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THE CONTROL OF RESPIRATION AND CIRCULATION IN FISH DURING EXERCISE AND HYPOXIA

BY DAVID RANDALL*

Department of Zoology, University of British Columbia, Vancouver, BC., Canada

SUMMARY

Gas exchange across fish gills is reviewed and the respiratory and cardiovascular changes associated with exercise and hypoxia described.

Heart rate is controlled by inhibitory vagal cholinergic activity which increases during hypoxia and decreases during exercise. Stimulation of receptors on the first gill arch during hypoxia initiates bradycardia. The increase in stroke volume during hypoxia in dogfish appears to be related to cardiac slowing rather than β-adrenergic stimulation of the heart.

Stimulation of cardiac β-adrenergic receptors causes positive inotropic and chronotopic responses in many fish, whether these are operative during exercise and hypoxia is not clear.

Gill water flow is inversely related to arterial oxygen content in resting fish and there is probably an arterial oxygen content receptor coupled to gill ventilation. Little is known of the control of breathing during exercise, the switch from rhythmic to ram ventilation at high water velocities may be initiated by mechanoreceptors on the gill surface.

INTRODUCTION

I will review gas exchange across fish gills during exercise and hypoxia and then discuss possible mechanisms of control and co-ordination. There are limited, but adequate, descriptions of what happens to gas exchange during exercise and hypoxia but information on mechanisms of integration is sparse and patchy.

GAS EXCHANGE ACROSS FISH GILLS

The gills of fishes vary in gross structure between species (Fig. 1), but at the level of the gas exchange unit, the secondary lamellae, there are only minor differences in morphology (Fig. 2). Water flow over the gills is countercurrent to blood perfusing the secondary lamellae (Fig. 3). Water flow is laminar and water is in contact with the respiratory surface for about 300 ms in resting fish and is reduced to less than 30 ms at the highest water flow rates.

The gill epithelium (Figs. 4 and 5) is generally somewhat thicker than the epithelium of lungs. It is usually between 1 and 10 μm thick, being 10 μm in dogfish (*Squalus acanthias*) and only 0·6 μm in tuna (*Katsuwanus pelamis*) (Hughes & Morgan, 1973).

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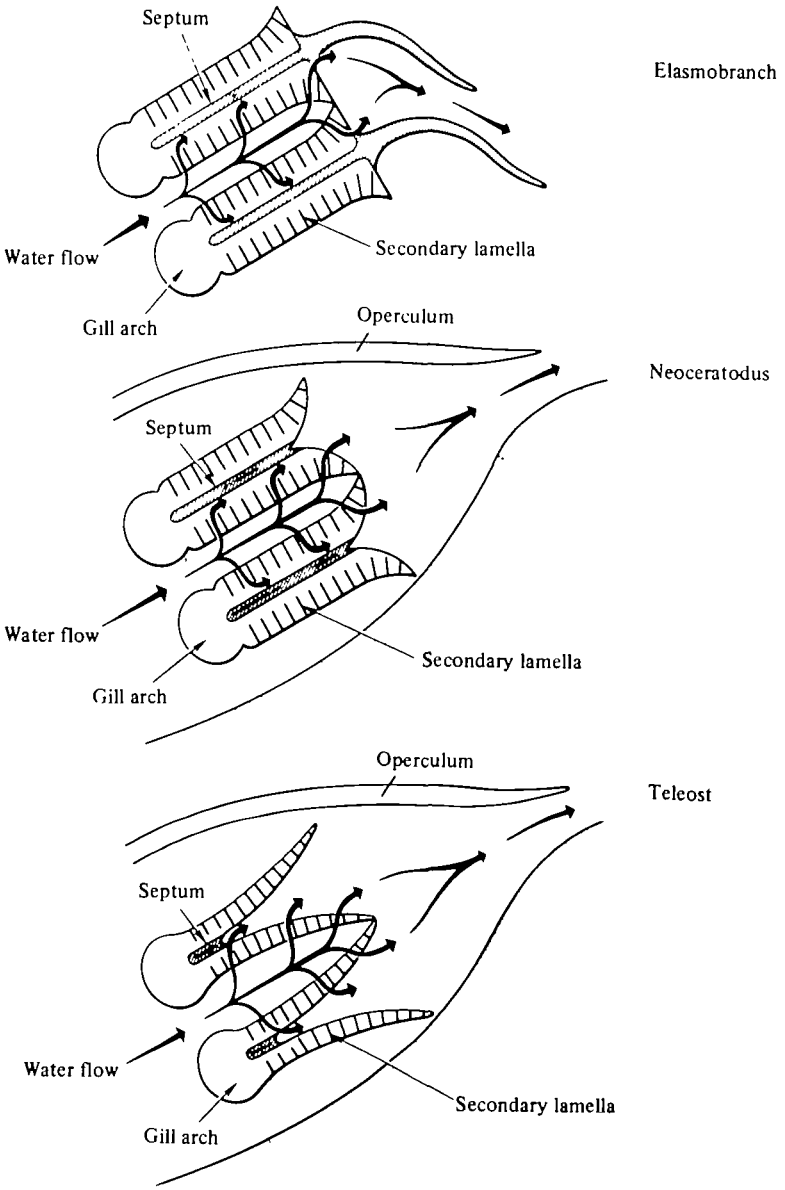

Fig. 1. Schematic diagram showing the general structure and pattern of water flow in the gills of different groups. Only two gill arches are shown for simplicity in each case. The gill structure in the Dipnoi is very variable, *Neoceratodus* being an example.

The diffusion resistance to gas transfer of the components of the gill epithelium have not been investigated in detail. Compartmental analysis of water fluxes (Isaia, Girard & Payan, 1978) indicated a major inner and a minor outer barrier, the structural correlates of these barriers, however, are not known. Adrenaline has been shown to increase gill water permeability (Isaia *et al.* 1978) and, therefore, may also increase gill permeability to gases.

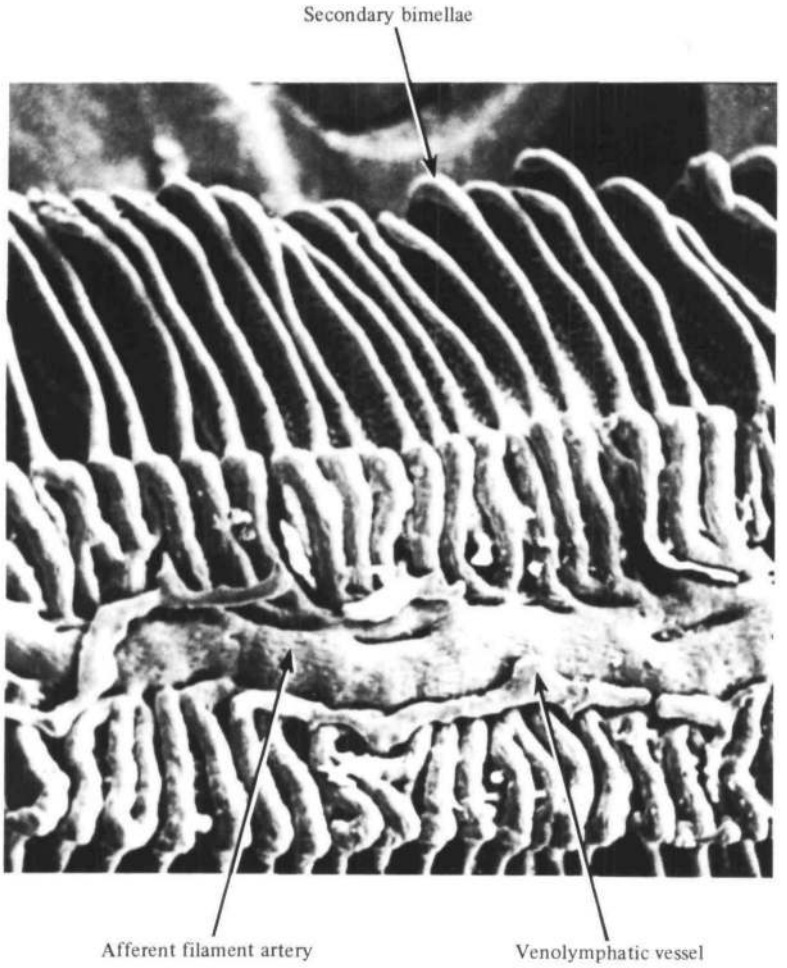

Fig. 2. A methacrylate cast of the gill filament of a trout (*Salmo gairdneri*) showing the filament efferent artery, secondary lamellae and a portion of the recurrent venolymphatic circulation. The water channels between lamellae are about 25 μm wide. (Unpublished material supplied by B. J. Gannon.)

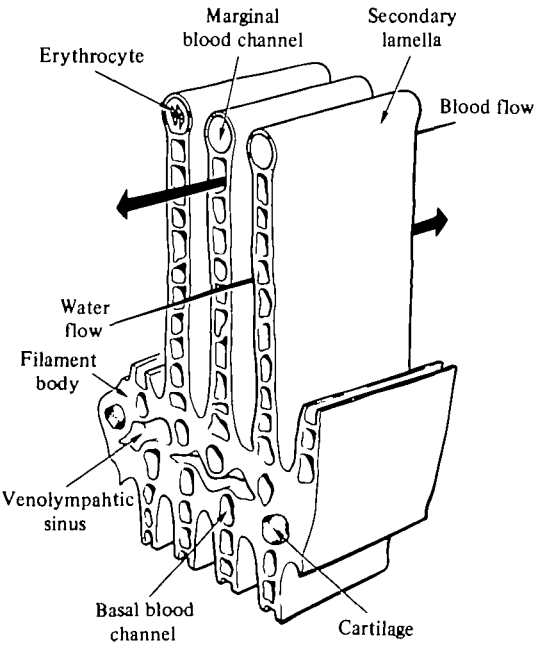

Fig. 3. A section through the secondary lamellae of a teleost drawn approximately to scale.

The cardiac output is directed through the gills and then into the body circulation. Thus, unlike mammals, the fish respiratory circulation is subjected to much higher pressures than the systemic circuit. Pressures within the secondary lamellae oscillate with each heart beat, having a mean pressure of about 3·5 kPa, with an oscillation of about 0·5 kPa.

Blood flows through the lamellae around pillar cells that hold the epithelial layers together. The pillar cells have collagen columns embedded in them and these collagen strands extend around the blood space over the pillar cell flanges (Fig. 5). The blood sheet is about 9–12 μm thick and is very dependent on blood pressure. The lamellae show no increase in length or height as blood pressure rises (Fig. 6), but the width of the blood sheet increases with pressure (Farrell *et al.* 1980). In this respect blood flow through the gill secondary lamellae and the lung alveoli have similar characteristics. Pressures in the lamellae oscillate by about 0·5 kPa with each heart beat, this means (assuming that the dynamic is the same as the static response to blood pressure) that the blood sheet thickness will increase by about 0·5 μm and the lamellar blood volume by about 5 % with each systole. One possible role of the myosin filaments found within pillar cells may be to contract in phase with the pressure pulse to reduce changes in lamellar volume and the thickness of the blood sheet with each contraction of the heart (Smith & Chamley-Campbell, 1981).

Blood flow within a secondary lamellae is greater through marginal and basal than central regions of each lamellae. Increases in blood pressure preferentially increase central lamellar flow and produce a more even flow distribution across the secondary lamellae (Farrell *et al.* 1980).

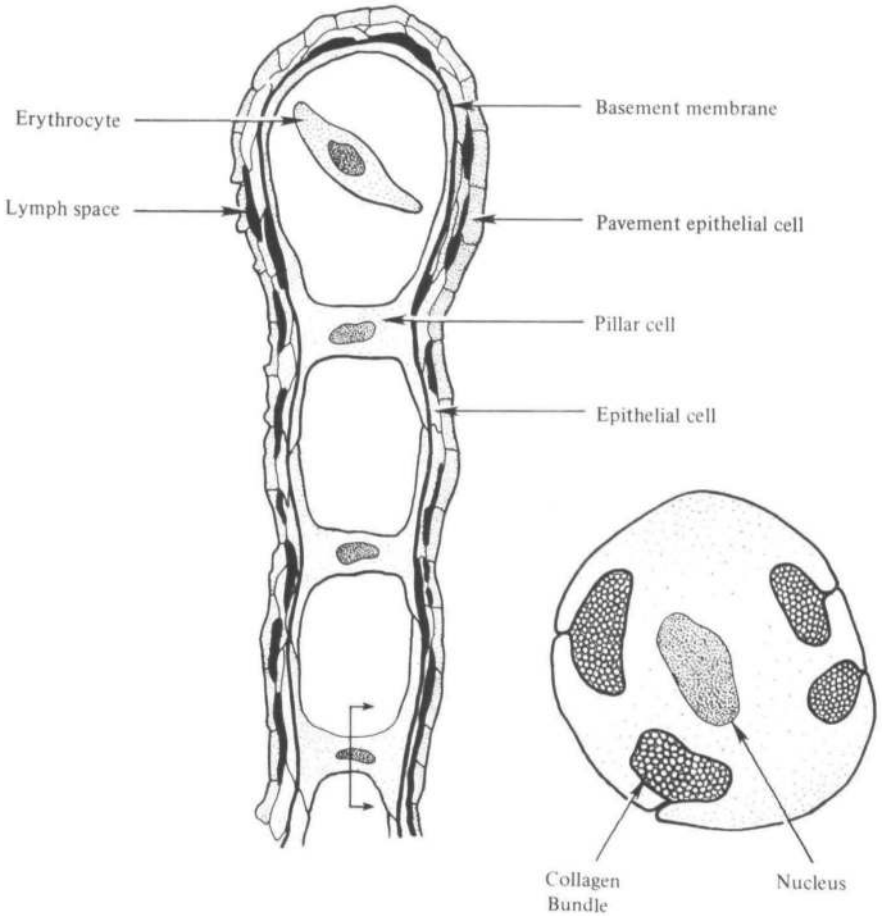

Fig. 5. Sections through a teleost secondary lamella and pillar cell showing the blood/water barrier. The drawing is approximately to scale for a trout, *Salmo gairdneri*.

Only 60% of all secondary lamellae are perfused at rest (Booth, 1978) there being preferential perfusion of more basal lamellae. Increases in blood pressure cause lamellar recruitment and this probably occurs during hypoxia and exercise (Randall, 1981). Total functional lamellar volume exceeds cardiac output, so more than one heart beat is required to move blood through lamellae (Jones & Randall, 1978). The lamellar blood transit time is about 3 s at rest and about 1 s during exercise (Randall, 1981; Hughes *et al.* 1981*a*). The time for blood oxygenation within the gills was shown to be approximately 1 s in carp and eel (Hughes & Koyama, 1974) – that is, within the transit time of blood through the secondary lamellae.

The efferent and, to a lesser extent, afferent filament artery supplying the secondary lamellae, give off capillaries to a veno-lymphatic system. This low-pressure system is found in the body of the gill filament and drains back to the heart. Lymph fluid drains into this extensively valved, central venolymphatic sinus. The low- and high-pressure circulations are juxtapositioned within the filament. Expansion of the elastic high pressure vessels probably squeezes the extensively valved low-pressure system,

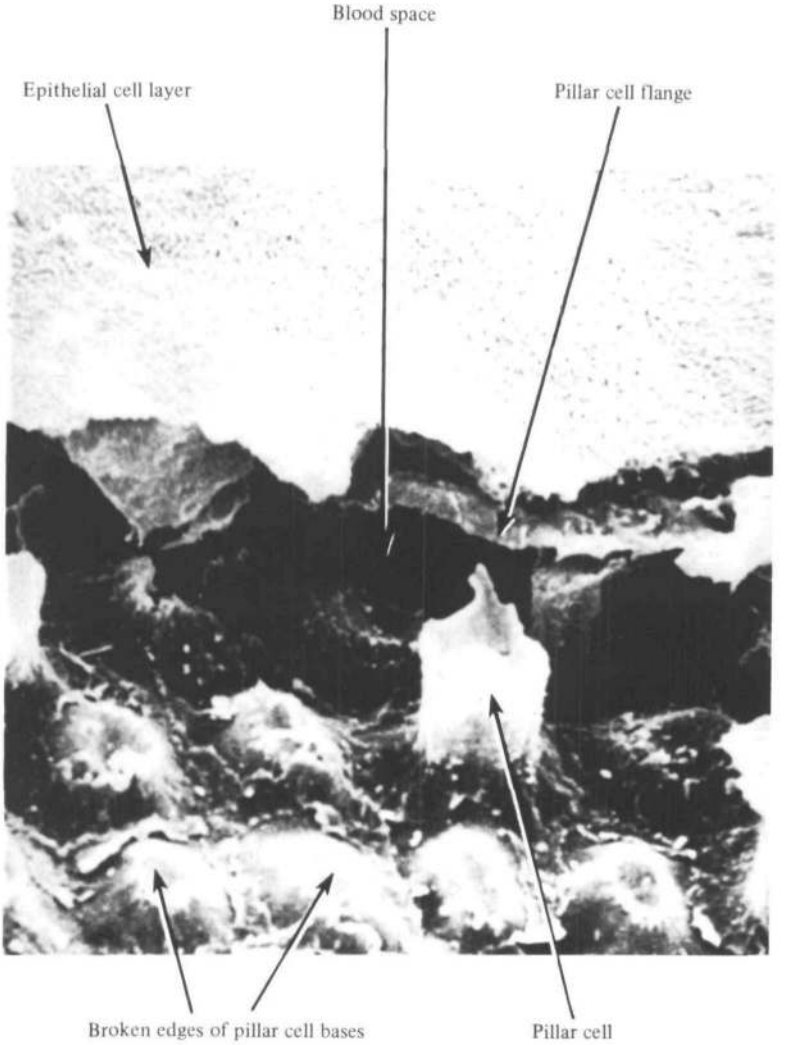

Fig. 4. Fractured section through the secondary lamellae of a trout showing a broken pillar cell, the pillar flange and the overlying epithelial layer. The blood space is approximately 10 μm wide. (Unpublished material from B. J. Gannon.)

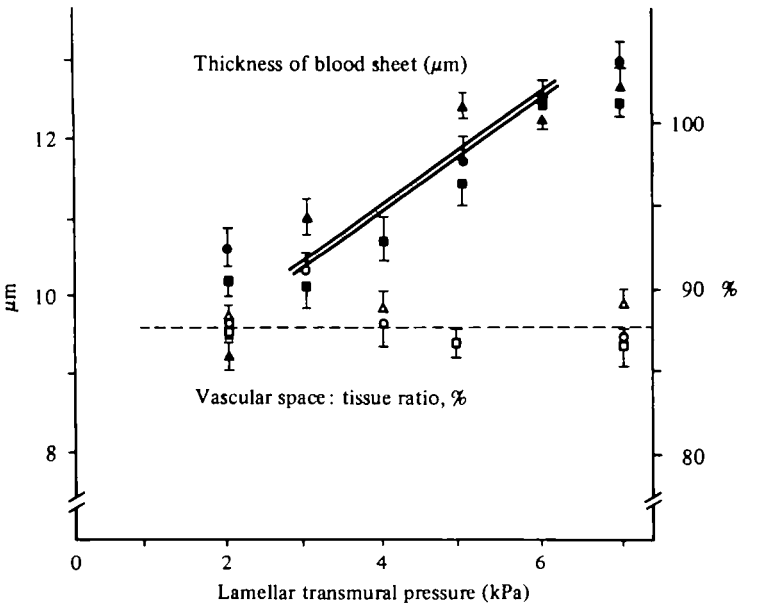

Fig. 6. The effect of transmural pressure changes on the thickness of the blood sheet and the vascular space:tissue ratio in the secondary lamellae of the gill of the lingcod (*Ophiodon elongatus*) (from Farrell *et al.* 1980). The vascular space:tissue ratio is the area occupied by blood expressed as a percentage of the total area observed in a side view of secondary lamellae. No change in this ratio indicates no change in the height and length of secondary lamellae.

augmenting flow in the veno-lymphatic vessels. Some of the cardiac output may by-pass the gills and enter this low-pressure system via the afferent filament artery to veno-lymphatic sinus capillaries. The extent of this flow will depend on the number of afferent connexions, which are small in salmonid fish but large in eels. Hughes *et al.* (1981*b*) concluded that up to 40% of the cardiac output could by-pass the gills via this route in eels (*A. anguilla*).

Hematocrit and, therefore, arterial oxygen content, varies considerably between fish, from zero in icefish to over 40% in some salmonids. The erythrocytes are nucleated, oval, platelike structures and are permeable to H^+, HCO_3^- (Heming & Randall, 1982) and Cl^- (Haswell *et al.* 1978) and show a chloride shift (Cameron, 1978). Intracellular pH is about 0·3 units below that of plasma. Teleost haemoglobin shows both a Bohr and a Root shift (Riggs, 1979) and the erythrocytes contain high levels of organic phosphates, usually ATP. Thus haemoglobin–oxygen affinity can be modulated by changes in pH and/or ATP within the erythrocyte.

O_2 TRANSFER ACROSS FISH GILLS

In a series of experiments on fish artificially perfused with blood (Daxboeck *et al.* 1982) oxygen uptake was found to be proportional to blood flow (Fig. 7). Manipulations of input pressure, found to promote lamellar recruitment in other preparations (Farrell, Daxboeck & Randall, 1979), did not affect oxygen transfer or arterial blood

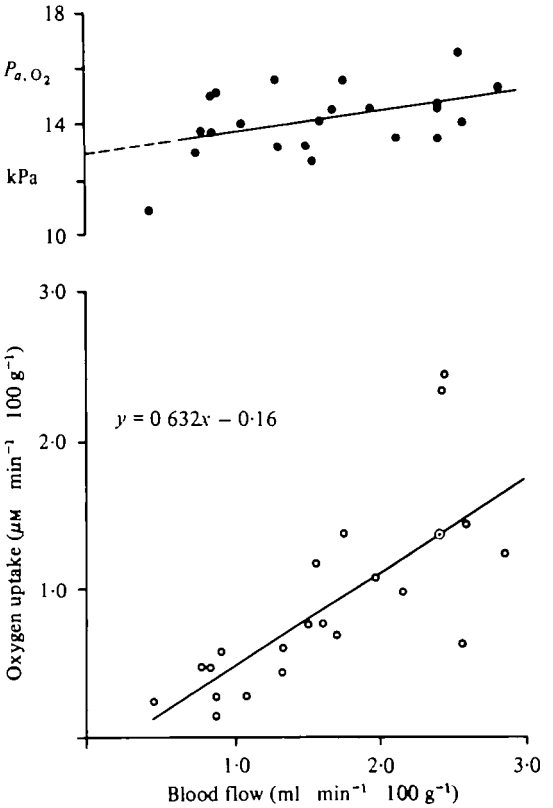

Fig. 7. The effect of changes in gill blood flow in oxygen transfer across the blood perfused, spontaneously ventilating trout (from Daxboeck *et al.* 1982). P_{a,O_2} = arterial blood oxygen tension.

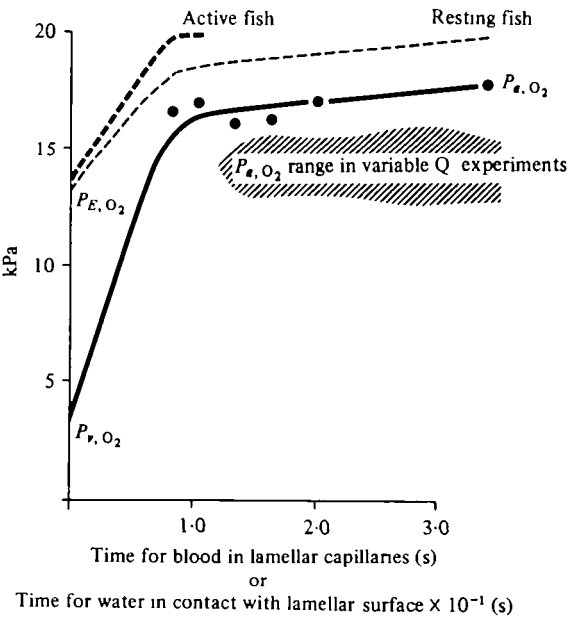

Fig. 8. The effect of decreasing residence time on P_{O_2} in blood and water leaving fish gills. The variable Q experiments refers to data shown in Fig. 7. The closed circles represent data points from Kicenuik & Jones (1977); figure modified from Randall (1981).

P_{O_2} at any flow rate, indicating that the system was not diffusion-limited but was entirely dependent on the rate of perfusion and gill ventilation. The range of transit times was similar in the blood-perfused fish to that observed *in vivo* (Fig. 8) over a wide range of exercise levels. In the fish artificially perfused with blood, oxygen transfer was clearly perfusion limited. The oxygen transfer rates in these experiments, however, spanned only a narrow range from rest to routine activity because blood hematocrit, and therefore arterial blood oxygen content, was low compared with that of intact fish. In intact fish much higher rates of oxygen uptake are observed at similar blood flows (see Jones & Randall, 1978). Under these conditions, increases in gill diffusing capacity, caused by lamellar recruitment and more even lamellar blood flow, may be significant in achieving the high rates of oxygen transfer associated with exercise.

CO_2 TRANSFER ACROSS FISH GILLS

The passage of venous blood through the gills results in a 10–20% reduction in blood total CO_2 levels, largely due to 20% reduction in plasma bicarbonate. The transit time for blood in the gills is between 1 and 3 s, and this is too rapid for any appreciable formation of CO_2 from bicarbonate at the uncatalysed rate (Haswell *et al.* 1980). Hoffert & Fromm (1973) found that acetazolamide produced a reduction in CO_2 excretion in trout (*Salmo gairdneri*). Thus bicarbonate excretion across fish gills presumably involves the catalysed dehydration of plasma bicarbonate. The enzyme, carbonic anhydrase, is found in high concentration in both the gill epithelium and the erythrocyte, but not the plasma. The gill epithelium is known to be quite permeable to protons and bicarbonate could diffuse into the gill epithelium along with protons to form CO_2, which then diffuses into the water. The gill epithelium, however, is probably not very permeable to bicarbonate because large increases in seawater bicarbonate have only minor effects on CO_2 excretion (Van der Thillart, Randall & Lin Hoa-ren, 1982) and elevations of bicarbonate in saline perfusing the gills has little effect on CO_2 excretion or the gill transepithelial potential (Perry *et al.* 1982). Most plasma bicarbonate therefore enters the erythrocyte (Fig. 9) and is dehydrated to CO_2, which then diffuses into the medium across the gill epithelium (Heming & Randall, 1982).

The gill epithelium is very permeable to protons (McWilliams & Potts, 1978) and they are passively distributed between water and blood, hence a reduction in blood pH will result in an efflux of acid into the water. Conversely a reduction in water pH will result in a net uptake of acid. Burst activity in fish leads to a large production of lactic acid and blood pH falls. Proton excretion is elevated in fish following a burst swim (Fig. 10). Thus, depending on the circumstances, there may be a flux of protons either into or out of the fish. There is some interaction between CO_2 and proton movements, however, because a reduction in water pH not only decreases H^+ excretion but also carbon dioxide excretion in exercising coho salmon (*Oncorhynchus kisatch*) (Fig. 10). The exact nature of this interaction is not clear.

The outer membrane of the gill epithelium is thought to contain mechanisms for the exchange of Na^+/H^+ and HCO_3^-/Cl^- (Perry *et al.* 1981), in which NaCl is taken up in exchange for H^+ and HCO_3^- (Fig. 9). These exchange processes operate at a

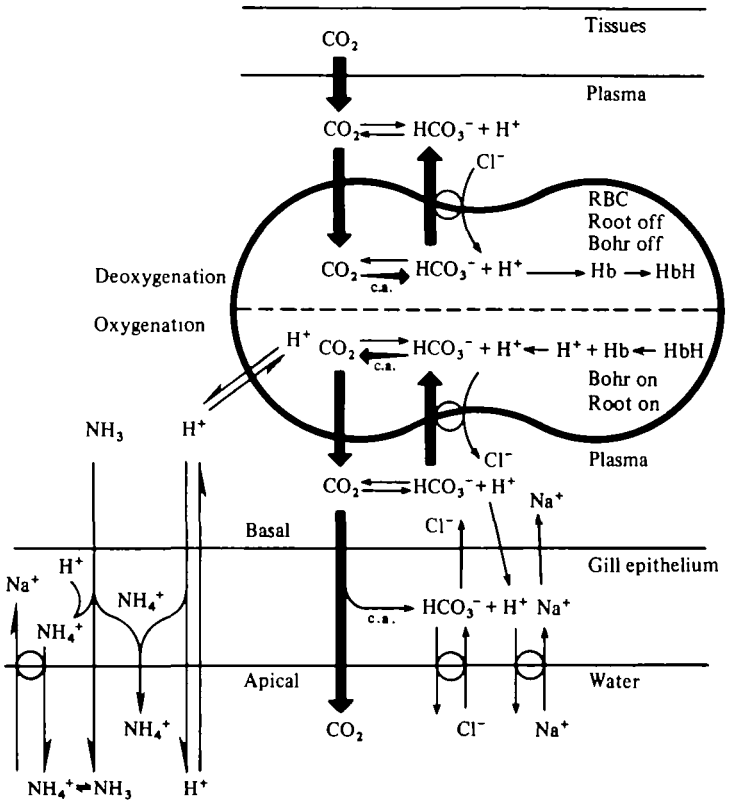

Fig. 9. A Schematic diagram of CO_2, H^+ and ion movement across fish gills.

rate such that the CO_2 excreted via these pathways accounts for about 10% of the total CO_2 excretion of the resting fish (Cameron, 1976). Inhibition of these processes results in acid-base changes in the animal. SITS (a stilbonic acid derivative) inhibition of Cl^-/HCO_3^- exchange results in a rise in blood pH whereas amiloride inhibition of Na^+/H^+ exchange results in a fall in blood pH (Perry & Randall, 1981). There is no evidence, however for modulation of this system in the intact fish (Perry *et al.* 1981). This is not to say it does not occur, only that it has not been observed.

Carbon dioxide enters the water in the form of molecular carbon dioxide because the gill epithelium is probably not very permeable to bicarbonate and HCO_3^-/Cl^- exchange constitutes only a small proportion of CO_2 excretion. The formation of bicarbonate from CO_2 in water at the uncatalysed rate occurs very slowly. The residence time for water at the respiratory surface is such that any formation of bicarbonate, and the resultant decrease in pH, will be negligible in the water phase in contact with the respiratory surface but will occur only after the water has left the gills. Thus changes in water bicarbonate levels and pH, resulting from CO_2 excretion across the gills occur downstream of the respiratory surface and will have little effect on proton flux across the gills.

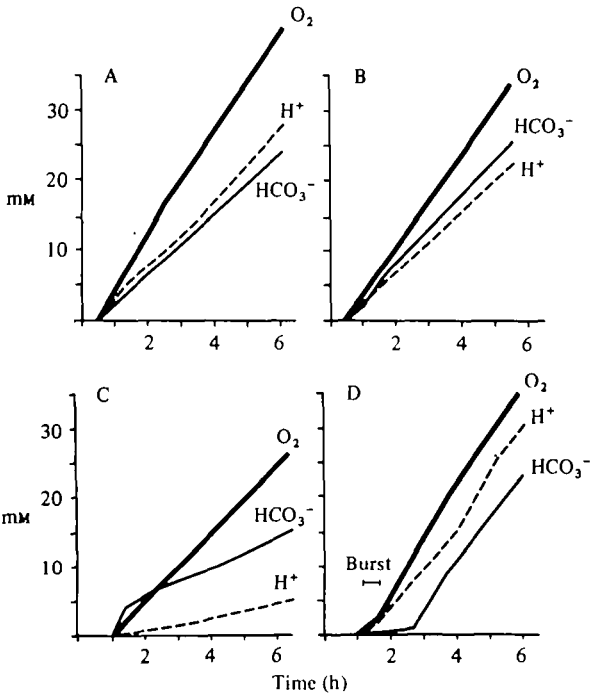

Fig. 10. Accumulated oxygen uptake and hydrogen ion and bicarbonate excretion into sea water containing a swimming coho salmon, *O. kisutch* (600 g wt), at 13 °C in a closed respirometer under four different conditions. U_{crit} is the critical swimming speed which can be defined as the maximum prolonged swimming speed. (A) Sea water pH 7·95, normal sea water, 80 % U_{crit}. (B) Sea water pH 7·95, low bicarbonate sea water, 80 % U_{crit}. (C) Sea water pH 7·10, normal sea water, 50 % U_{crit}. (D) Sea water pH 7·95, normal sea water, 50 % U_{crit} after a burst swim at 120 % U_{crit} to exhaustion. (From van der Thillart *et al.* 1982.)

EXERCISE

Exercise in fish can be categorized as sustained, prolonged or burst swimming (Hoar & Randall, 1978). Burst swimming is of only a few seconds duration and is anaerobic and will not be considered in this article. The other forms of swimming are aerobic and involve adjustments of the respiratory and cardiovascular systems. During prolonged swimming in fish, oxygen uptake may increase by as much as 12–15 times the resting value and 93 % of this increased oxygen uptake is directed towards the working muscles (Randall & Daxboeck, 1982). Cardiac output is increased by up to 3 or 4 times, largely by increases in stroke volume. Blood transit time through the secondary lamellae is reduced from around 3 to 1 s; even so, arterial blood remains saturated (Fig. 8). Venous oxygen content is reduced and the arterial-venous oxygen difference increases by a factor of 2 to 3. An increase in blood hematocrit and therefore arterial oxygen capacity has been reported in some (Randall & Daxboeck, 1982) but not all (Kicenuik & Jones, 1977) studies of exercise in fish. The increased hematocrit is probably due to release of erythrocytes from the spleen and/or a reduction in plasma volume.

Ventral aortic mean and pulse blood pressures increase with the onset of exercise peaking at about 10 min after the initiation of swimming, then falling to a value slightly above that observed during rest. Similar but smaller increases occur in dorsal aortic blood pressure.

Chasing or otherwise disturbing fish causes rise in blood catecholamine levels (Nakano & Tomlinson, 1968), whether this is associated with fear or swimming is not clear but it seems probable that there are increases in circulating catecholamines during exercise.

Water flow over the gills increases in proportion to oxygen uptake and the ventilation: perfusion ratio increases from about 10:1 to 30:1 (Jones & Randall, 1978). The increase in water flow results in a reduction in water residence time from about 250 ms at rest to about 30 ms at high rates of exercise. The magnitude of the water boundary layer will be reduced with increasing velocity. Any advantages of a reduced boundary layer to gas transfer, however, are offset by a simultaneous reduction in the time available for axial diffusion and backmixing of oxygen in water flowing over the gills. The net result is that the amount of oxygen removed from each volume of water as it passes over the gills does not change with increases in water flow during exercise and hypoxia (Kiceniuk & Jones, 1977; Lomholt & Johansen, 1979).

The increase in gill water flow is achieved by small increases in breathing rate and large changes in stroke volume (Jones & Randall, 1978). At high speeds many fish stop rhythmic breathing and 'ram'-ventilate their gills by simply moving forward with their mouths open.

HYPOXIA

Fish are able to maintain oxygen uptake during aquatic hypoxia by elevating gill ventilation. This is caused by increases in breathing rate and stroke volume, the actual response varying with the species (Smith & Jones, 1981).

Cardiac output is maintained during hypoxia because a marked bradycardia is offset by an increase in stroke volume. The systemic resistance increases during hypoxia and results in a rise in both dorsal and ventral aortic blood pressure. The elevated heart-stroke volume and the decreased heart rate result in a marked rise in pulse pressure. Blood catecholamine levels increase and Butler *et al.* (1979) showed that dopamine, adrenaline and noradrenaline levels in the blood of dogfish (*Scyliorhinus canicula*) all increase in response to hypoxia.

Both arterial and venous blood oxygen contents fall during hypoxia (Holeton & Randall, 1967). Erythrocytic ATP levels are reduced (Soivio, Nikinmaa & Westman, 1980), resulting in a marked increase in haemoglobin oxygen affinity. Hypoxia causes a rise in the number of circulating erythrocytes and the cells are known to swell in some fish, resulting in a marked increase in haematocrit. An increase in haemotocrit, however, has not been observed in the dogfish (*S. canicula*) in response to hypoxia (Short, personal communication in Butler *et al.* 1979).

CONTROL OF CARDIAC OUTPUT DURING HYPOXIA AND EXERCISE

Increased activity in vagal cholinergic fibres innervating the heart causes the reduction in heart rate during hypoxia. The afferent arm of this reflex is from receptors

which respond to hypoxia and are located on the first gill arch in the region of the efferent vessel (Daxboeck & Holeton, 1978). A reduction in vagal cholinergic tone contributes to the rise in heart rate, at least in some fish, during exercise (Jones & Randall, 1978). The afferent arm of this reflex is not known.

The teleost heart has an extensive adrenergic innervation whereas elasmobranchs have only a sparse adrenergic innervation of the sinus venosus (Gannon, Campbell & Satchell, 1972). Both teleost and elasmobranch hearts have been shown to have β-adrenergic receptors and show both a positive inotropic and chronotropic response to catecholamines. Circulating catecholamine levels increase during exercise and hypoxia and may be involved in augmenting heart stroke volume. Short, Butler & Taylor (1977), however, have shown that the increase in stroke volume during hypoxia in the dogfish was a consequence of cardiac slowing (via the Starling relationship) rather than the result of β-adrenergic stimulation of the myocardium by increased levels of circulating catecholamines.

Systemic resistance to flow decreases during exercise due to massive dilation of muscle capillaries. Gut blood flow is reduced (Randall & Daxboeck, 1982), probably as a result of α-adrenergic nervous constriction of the coeliac artery (Smith, 1978). This constriction also probably accounts for the reduction in systemic arterial compliance seen during exercise in the cod (*Gadus morhua*) (Jones *et al.* 1974).

The teleost gill vasculature has an extensive adrenergic innervation in the region of the afferent and efferent lamellar arterioles and both a cholinergic and adrenergic innervation of the efferent filament artery close to the gill arch (Randall, Perry & Heming, 1982). The innervation of the gill vasculature in other groups of fishes is less clear. The gills of both elasmobranchs and teleosts have been shown to contain both β-adrenergic and α-adrenergic receptors, the former causing vasodilation, the latter constriction (Capra & Satchell, 1977; Wood, 1974). Gill vascular resistance to blood flow changes little during exercise and hypoxia. Catecholamines cause lamellar recruitment *in vivo* (Holbert, Boland & Olsen, 1979) and they may play a role in ensuring that all lamellae are perfused during hypoxia and exercise. The effect of catecholamines in this case may be direct on the lamellar arterioles or indirect via a rise in blood pressure which has also been shown to cause lamellar recruitment in fish (Farrell *et al.* 1979).

The rise in blood pressure during hypoxia and exercise will not only promote lamellar recruitment but will also ensure a more even distribution of blood flow within the lamellae. The rise in pressure will also make the lamellae more rigid. Observations of living eel gills under a microscope showed fluttering of eel lamellae in the water flow. With each heart beat the lamellae became more erect and flutter was reduced. These eels had a very low heart rate and were anaesthetized; nevertheless, it is probable that during hypoxic bradycardia in fish the lamellae became more rigid with each heart beat. This may be important for maintaining oxygen transfer during hypoxia which is characterized by large blood pulse pressure, a low heart rate and a large stroke volume.

Lamellar recruitment, a more even lamellar blood flow, and more rigid lamellae probably all contribute to an increase in gill diffusing capacity that occurs during both hypoxia (Fisher, Coburn & Forster, 1969) and exercise (Randall, Holeton & Stevens,

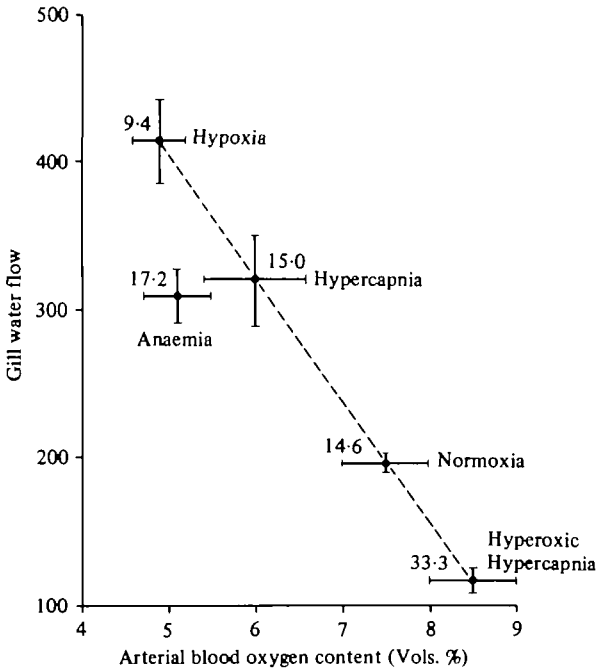

Fig. 11. The relationship between water flow over the gills and arterial oxygen content of dorsal aortic blood from *Salmo gairdneri*. The lines indicate ±S.E. The number by each point is the corresponding arterial oxygen tension in KPa. Arterial oxygen content was changed by bubbling N_2, CO_2 and/or O_2 into the water containing the fish. (Data from Smith & Jones, 1981.)

1967). The effect of these changes in diffusing capacity in a largely perfusion limited system may be apparent only at the extremes of exercise and hypoxia (Taylor, Short & Butler, 1977).

CONTROL OF GILL WATER FLOW DURING HYPOXIA AND EXERCISE

Water flow over the gills increases in proportion to oxygen uptake during exercise and is increased to maintain oxygen delivery during aquatic hypoxia. Smith & Jones (1981) have shown that gill water flow is correlated with arterial blood oxygen content, independent of the method used to manipulate content. For example, hypercapnia reduces arterial oxygen content via the root effect and this promotes a reflex increase in gill water flow similar to that seen when arterial oxygen content is reduced by a fall in P_{O_2} (Fig. 11). Similarly, hyperoxia increases the amount of oxygen in physical solution and will reduce ventilation even in the face of mild hypercapnia. The major hypothesis derived from this work is that there is a receptor that monitors arterial blood oxygen content and causes increases in gill ventilation with a reduction in blood oxygen content. This receptor may, in fact, respond to the amount of oxygen delivered to the receptor, rather than simply blood oxygen content. The evidence for this is tenuous, but it can be seen that the response to anaemia varies from that seen with other manipulations of blood oxygen content (Fig. 11). Anaemia is associated with an

increase in cardiac output (Cameron & Davies, 1970) and if similar changes occurred in the experiments of Smith & Jones (1981), then it is possible that the reduction in arterial oxygen content was partially offset by an increase in blood flow to the receptor, lessening the magnitude of the increase in gill ventilation. The nature and location of these blood oxygen content receptors are unknown, except that they are presumably somewhere in the post gill arterial complex.

Hypercapnia causes an increase in gill ventilation and at low levels of CO_2 these ventilatory responses seem to be related to changes in blood oxygen content rather than P_{CO_2} or pH. At higher levels of hypercapnia, however, increases in gill water flow are not ameliorated by hyperoxia (Smith & Jones, 1981), indicating a possible direct P_{CO_2}/pH stimulation of gill ventilation.

These blood oxygen content receptors cannot be involved in the increases in water flow observed during exercise because, as arterial oxygen content remains the same and blood flow increases, one would predict a decrease, rather than increase, in gill water flow during exercise. The control of breathing movements during exercise and the switch from rhythmic to ram ventilation is not understood. Changes in breathing rate are rapid, indicating control via central nervous drive. The switch to 'ram' ventilation occurs at high velocities and could be controlled by receptors that detect water velocity or body movement. The former seem more likely candidates because some fish, for example the remora (*R. remora*), which rides on the back of sharks, stops rhythmic breathing and ram-ventilates in the presence of high water flows and no swimming movements (Jones & Randall, 1978).

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