect of bicarbonate loading. J Appl Physiol 75:1070–1074
Komi PV, Rusko H, Vos J, Vihko V (1977) Anaerobic performance capacity in athletes. Acta Physiol Scand 100:107–114
Lundby C, Saltin B, van Hall G (2000) The "lactate paradox", evidence for a transient change in the course of acclimatization to severe hypoxia in lowlanders. Acta Physiol Scand 170:265–269
Margaria R, Edwards HT, Dill DB (1933) The possible mechanism of contracting and paying the oxygen debt and the role of lactic acid in muscular contraction. Am J Physiol 106:689–714
Margaria R, Cerretelli P, Aghemo P, Sassi G (1963a) Energy cost of running. J Appl Physiol 18:367–370
Margaria R, Cerretelli P, di Prampero PE, Massari C, Torelli G (1963b) Kinetics and mechanism of oxygen debt contraction in man. J Appl Physiol 18:371–377
Margaria R, Cerretelli P, Mangili F (1964) Balance and kinetics of anaerobic energy release during strenuous exercise in men. J Appl Physiol 19:623–628
Margaria R, Aghemo P, Rovelli E (1966) Measurement of maximal power (anaerobic) in man. J Appl Physiol 21:1662–1664
Margaria R, Aghemo P, Sassi G (1971a) Lactic acid production in supramaximal exercise. Pflügers Arch 326:152–161
Margaria R, di Prampero PE, Aghemo P, Derevenco P, Mariani M (1971b) Effect of a steady state exercise on maximal anaerobic power in man. J Appl Physiol 30:885–889

Margaria R, Camporesi E, Aghemo P, Sassi G (1972) The effects of oxygen breathing on maximal aerobic power. Pflügers Arch 336:225–235

Milesi S, Capelli C, Denoth J, Hutchinson T, Stüssi E (2000) Effects of 17 days bedrest on the maximal voluntary isometric torque and neuromuscular activation of plantar and dorsal flexors of the ankle. Eur J Appl Physiol 82:197–205

Minetti AE, Moia C, Roi GS, Susta D, Ferretti G (2002) Energy cost of walking and running at extreme uphill and downhill slopes. J Appl Physiol 93:1039–1046

Molé PA, Coulson RL, Caton JR, Nichols BG, Barstow TJ (1985) In vivo ^{31}P-NMR in human muscle: transient patterns with exercise. J Appl Physiol 59:101–104

Murphy MM, Patton JF, Frederick FA (1986) Comparative anaerobic power of men and women. Aviat Space Environ Med 57:636–641

Nummela A, Mero A, Stray-Gundersen J, Rusko H (1996) Important determinants of anaerobic running performance in male athletes and non-athletes. Int J Sports Med 17(suppl 2):S91–S96

Osnes JB, Hermansen L (1972) Acid-base balance after maximal exercise of short duration. J Appl Physiol 32:59–63

Oyono-Enguelle S, Marbach J, Heitz A, Ott C, Gartner M, Pape A, Vollmer JC, Freund H (1990) Lactate removal ability and graded exercise in humans. J Appl Physiol 68:905–911

Oyono-Enguelle S, Freund H, Lampert E, Lonsdorfer A, Lonsdorfer J (1993) Modelling lactate kinetics during recovery from muscular exercise in human. Influence of some physiological factors. Sci Sports 8:181–187

Pendergast DR, di Prampero PE, Craig AB, Rennie DW, Wilson DW (1977) Quantitative analysis of the front crawl in men and women. J Appl Physiol 43:474–479

Piiper J, di Prampero PE, Cerretelli P (1968) Oxygen debt and high-energy phosphates in the gastrocnemius muscle of the dog. Am J Physiol 215:523–531

Pirnay F, Crielaard JM (1979) Mesure de la puissance anaérobie alactique. Med Sport 53:13–16

Reeves NJ, Maganaris CN, Ferretti G, Narici MV (2002) Influence of simulated microgravity on human skeletal muscle architecture and function. J Gravit Physiol 9:P153–P154

Roos A (1975) Intracellular pH and distribution of weak acids across cell membranes. A Study of D- and L- lactate and of DMO in rat diaphragm. J Physiol 249:1–25

Tam E, Rossi H, Moia C, Berardelli C, Rosa G, Capelli C, Ferretti G (2012) Energetics of running in top-level marathon runners from Kenya. Eur J Appl Physiol 112:3797–3806

Taoutaou Z, Granier P, Mercier B, Mercier J, Ahmaidi S, Préfaut C (1996) Lactate kinetics during passive and partially active recovery in endurance and sprint athletes. Eur J Appl Physiol 73:465–470

van Hall G, Calbet JAL, Sondergaard H, Saltin B (2001) The re-establishment of the normal blood lactate response to exercise in humans after prolonged acclimatization to altitude. J Physiol 536:963–975

Wilkie DR (1980) Equations describing power input by humans as a function of duration of exercise. In: Cerretelli P, Whipp BJ (eds) Exercise bioenergetics and gas exchange. Elsevier, Amsterdam, pp 75–80

Zamparo P, Antonutto G, Capelli C, Girardis M, Sepulcri L, di Prampero PE (1997) Effects of elastic recoil on maximal explosive power of the lower limbs. Eur J Appl Physiol 75:289–297

Ziegenfuss TN, Rogers M, Lowery L, Mullins N, Mendel R, Antonio J, Lemon P (2002) Effect of creatine loading on anaerobic performance and skeletal muscle volume in NCAA Division I athletes. Nutrition 18:397–402

Zouloumian P, Freund H (1981) Lactate after exercise in man. II. Mathematical model. Eur J Appl Physiol 46:135–147