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REVIEW ARTICLE

Closing volume: a reappraisal (1967–2007)

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Abstract Measurement of closing volume (CV) allows detection of presence or absence of tidal airway closure, i.e. cyclic opening and closure of peripheral airways with concurrent (1) inhomogeneity of distribution of ventilation and impaired gas exchange; and (2) risk of peripheral airway injury. Tidal airway closure, which can occur when the CV exceeds the end-expiratory lung volume (EELV), is commonly observed in diseases characterised by increased CV (e.g. chronic obstructive pulmonary disease, asthma) and/or decreased EELV (e.g. obesity, chronic heart failure). Risk of tidal airway closure is enhanced by ageing. In patients with tidal airway closure (CV > EELV) there is not only impairment of pulmonary gas exchange, but also peripheral airway disease due to injury of the peripheral airways. In view of this, the causes and consequences of tidal airway closure are reviewed, and further studies are suggested. In addition, assessment of the ''open volume'', as opposed to the ''closing volume'', is proposed because it is easier to perform and it requires less equipment.

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Keywords Lung volumes · Closing volume · Peripheral airway injury

Abbreviations

AC	Airway closure
BAL	Bronchoalveolar lavage
COPD	Chronic obstructive pulmonary disease
CC	Closing capacity
CHF	Chronic heart failure
CV	Closing volume
EELV	End-expiratory lung volume
EFL	Expiratory flow limitation
ERS	European Respiratory Society
ERV	Expiratory reserve volume
FL	Flow limitation
FRC	Functional residual capacity
FVC	Forced vital capacity
FEV_1	Forced expiratory volume in 1 s
IC	Inspiratory capacity
MV	Mechanical ventilation
NEEP	Negative end expiratory pressure
NOe	Exhaled NO concentration
OC	Open capacity
PaO_2	Partial arterial oxygen pressure
PAD	Peripheral airway disease
PAI	Peripheral airway injury
$P_{c,max}$	Maximal closing pressure
$P_{c,min}$	Minimal closing pressure
P_L	Transpulmonary pressure
$P_{o,max}$	Maximal opening pressure
P_{pl}	Pleural surface pressure
PEEP	Positive end expiratory pressure
PO_2	Partial oxygen pressure
RV	Residual volume
TGV	Trapped gas volume

TLC	Total lung capacity
TNF-α	Tumour necrosis factor alpha
V_{30}	Lung volume at P_L of 30 cmH_2O
VILI	Ventilator induced lung injury
VIP	Vaso intestinal peptide
V'_{max}	Maximal flow
V–P	Volume–pressure
V'/Q'	Ventilation perfusion ratio
$V_{r,L}$	Resting lung volume
ZEEP	Zero end expiratory pressure

Background

Early contributions

The lung is an air-filled organ containing a multitude of small, densely packed air-spaces (alveoli) partitioned by delicate tissue membranes (septa) which separate blood from air. This complex structure, which is very efficient for gas-exchange because it provides a large area of intimate contact between air and blood, includes the ''infundibula'', i.e. the spaces subtended by the terminal bronchioles. The infundibula include the respiratory bronchioles, vestibula, atria, air-sacs and alveoli proper (Keith 1909). The maintenance of open (gas filled) alveoli is jeopardised by the surface tension generated at their air–tissue interface, which promotes alveolar collapse (atelectasis). Physiologists have been aware of this problem since 1929 (Von Neergaard 1929). Since then, it has been the object of many studies (cf. Goerke and Clements 1986).

The pulmonary air spaces are connected to the environmental air by the tracheobronchial tree consisting of a *conducting zone*, which comprises the non-alveolated airways that are not in direct contact with the pulmonary capillaries, and a *transitional zone*. This infundibular zone, which consists of small, alveolated tubes that cannot be easily separated from the alveoli, contributes to gas exchange between air and blood. The infundibular tubes and the terminal bronchioles are subjected to similar surface tension forces as the alveoli, which tend to collapse them (airway collapse or closure). Pulmonary atelectasis is in general associated with concurrent collapse of the adjacent airways of the transitional zone. In contrast, closure of the terminal bronchioles, which are the most peripheral, non-alveolated airways of the conducting zone, can occur in the absence of atelectasis and collapse of the tubes within the infundibula. The terminal bronchioles, whose dimensions are similar to those of the tubes within the infundibula, are also prone to collapse due to surface tension forces. Surprisingly, peripheral airway closure, which is a more common physiologic phenomenon than atelectasis, has not been studied until 1967 (Dollfuss et al. 1967). Furthermore, although peripheral airway closure is of great clinical importance, most of the active research done in this area has been transitory (1967–1980), focusing on early detection of peripheral airway disease (PAD) due to cigarette smoke.

Chronic obstructive pulmonary disease (COPD) is a condition usually associated with cigarette smoke that has an insidious onset and a prolonged period during which the lung is in transition between health and overt disease. Niewoehner et al. (1974) were among the first to demonstrate that in young smokers the earliest pathological changes within the lung were characterised by denuded epithelium and intramural inflammatory cells in the respiratory and membranous bronchioles. This is referred to as PAD. Since at this early stage the forced expired volume in 1 s (FEV_1) and the forced vital capacity (FVC) are within normal limits, a battery of new tests was proposed in the 1970s for early detection of PAD because this condition was thought to be a precursor of overt COPD. These tests, however, were soon dismissed on the grounds that they were markers of smoke exposure rather than being of prognostic significance. This criticism was unjustified because one of these tests, namely the ''single-breath nitrogen test'', has been shown to have good prognostic value (Olofsson et al. 1986; Stanescu et al. 1998). However, by completion of these studies, which lasted up to 13 years, the interest in early detection of PAD in smokers had vanished because smoking was to be banned.

The single-breath N_2 test includes assessment of the closing volume (CV). This parameter is useful not only for early detection of PAD, but also to explain two pivotal abnormalities which may be associated with increased CV: (1) maldistribution of ventilation with impaired gas exchange within the lung; and (2) peripheral lung injury. These will be the main focus of the present review.

Because of space constraints, methodology will be only briefly described. A more detailed account can be found elsewhere (Milic-Emili 1974; Anthonisen et al. 1974).

Physiologic markers of closing volume

Although the CV was first measured only in 1967 (Dollfuss et al. 1967), the presence of airway closure at low lung volume had been postulated long before by

Laennec (1791–1826) who noted that excised lungs cannot be completely emptied of gas even by squeezing on their surface (i.e. applying a positive external pressure). He concluded that this should reflect airway closure. In this context it is puzzling that, although volume–pressure (V–P) relationships of the lung had been studied since 1846 (Hutchinson 1846), until 1973 the studies were limited to the positive transpulmonary pressure (P_L) domain. The first published V–P curves extending below zero P_L are shown in Fig. 1 (Glaister et al. 1973b).

Because analysis of static or quasi-static deflation V–P curves of the lung allows assessment of the ''closing airway pressure'', which is fundamental for understanding the genesis of CV, this will be described in the following section on pulmonary static.

Static behaviour of isolated lung

Volume–pressure curves of excised lungs vary among species and depend on experimental parameters such as temperature and previous volume history. When these sources of variability are controlled, the V–P relationships are highly reproducible. Quasi-static inflation and deflation V–P curves of a normal excised exsanguinated dog lung are shown in Fig. 1. The effect of acute vascular engorgement on static behaviour of isolated cat lung has been studied by Frank (1959) who found surprisingly little effect, except for a slight reduction of compliance at high volumes (slight shift to the right of V–P curves).

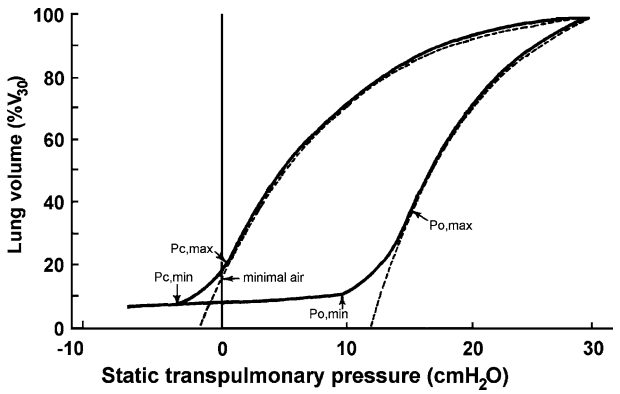

Fig. 1 Quasi-static volume–pressure curves of a freshly excised, exsanguinated dog lung on inflation and deflation. Lung volume is expressed as percentage of that at transpulmonary pressure of 30 cm H_2O (V_{30}). *Solid lines*: experimental relationships during lung deflation and inflation, respectively. *Dotted lines*: exponential fits (see text for further information). *Pc* closing pressure; *Po* opening pressure. Adapted from Glaister et al. (1973b)

V–P hysteresis

The V–P curves during lung inflation and deflation are different (Fig. 1), reflecting ''hysteresis'' due to several mechanisms: plastic behaviour of tissues, true tissue hysteresis, surface (air–liquid) hysteresis, and differences in the sequence of recruitment or derecruitment of lung units between inflation and deflation (Radford 1964; Glaister et al. 1973a, b).

Resting lung volume

The volume at zero P_L is commonly referred to as ''minimal volume'' or ''minimal air''. Both terms are misnomers because by decreasing P_L below zero there is a further decrease in volume (Fig. 1). Accordingly the term ''resting lung volume'' ($V_{r,L}$) is more appropriate (Milic-Emili 1974). The magnitude of $V_{r,L}$ varies within and between different animal species. During deflation (Fig. 1), $V_{r,L}$ amounts to 16% of the lung volume at P_L of 30 cmH_2O (V_{30}). In excised dog and cat lungs, $V_{r,L}$ amounts to 10–20% of V_{30}, while in man higher values have been reported (Radford 1964; Glaister et al. 1973a; Milic-Emili 1974; Milic-Emili et al. 2005). This variability may reflect presence of stable foam in the airways and/or differences in pulmonary blood content (Frank 1959; Stigol et al. 1972). Among other factors, $V_{r,L}$ depends on the previous volume history of the lungs (Glaister et al. 1973a; Hoppin 1999).

Frank (1959), repeating an earlier observation by Basch (1887), found that with pulmonary vascular engorgement the ''minimal air'' increased by a small amount, i.e., at zero P_L the extent of peripheral airway closure was reduced reflecting increased resistance to collapse. This was attributed by Basch to the ''erectile'' nature of the pulmonary capillaries. Unfortunately in these studies the trapped gas volume and the critical closing pressures of the lung were not measured.

In excised, exsanguinated lobes (n = 208) of normal dogs, the overall resting lobar volume (% lobar volume at P_L of 30 cmH_2O) is essentially the same in upper or lower lobes, and in left or right lobes (Faridy et al. 1967). Using ^{133}Xe it was found, however, that within lobes the regional resting volume was at times appreciably different (Faridy et al. 1967).

Trapped gas volume

In the older texts, where '' minimal air'' was used to define the volume of gas in the lung at zero P_L, it was often stated that this gas was trapped by closure of the non-cartilaginous airways, the assumption being that at

zero P_L the airways leading to all pulmonary alveoli are closed. Kleinmann et al. (1964) were the first to point out that at $V_{r,L}$ some airways must remain patent throughout their length. In fact, when P_L is decreased below zero, there is a further decrease in lung volume until a critical P_L of –3 to –5 cm H_2O is reached (Fig. 1). Expulsion of gas from the lung then ceases, suggesting that all pulmonary pathways are now closed (Glaister et al. 1973a). The volume of gas trapped behind the closed airways is termed trapped gas volume (TGV). Hughes et al. (1970) demonstrated that in excised dog lungs it was the terminal bronchioles that closed.

Exponential character of *V–P* curve

In the volume range between V_{30} and about 20% V_{30} (Fig. 1), the relation between volume and pressure during deflation can be described with good approximation by the exponential function:

$$V = V_{max} - b \cdot e^{-KP_L} \quad (1)$$

where P_L is static transpulmonary pressure, V_{max} is volume at infinite P_L, K a constant, and b the difference between V_{max} and the predicted lung volume at zero P_L (Glaister et al. 1973a). Thus above 20% of V_{30} the static deflation *V–P* curve is exponential, as defined by Eq. 1. Such a function also fits in vivo volume–pressure relations of human lungs (Milic-Emili et al. 1966). The non-linearity of the *V–P* curves makes it difficult to use accepted terms such as compliance which presuppose a linear system. Instead, the constant K of Eq. 1 can be used as an *index* of the overall distensibility.

Closing pressure

The critical P_L at which lung emptying ceases is termed *minimum airway closing pressure* ($P_{c,min}$). Since some airways begin to close at P_L values higher than $P_{c,min}$ (Fig. 1), *maximum airway closing pressure* ($P_{c,max}$) should refer to the P_L at which airway closure begins during deflation (Glaister et al. 1973a). The $P_{c,max}$ is denoted by the point (inflection point) at which the experimental deflation curve deviates permanently from the exponential function (Fig. 1). There are no $P_{c,max}$ values for isolated human lungs. In six dog lungs, $P_{c,max}$ ranged from 1.1 to 4.0 cmH_2O (Glaister et al. 1973a).

In the past, the substantial difference between $P_{c,max}$ and $P_{c,min}$ has been attributed to non-homogeneous resistance to collapse of the different peripheral airways (Glaister et al. 1973a). Such inhomogeneity is predictable in pulmonary disease and possibly also in the aged lung. In normal young lung (Fig. 1), the difference between $P_{c,max}$ and $P_{c,min}$ probably mainly reflects ''tissue interdependence'' (Mead et al. 1970). Because of interconnected interstitial fibres, the local distortion caused by the initial peripheral airway collapse ($P_{c,max}$) opposes further collapse of the adjacent airways. As a result, the critical closing pressure progressively decreases from $P_{c,max}$ to $P_{c,min}$ (Fig. 1). Thus, the progressive decrease in slope $\Delta V/\Delta P_L$ of the lung deflation *V–P* curve between $P_{c,max}$ and $P_{c,min}$ is related to (1) increased critical closing pressure due to tissue interdependence, and (2) decreased number of alveoli contributing to exhaled air (Sutherland et al. 1968). Clearly, when the airways to part of the lung close, a greater transpulmonary pressure change is required to produce a given overall volume change, i.e. $\Delta V/\Delta P_L$ decreases. As a result of tissue interdependence the peripheral airway resistance to collapse is effectively increased.

Static behaviour of lung in vivo

Morphology of static *V–P* curves

In the absence of airspace or airway closure, the isolated lungs or lobes expand relatively uniformly (Faridy et al. 1967; Katsura et al. 1970; D'Angelo 1972; Hughes et al. 1972). This is not the case when the lungs are inside the thorax (Milic-Emili et al. 1966; Sutherland et al. 1968). This different behaviour is mainly due to the fact that in isolated preparations the pleural surface pressure (P_{pl}) is uniform, whereas in the intact thorax there is a vertical P_{pl} gradient with the more negative values in the upper parts. As a result, the static P_L is greater in upper lung zones, and consequently the upper lung units are more expanded than those in the lower zones.

The effects of the vertical P_{pl} gradient on ventilation distribution and gas exchange are described in detail elsewhere (Sutherland et al. 1968; Milic-Emili 2005). Here we briefly consider only the implications of the vertical P_{pl} gradient on the morphology of the static *V–P* curves of the human lung. Figure 2 shows the static *V–P* curves of a normal subject measured in vivo using the oesophageal balloon technique (Sutherland et al. 1968). At high volumes, exponential functions of the type of Eq. 1, shown in Fig. 1, describe the *V–P* relationships during deflation and inflation. However, because of the vertical P_{pl} gradient, the inflection point ($P_{c.max}$) occurs at a higher volume (~50% TLC) than in

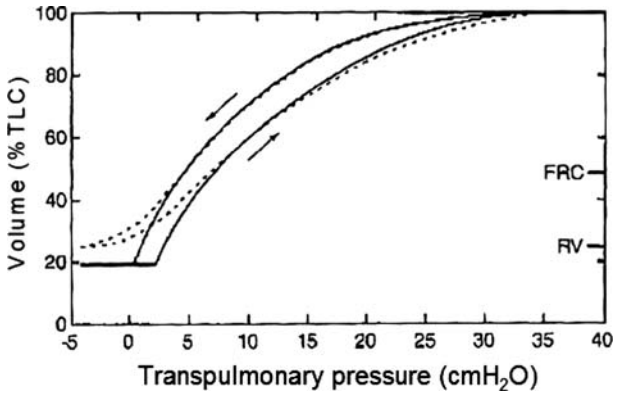

Fig. 2 Quasi-static volume–pressure curves of the lungs of a normal, seated, young subject. Lung gas volume is expressed as a percentage of total lung capacity (*%TLC*). *Broken lines*: relationships obtained in vivo from the measurements of oesophageal pressure. *Solid lines*: idealised relationships that should be obtained in the absence of the vertical gradient of pleural surface pressure due to gravity and if maximal and minimal values of closing pressure (0 cmH_2O) and opening pressure (2.5 cmH_2O) were the same. *FRC* functional residual capacity *RV* residual volume. The inflection points at which the experimental relationships during deflation and inflation deviate from the corresponding exponential curves indicate the maximal closing and opening pressures, respectively. Adapted from Sutherland et a1. (1968)

the isolated lung (~20% V_{30}). An increase of $P_{c,max}$ is also found in isolated lungs and lobes subjected to an artificial P_{pl} gradient (Glaister et al. 1973a, b). It should be noted, however, that in vivo there may be oesophageal pressure artefacts which at low volumes distort the measured *P–V* curves of the lung (Sutherland et al. 1968; Milic-Emili et al. 1964b).

Trapped gas volume

In young individuals at RV, the TGV is reached only in the dependent lung regions (Milic-Emili et al. 1966). With ageing the extent of gas trapping at RV increases and may encompass most of the lung (Sutherland et al. 1968).

Closing pressure

Holland et al. (1968) found that in elderly subjects both the closing and opening volumes are consistently larger than those measured in younger individuals (Dollfuss et al. 1967). This has been attributed in part to age-related loss of lung recoil (Turner et al. 1968), but a decreased resistance to collapse of the aged airways was also playing a role. Indeed, in five normal young subjects (29–41 years) $P_{c,max}$ averaged 2.5 cmH_2O, while in five elderly individuals (65–75 years) it averaged 3.7 cmH_2O (Holland et al. 1968). Because these values were obtained with the oesophageal balloon method, which reflects P_{pl} near the mid-level down the lungs (Milic-Emili et al. 1964a), it is necessary to estimate P_{pl} at the bottom of the lung where airway closure starts in order to assess the true $P_{c,max}$. Assuming a vertical lung length of 30 cm and a P_{pl} gradient of 0.25 cmH_2O/cm descent (Milic-Emili et al. 1964b), the estimated $P_{c,max}$ values at lung bottom correspond to a P_L of zero in the old and –1 cmH_2O in the young subjects. In contrast, according to Cavagna et al. (1967), a more negative P_L is required to start airway closure in experimental animals. In this elegant study, airway and alveolar collapsibility were assessed in vivo by measuring quasi-static deflation *P–V* curves of lung during progressive reduction of volume (measured plethysmographically) achieved by gas absorption following tracheal clamping in oxygen filled lungs (case *a*), or by withdrawing air from the trachea with a syringe (case *b*). In those experiments the onset of airway closure was taken as the point at which the *P–V* curve of case *b* departed from that of case *a*. In open chest cats, dogs and rabbits the values of P_L obtained at the point of departure ranged from –1.5 to –4.5 cmH_2O, indicating that the airways resisted collapse. In contrast in excised, exsanguinated, normal dog lungs, airway closure starts at positive P_L values (Fig. 1). This discrepancy may be due to the presence of blood in the lungs of the open chest animals which reduces airway collapsibility. It is unfortunate that Cavagna et al. did not compare their estimates of $P_{c,max}$ with those obtained with the approach of Glaister et al. (1973a) depicted in Fig. 1. In this connection it should be noted that the $P_{c,max}$ values obtained by assessment of the inflection point on the deflation *V–P* curve of the lungs (oesophageal balloon method) closely reflect the CV (Holland et al. 1968; Ingram et al. 1974). This is also the case in isolated lungs and lobes subjected to an artificial P_{pl} gradient (Glaister et al. 1973b).

In conclusion, peripheral airway closure is one of the most important hallmarks of pulmonary mechanics. When static P_L is lower than $P_{c,max}$, there is (1) gas trapping characterised by inflection points on the static lung inflation and deflation *V–P* curves; (2) increased hysteresis with a concomitant increase in hysteresis-related work, as reflected by increased hysteresis area; (3) time-related changes in respiratory mechanics; (4) cyclic reopening and closure of peripheral airways, with risk of parenchymal and bronchiolar injury; and (5) maldistribution of ventilation and impaired gas exchange.

Closing volume

Figure 3 depicts the original closing volume tracing obtained by Dollfuss et al. (1967) on a normal upright subject using the ^{133}Xe bolus method. The record shows the four phases first described by Fowler (1952). In this elegant paper, Fowler suggested that phase IV was a '' first in, last out'' phenomenon, though his explanation of the phenomenon was not correct. The use of radioactive gases in the study of regional lung function has provided direct evidence that phase IV is due to regional inhomogeneity of ventilation distribution (Dollfuss et al. 1967).

Assessment of closing volume

The terms closing volume (CV) and closing capacity (CC) are used generically to denote the lung volume at which peripheral airway closure begins. In practice, CV is also used to denote the volume difference from the onset of airway closure to RV, while CC includes RV (CC = CV + RV). The CV can be measured with the bolus (Dollfuss et al. 1967) or resident gas methods (Anthonisen et al. 1970). The former technique consists of administering a bolus of tracer gas (He, Ar, SF_6, ^{133}Xe) near residual volume (RV) while air is slowly inhaled to total lung capacity (TLC). Since at RV the airways in the dependent lung zones are closed, the tracer gas is delivered to the upper lung regions. During the subsequent slow expiration from TLC to RV, a critical volume is reached at which the airways in the lower lung region begin to close. As a result, the contribution of the upper zone to the expirate increases with a sudden upswing in the expiratory tracer gas concentration (Fig. 3). As expiration proceeds to RV, closure spreads to the middle lung zone causing a progressive increase in expired tracer concentration. Hence, the CV record is characterised by the following four phases: Phase I which is tracer free (dead-space gas) and amounts 0.1–0.2 l; phase II which consists of alveolar and dead-space gas and exhibits a rapid increase in expired tracer concentration to an apparent ''plateau'' (phase III). This is followed by a terminal increase of tracer concentration (phase IV) as expiration continues to residual volume. The junction of phase III and phase IV denotes the CV.

The resident gas technique is similar except that in this case the difference in nitrogen (N_2) concentration between the upper and lower lung regions is obtained by the inhalation of pure oxygen from RV to TLC. Since at RV the alveoli are larger in the upper lung regions (Milic-Emili et al. 1966), the nitrogen (resident gas) concentration at TLC is higher in upper than lower lung zones. As a result, during the subsequent slow expiration from TLC to RV, records similar to that in Fig. 3 are obtained by measuring expired N_2 concentration. The previous volume history of the lung, namely expiration from 100 to 50% VC, has little or no effect on CV (Linn and Hackney 1973). There is some evidence, however, that suggests time-dependence of airway closure (Ruff et al. 1970). Although it has been claimed that the expiratory flow influences the magnitude of closing capacity (Rodarte et al. 1975), this effect is very small over the range of flow used during the assessment of the closing volume (0.2–0.5 l/s).

Genesis of phases III and IV

Many studies on distribution of inspired air have been based on analysis of the alveolar ''plateau''(phase III)

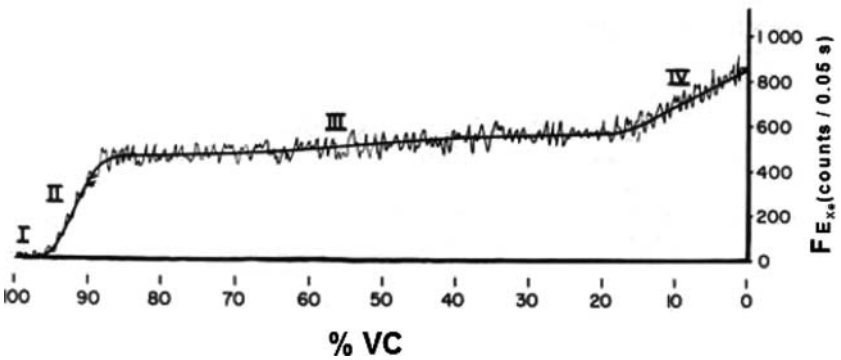

Fig. 3 Expired ^{133}Xe concentration as a function of expired volume, expressed as percentage of vital capacity (*VC*%). This expiration followed a vital capacity inspiration during which a bolus of ^{133}Xe was injected into the inspired air at the onset of inspiration. Phases I, II, III and IV are described in the text. The oscillations of the record are due to the random nature of radioactive decay and cardiogenic oscillations. The volume expired from total lung capacity (100% VC) to the junction of phases III and IV is the ''open capacity'' (*OC*), while that from the junction to residual volume (0% VC) is the closing volume (*CV*). The closing capacity is the sum of CV and the residual volume. Adapted from Dollfuss et al. (1967)

in the single breath expirate. It was concluded that even in the normal lung the ventilation distribution is not uniform, due to many potential mechanisms (Bouhuys 1964; Verbanck and Paiva 2002).

To explain the closing volume tracings obtained under normal gravitational conditions, a simple model was proposed (Milic-Emili 1974; Milic-Emili et al. 2005). This model is based on the assumption that (1) the intrinsic properties of the lungs are uniform and fit Eq. 1; (2) there is an unique airway closing pressure ($P_{c,max} = P_{c,min}$); and (3) the changes in P_{pl} during lung deflation are the same in all lung regions. Although such strict criteria are not met even in the normal lung, the model proves useful in understanding the mechanisms involved in the generation of the closing volume tracings.

Open capacity

Tidal airways closure is present when CC > FRC or CV is greater than the expiratory reserve volume (ERV). Assessment of CC is problematic because it requires (1) expensive equipment to measure the residual volume (body plethysmograph, helium analyser, etc.), and (2) performance of two expirations to RV, which may represent an unbearable burden for subjects who are old and/or sick. In fact Teculescu et al. (1996) and Viegi et al. (1988) reported that assessment of CC is not ''a useful test for epidemiological purposes'' because of a high task failure rate, especially in elderly subjects. An useful alternative is the assessment of the ''open capacity'' (OC), i.e. the difference between TLC and CC (OC = TLC–CC). This measurement does not require that the second expiration be continued till RV is reached, because the junction of phase III and phase IV in general occurs well above RV (Fig. 3). The volume exhaled from full inspiration (TLC) to CC (junction of phases III and IV) denotes the volume range with open airways, while CC–RV denotes the volume range with closed peripheral airways, the extent of closure increasing progressively as RV is approached. Strictly speaking, by analogy to OC, the CC should be termed ''closed capacity''. Because of precedent, however, we will continue to use the term closing capacity.

Normal values of closing capacity

The first study of CC on non-smokers ($n = 80$) of different age (18–82 years) was done using the ^{133}Xe bolus method by Leblanc et al. (1970). They expressed CC as a percentage of TLC to normalise for body size. This ratio (CC/TLC,%) is useful in normal individuals, but not in patients because both CC and TLC can be altered by disease. In patients it is preferable to measure CC in litres and compare it with corresponding normal predicted values (Torchio et al. 2006a). Leblanc et al. (1970) found a marked age-dependence of CC, as confirmed by numerous studies using both the bolus and the resident gas methods. Since comparisons of normative CC data obtained with different techniques are controversial, it seems prudent to use normative values obtained with the same technique as the experimental data.

Since most studies are carried out with the single-breath N_2 method, we provide normative CC values for this technique only. Using this method on a large population ($n = 284$) of healthy non-smokers aged 16 to 85 years, Buist and Ross (1973) confirmed the marked increase of CC/TLC (%) with age and furthermore found a small gender effect. Their regressions for males and females were as follows:

$$\text{Males } (n = 132) : \text{CC/TLC } (\%) = 14.9 + 0.50 \times \text{age (years)} \pm 4.1\,(\text{SE}) \quad (2)$$

$$\text{Females } (n = 152) : \text{CC/TLC } (\%) = 14.4 + 0.54 \times \text{age (years)} \pm 4.4\,(\text{SE}) \quad (3)$$

These regressions differ significantly in terms of slope but not intercept. At an age of 70 years, the mean difference in CC between females and males amounts to 2.5% TLC.

Using a computerised (automatic) analysis of phase IV, Teculescu et al. (1996) found similar results in 158 healthy non-smokers in whom the rate of increase of CC/TLC with age was slightly higher in females than in males, though in this case not significantly. The regression equations of Teculescu et al. (1996) are as follows:

$$\text{Males } (n = 90) : \text{CC/TLC } (\%) = 13.8 + 0.46 \times \text{age (years)} \pm 3.5\,(\text{SE}) \quad (4)$$

$$\text{Females } (n = 152) : \text{CC/TLC } (\%) = 12.5 + 0.51 \times \text{age (years)} \pm 3.5\,(\text{SE}) \quad (5)$$

While the regressions of Buist et al. and Teculescu et al. were similar, the normative CC/TLC data of Knudson et al. (1977) obtained with the single-breath N_2 method were somewhat lower at all ages. Since little methodological information is given (e.g. equipment dead space, response time of analysers, etc.), the discrepancies among the various studies cannot be explained. Furthermore, in these studies different methods were used to assess RV and the junction of

phases III and IV: visual inspection (Buist and Ross 1973) or automatic analysis (Teculescu et al. 1996). Clearly better standardised normative data should be provided in future studies.

In the literature most normative values for CC are expressed as CC/TLC, but predicted CC in litres can be immediately obtained multiplying predicted CC/TLC by predicted TLC, while predicted OC in litres can be computed as the difference between predicted TLC and predicted CC.

Subdivision of lung volumes

Functionally, CC is as important as RV, FRC and TLC. Figure 4 depicts the changes of these volumes with age (range 20–80 years) in a normal seated man (height 1.7 m). The conventional volumes were predicted according to ERS (Quanjer et al. 1993) and CC according to Buist and Ross (1973). There are two important features in this figure: (1) only CC and RV exhibit a marked age-dependence. The increase in RV, which essentially parallels that of CC, probably mainly reflects increased extent of airway closure and gas trapping at RV due to increased CC; and (2) the difference between CC and FRC decreases progressively with age.

The age-related increase of CC reflects both loss of lung recoil and decreased resistance to collapse of the peripheral airways (Holland et al. 1968; Turner et al. 1968).

The more rapid increase of CC with advancing age compared to that of FRC results in a reduction of Δ(FRC–CC) with age. In the sitting position, the CC exceeds FRC at an age of about 75 years (Fig. 4). In the supine position, CC exceeds FRC much earlier (~44 years) because of the gravity-dependent decrease in FRC (Leblanc et al. 1970). The decreased Δ(FRC–CC) with advancing age renders older individuals more susceptible to ''tidal airway closure'', particularly in decubitus. Hence, much smaller reductions in FRC and/or increases in CC are required to elicit ''tidal airway closure'' in elderly than young individuals (Torchio et al. 2006b). In the presence of ''tidal airway closure'' (CC > FRC), some of the airways may remain closed throughout the breathing cycle while others may be closed only during part of the cycle. Indeed, some airways may attain the critical opening pressure at the beginning of the inspiration, while others may open only toward the end of inspiration, i.e. when pleural pressure is most negative (Holland et al. 1968). Similarly, some airways reach their critical closing pressure at the beginning of expiration while others can reach it later. Thus, some lung units will be entirely non-ventilated and others will be underventilated to varying degrees. Abernethy et al. (1967) have shown that recumbency caused a significant increase of urinary-alveolar nitrogen difference in the healthy mid-aged man. The nitrogen difference is an index of increased inhomogeneity of ventilation-to-perfusion (V'/Q') distribution within the lung, particularly if the latter is due to the development of regions with low V'/Q' ratio. Low V'/Q' areas, together with non-ventilated areas, increase the alveolar-to-arterial PO_2 difference and hypoxemia. In normal elderly subjects, the arterial PO_2 is indeed lower in supine than in sitting position (Ward et al. 1966). Furthermore, in 152 normal supine non-smokers (aged 14–84 years) Sorbini et al. (1968) have found an average decrease of PaO_2 of 0.42 mmHg per year, whereas according to Mellemgard (1966) the corresponding rate

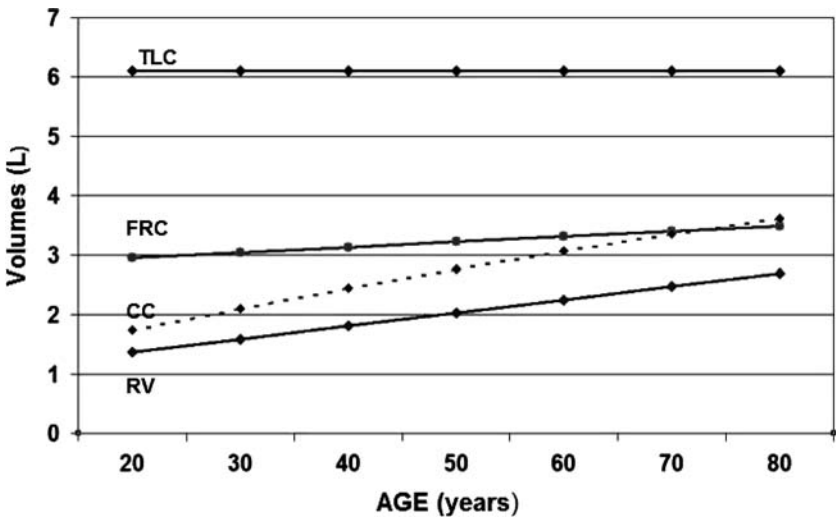

Fig. 4 Subdivision of lung volume as a function of age for a normal male (height 1.7 m). *TLC* total lung capacity; *FRC* functional residual capacity; *CC* closing capacity; *RV* residual volume. The open capacity (*OC*) is TLC–CC. The conventional volumes were predicted from Quanjer et al. (1993) and CC from Buist et al. (1973)

for normal seated subjects amounts to only 0.27 mmHg. The latter study included 80 normal seated non-smokers aged between 15 and 75 years.

These results have clinical implications since in bedridden patients the PaO_2 is frequently measured in blood samples taken from supine subjects, and compared to normal standards obtained on seated subjects. Such comparisons are not valid because in the supine position the values of PaO_2 tend to be lower than seated, particularly in elderly subjects. The same applies to estimates of arterial oxygen saturation.

Age-related changes in V'_{max}

As shown in Fig. 5, with advancing age there is a preferential reduction of maximal expiratory flows (V'_{max}) at low lung volume (Knudson 1991). Although the nature of this phenomenon is multifactorial, the increase in closing volume with advancing age probably plays a pivotal role. Indeed, since the peripheral airways close at higher lung volume in the elderly, their V'_{max} in the lower 50% of FVC decreases because the lung units served by the closed airways cease to contribute to expiratory flow.

As a result of the preferential reduction of V'_{max} in the tidal volume range (Fig. 5), elderly individuals are susceptible to tidal expiratory flow limitation (FL), particularly in decubitus positions (cf. Milic-Emili et al. 2005). The presence of tidal expiratory flow limitation (tidal EFL) implies increased inhomogeneity of ventilation distribution with risk of lung injury (Nucci et al. 2003). While in most normal elderly individuals tidal FL is absent both seated and supine, in respiratory disease both tidal airway closure and tidal EFL are present either seated or more commonly in decubitus.

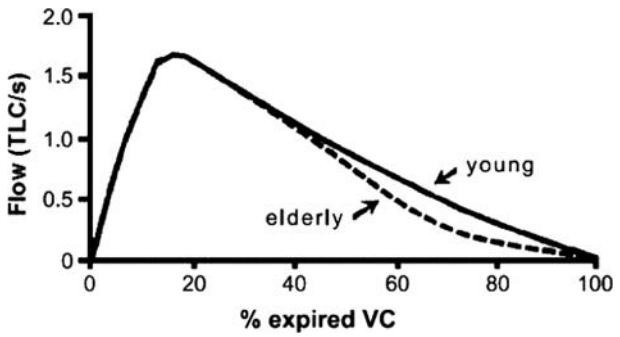

Fig. 5 Maximal expiratory flow–volume curves for young (25–35 years) and old (65–75 years) normal subjects. To normalise for different size, the axes have been standardised for lung volume. The decrease of maximal expiratory flows in the elderly occurs preferentially at low lung volume, reducing the expiratory flow reserve in the tidal volume range. Adapted from Knudson (1991)

Tidal airway closure

Using radioactive Xenon, Anthonisen et al. (1968) were the first to note that some patients with simple chronic bronchitis (normal lung function) exhibit distinct abnormalities of distribution of ventilation within the lung. They attributed these abnormalities to obstruction of small airways. This raised the following question: how can small airway obstruction be present without being detected by tests designed specifically to detect it, such as measurements of airway resistance or FEV_1? The answer was provided by Hogg et al. (1968), who demonstrated that the resistance of the peripheral airways represents only a small fraction of the total pulmonary resistance. Therefore, diseases affecting the small airways may go through a phase in which there is considerable peripheral airway obstruction while total airway resistance and/or FEV_1 may remain within normal limits.

Several tests have been proposed for early detection of PAD, including frequency-dependence of compliance (Woolcock et al. 1969), density-dependence of maximal expiratory flows (Dosman et al. 1975), and CV. The latter is simple and non-invasive. The increase in CV, which has been found in patients with asymptomatic asthma (McCarthy et al. 1972) and in smokers with normal conventional lung function tests (McCarthy and Milic-Emili 1973), has been attributed to ''inflammation'' of the peripheral airways due to smoking, though the precise nature of this phenomenon remains as yet conjectural. Since airway closure is thought to occur in the terminal bronchioles (Hughes et al. 1970), it is likely that the premature closure occurs as a result of local changes in surfactant production or delivery, and/or local changes in compliance or resistance to collapse. Assessment of such local abnormalities is a challenge for future studies.

Though the precise nature of the enhanced airway closure in COPD and asthma has not been explained, smokers and asthmatics with increased CC but normal conventional lung function tests and CC < FRC are suitable candidates for testing the efficacy of ''anti-inflammatory'' drugs, i.e. if they can reverse the airway inflammation with a concurrent increase of CC. When CC > FRC, such pharmacological studies become problematic because the peripheral airway injury which accompanies tidal airway closure may play a confounding role (see below).

Tidal airways closure leads both to impaired gas exchange within the lung and peripheral airway injury.

Functional implications

The maldistribution of ventilation and impaired gas exchange within the lung due to presence of tidal airway closure (CC > FRC or CV > ERV or inspiratory capacity (IC) > OC) has been noted in one of the earliest studies of peripheral airway closure by Leblanc et al. (1970), who pointed out the implication of this phenomenon in terms of the age-related changes in arterial blood gases in normal individuals (see above). In some asymptomatic asthmatics with normal conventional lung function the CC was found to exceed FRC, implying presence of tidal airway closure (McCarthy and Milic-Emili 1973), which could, in turn, explain the hypoxemia frequently encountered in asthmatic patients in remission. These results indicate that PAD is present in asthma (McCarthy and Milic-Emili 1973).

Tidal airway closure is common in obesity (Holley et al. 1967), anaesthesia (Hedenstierna 2003), idiopathic scoliosis (Bjure et al. 1972) and spinal cord injury (Bake et al. 1972). The tidal airway closure and concurrent hypoxemia found in obesity and anaesthesia have been attributed mainly to reduction in FRC. In spinal cord injury, these abnormalities were attributed to PAD due to recurrent airway infection and cough impairment. It is likely, however, that the marked decrease of FRC found in these patients (De Troyer and Estenne 1995) also plays an important role. In idiopathic scoliosis several mechanisms were proposed; it was also noted that the abnormalities of ventilation and V'/Q' distribution worsened with ageing. This is in line with Fig. 4 which shows that ageing promotes tidal airway closure (CC > FRC). The pivotal role played by age was evident in a study on 20 patients with chronic heart failure (CHF) whose mean age (±SD) was 59 ± 11 years (Torchio et al. 2006a). In sitting position, CC exceeded FRC in 13 of them and was very close to FRC in the other 7. Their alveolar-arterial PO_2 gradient was abnormally high, and correlated significantly with the difference between CC and FRC. In supine position CC > FRC in 19 patients (19/20), and 12 of them also exhibited tidal EFL (Torchio et al. 2006b). In contrast, in sitting position tidal EFL was absent in all 20 CHF patients. Tidal EFL is also common in obesity, especially in decubitus (Pankow et al. 1998; Ferretti et al. 2001). The presence of tidal EFL and/or airway closure imply inhomogeneous distribution of ventilation with risk of peripheral airway injury.

Peripheral airway injury

Animal models

Prolonged mechanical ventilation at low lung volumes with physiological or markedly reduced tidal volumes promotes lung injury in abnormal rabbit and rat lungs (McCulloch et al. 1988, Sandhar et al. 1988, Muscedere et al. 1994). It has been suggested that enhancement of lung damage caused by cyclic recruitment and derecruitment of lung units with tidal ventilation could only occur in the presence of a pre-existent pathological or experimentally induced surfactant dysfunction (Taskar et al. 1997). In contrast, recent studies have demonstrated that prolonged mechanical ventilation at low lung volumes with physiological tidal volumes causes permanent mechanical alterations and histological damage of peripheral airways also in normal rabbit lungs, whereas, with the same ventilator settings, no functional and morphological alterations occur when the normal end-expiratory lung volume (EELV) is preserved (D'Angelo et al. 2002, 2004).

In normal, open-chest rabbits prolonged mechanical ventilation with physiological tidal volumes on zero end-expiratory pressure (ZEEP) causes epithelial necrosis and sloughing in the respiratory and membranous bronchioles, discontinuities or ruptures of the alveolar attachments to non-respiratory bronchioles, and a concurrent increase in airway resistance, which persists after restoration of normal end-expiratory volumes (D'Angelo et al. 2002, 2004). Similar functional alterations were also observed in normal, closed-chest rabbits after prolonged mechanical ventilation with physiological tidal volumes on negative end expiratory pressure (NEEP). At variance with open-chest animals, in which a significant increase in quasi-static lung elastance on return to positive end expiratory pressure (PEEP) ventilation was seldom observed, quasi-static lung elastance was permanently increased in all closed-chest rabbits, mainly because of the concomitant development of interstitial oedema, as evidenced by an increased wet-to-dry ratio of the lung and normal albumin concentration in the bronchoalveolar lavage fluid (D'Angelo et al. 2005).

These morphological and mechanical alterations have been attributed to abnormal stresses caused by cyclic opening and closing of peripheral airways in combination with increased surface tension due to surfactant depletion or inactivation with tidal ventilation at low lung volumes. In normal open-chest rabbits ventilated on PEEP, the quasi-static V–P curve of the lung in the tidal volume range is concave towards the pressure axis, indicating that no cyclic airway opening

and closing occurs during tidal ventilation, whereas on ZEEP the *V–P* curve becomes S-shaped or even convex towards the pressure axis (Fig. 6). The ratio of quasi-static lung elastance assessed at the lowest and control tidal volume is, therefore, less than unity on PEEP, but greater than unity on ZEEP, and it can be used as a rough index of the amount of airways involved in tidal recruitment–derecruitment of lung units. The occurrence of recruitment–derecruitment and non-recruitment of lung units during tidal ventilation implies the development of abnormal stresses at the alveolar-bronchiolar junctions of occluded airways, as well as within the lung parenchyma (Mead et al. 1970). This can eventually cause rupture of alveolar–bronchiolar attachments and airway-parenchyma mechanical uncoupling. Such abnormal stresses should be larger the larger the relative amount of airways involved in tidal recruitment–derecruitment and non-recruitment of lung units, and for a given strain, i.e. tidal volume, they should be larger the larger the rate of strain, i.e. flow. Indeed, with fixed tidal volume and frequency, the number of damaged alveolar–bronchiolar attachments was larger when open-chest rabbits were ventilated on ZEEP with high rather than low inflation flows (D'Angelo et al. 2004).

In normal open-chest rabbits, no immediate changes in surface tension and dependent airway closure occur on going from the physiological end-expiratory to the resting volume of the lung. Indeed, relative to ventilation on PEEP, tissue elastic and viscoelastic properties remained unchanged during the first inflation on ZEEP (D'Angelo et al. 2006). This is consistent with the observation that in general airway closure during deflation from large volumes occurs at negative transmural pressures (Cavagna et al. 1967; Otis et al. 1996). However, the volume-related compression of the film lining the alveolar and bronchiolar walls eventually results in film rupture and surfactant inactivation on repeated re-expansion (Wyszogrodski et al. 1975) with dependent airway closure. This explains the rapid, progressive increase of static and dynamic elastance and airway resistance during ventilation on ZEEP (D'Angelo et al. 2006). The central role played by these volume and time dependent changes of surface tension in causing small airway closure and, consequently, cyclic airway opening and closing with tidal ventilation, is further illustrated by (1) the immediate and marked increase of tissue elastic and viscoelastic properties and airway resistance observed with ventilation on ZEEP in rabbits with an artificially induced, mild surfactant dysfunction, and (2) the absence of the progressive increase of static and dynamic lung elastance with ventilation on ZEEP in rabbits receiving exogenous surfactant (D'Angelo et al. 2006).

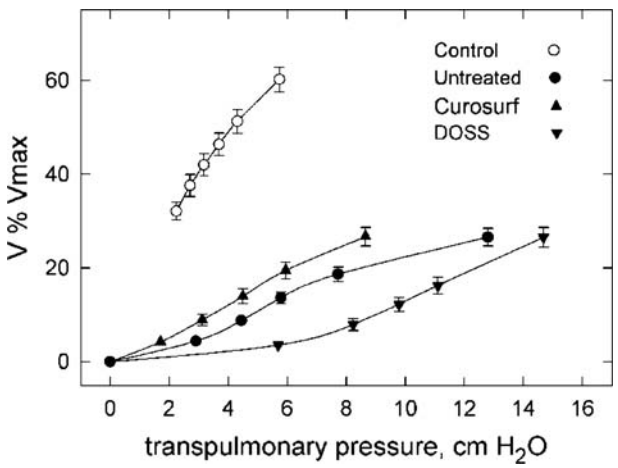

Fig. 6 Quasi-static volume–pressure curves of the lung in the tidal volume range obtained after 3–4 h of mechanical ventilation on positive (control) or zero end-expiratory pressure in normal (untreated) open-chest rabbits and in rabbits receiving exogenous surfactant (Curosurf) or dioctylsodiumsulfosuccinate (*DOSS*) intratracheally. *Bars* are SE. Data from D'Angelo et al. (2006)

Increased surface forces leading to greater lung stiffness and, in combination with reduced dimensions, to airway closure, gas trapping, microatelectasis, and, hence, decrease of ventilated tissue should explain the increase of lung quasi-static elastance and viscoelastic resistance, as well as airway resistance, that has been observed in normal animals during ventilation at low volumes. Indeed, an increased surface tension has been advocated to explain the changes of lung compliance observed at low transpulmonary pressure in the absence of detectable airway closure (Young et al. 1970, Wyszogrodski et al. 1975). In addition to reduction of ventilated tissue with small airway closure, the increase in airway resistance should be due to the mechanical uncoupling between peripheral airways and lung parenchyma, as suggested by the occurrence of a large number of abnormal alveolar attachments, such that airway calibre is reduced in spite of increased lung recoil. This mechanism probably explains a substantial part of the changes of airway resistance in normal, untreated animals and in rabbits with artificially induced surfactant dysfunction, because the largest increase in airway resistance occurred in these groups of animals, which also exhibited a marked augmentation of abnormal alveolar-bronchiolar attachments, whereas the smallest changes in airway resistance occurred in animals receiving exogenous surfactant, which did not show any significant increase of abnormal alveolar-bronchiolar attachments (D'Angelo et al. 2006). Increased bronchomotor tone due to release of

inflammatory mediators, as suggested by the presence of polymorphonuclear leucocytes in the alveolar walls, should play a minor role because (1) no relation has been found between number of polymorphonuclear leucocytes per unit length of alveolar septa and increase in airway resistance (D'Angelo et al. 2006); and (2) no significant cytokine release has been observed in untreated rabbits ventilated on ZEEP, at least as evaluated from tumour necrosis factor (TNF-α) concentration in serum and bronchoalveolar lavage fluid (D'Angelo et al. 2005).

With restoration of normal EELV by means of PEEP, re-expansion of the film lining the alveolar and bronchiolar walls, and prevention of its collapse, surface tension eventually resumes its normal values, airway closure, gas trapping and microatelectasis are eliminated, and tissue elastic and viscoelastic properties of untreated animals and those treated with exogenous surfactant return to control (D'Angelo et al. 2002, 2004, 2006). In contrast, airway resistance remains elevated in normal and surfactant deficient rabbits with restoration of physiological end-expiratory volume, whereas it returns to baseline values in animals treated with exogenous surfactant, like in control animals ventilated on PEEP only (D'Angelo et al. 2002, 2004, 2006). This behaviour of airway resistance parallels that in histological injury scores: indeed, indices of bronchiolar epithelial damage and destruction of alveolar–bronchiolar attachments are high in the first two groups of animals, but similar in control and surfactant treated animals. These indices parallel in turn the estimates of airway involvement in cyclic opening and closing during ventilation on ZEEP obtained form the ratio of quasi-static lung elastance assessed at the lowest and control tidal volume (see above; Fig. 6). Accordingly, it appears that (1) the histological damage of small airways occurring with cyclic opening and closing during prolonged mechanical ventilation of normal lungs at low volume is the cause of the increase in airway resistance that persists after restoration of physiological end-expiratory volumes; and (2) these histological alterations in both normal and surfactant deficient lungs are due to high surface forces, as they are prevented with the administration of exogenous surfactant. This is consistent with the conclusions from theoretical model studies showing the primary role played by the surface tension in reducing airway opening pressure and limiting the stresses and deformation applied on reopening to airway epithelium and walls (Gaver et al. 1990; Hsu et al. 1994; Naire and Jensen 2005), as well as the results of a physical model study showing that the injury caused to pulmonary epithelial cells lining the bottom of a channel through which a bubble is made to progress is completely abated by the presence of adequate amounts of surfactant (Bilek et al. 2003). Moreover, the ''anti-glue'' action which has been attributed to lung surfactant (Sanderson et al. 1976) could represent another mechanism preventing epithelial injury with repeated small airway reopening.

Rat lungs, injured by means of lung lavage, hydrochloric acid instillation, or intravenous injection of lipopolysaccharide, develop an inflammatory response that is enhanced with mechanical ventilation at low volumes (Muscedere et al. 1994; Tremblay et al. 1997; Chiumello et al. 1999). In normal, open-chest rabbits, prolonged mechanical ventilation on ZEEP causes recruitment of polymorphonuclear leucocytes in the alveolar walls (D'Angelo et al. 2004, 2005, 2006), thus fitting a recently described type of ventilator-induced lung injury called *biotrauma* (Dos Santos and Slutsky 2000). Under this condition, parenchymal overdistension and abnormal stresses could represent the mechanical stimuli leading to release of mediators that prime polymorphonuclear leucocytes, which may represent the major effector cells in the generation of tissue injury, upregulation of the inflammatory response, and release of proinflammatory cytokines, mainly TNF-α and interleukin (IL)-6 (Dos Santos and Slutsky 2000; Tschumperlin et al. 2000). In normal rabbits, no differences in TNF-α levels of serum and bronchoalveolar lavage fluid occurred, however, between prolonged mechanical ventilation on ZEEP and PEEP (D'Angelo et al. 2005), in line with previous observations in isolated, normal mouse lungs, showing that relative to control, concentrations of TNF-α, monocyte chemoattractant protein-1, and lactate dehydrogenase in lung lavage were increased only during ventilation with a NEEP of –15 cmH_2O (Cheng et al. 2002). Hence, in normal animals and within the 3–4 h during which the observations were made, the inflammatory response does not play an important role in producing the histological and functional alterations of ventilation at low volume. In contrast, these alterations are the consequence of mechanical events, as they were largely prevented by the administration of exogenous surfactant (D'Angelo et al. 2006).

Prolonged mechanical ventilation at low volume substantially lowers exhaled NO concentration (NOe) both in closed and open chest animals, a reduction which persists after restoration of the end-expiratory volume, but does not occur with prolonged ventilation on PEEP only. Since in animals ventilated through an endotracheal tube terminal and respiratory bronchioles are the main source of exhaled NO (Persson et al. 1993), it seems reasonable to ascribe the fall of NOe to

small airway injury with epithelial necrosis and sloughing that occurs in normal rabbits with mechanical ventilation at low volumes (D'Angelo 2002, 2005). Moreover, the fall of NOe occurred with no change in the pH of exhaled vapour condensate and concentration of the proinflammatory cytokine TNF-α in bronchoalveolar lavage fluid and serum, development of hypoxia and oedema, all events capable to affect NO production and elimination (Cremona et al. 1995, Carlin et al. 1997; Strömberg et al. 1997; Hunt et al. 2000; Maniscalco et al. 2001). While these findings suggest that the decrease in NOe could represent an index of small airway damage, it should be pointed out that also other factors can reduce NO production and elimination from airway epithelium. Prostaglandins E_2 and F_{2a}, VIP, and free radicals (Nadel 1990; Delgado et al. 1999; Kharitonov et al. 1999) exert, in fact, a depressant action on NO production Indeed, abnormal stimulations of sensory nerve endings and fibroblasts can eventually cause release of tachykinins and vasoactive intestinal peptide (VIP), activation of bradykinin with release of prostaglandins E_2 and F_{2a}, and formation of free radicals (Proud 1997; Uddman et al. 1997), while alveolar epithelial cells, macrophages and polymorphonuclear leucocytes activated by mechanical insults could represent an additional source of VIP and prostaglandins E_2 and F_{2a} (Moncada and Vane 1979; Delgado et al. 1999). Moreover, because bradykinin causes constriction of mainly peripheral airways (Proud 1997), it could have contributed to the persistent increase of airway resistance after mechanical ventilation at low volumes.

Definition of peripheral airway injury

Originally, ventilator induced lung injury (VILI) was synonymous with barotrauma due to high pressure and volume changes applied by the ventilator (cf. Dreyfuss and Saumon 1998). This condition, which is beyond the scope of the present review, is commonly referred to as ''high lung volume injury''. In contrast, the term ''low volume injury'' refers to VILI due to cyclic opening and closure of peripheral airways. Robertson (1984) was the first to suggest that in mechanically ventilated lungs with surfactant deficiency (e.g. adult respiratory distress syndrome) there was injury due to cyclic opening and closure of the peripheral airways. D'Angelo et al. (2005) showed that such injury also occurs in normal lungs during low volume breathing (see above). Since this type of injury may actually also occur at relatively high lung volumes in subjects in whom the CC has increased due to ageing (Fig. 4) or because of respiratory abnormalities (smoking, asthma), it seems preferable to use the term peripheral airway injury (PAI) to describe the injury which can result from cyclic opening and closing of the peripheral airways during tidal breathing, henceforth labelled as tidal airway closure (AC). It should be stressed that PAI can also be caused by tidal EFL, which is commonly associated with tidal AC (Calverley and Koulouris 2004). Both conditions lead to inhomogeneity of ventilation distribution with unevenly distributed strain and shear stress within the lung, which is amplified by tissue interdependence (Mead et al. 1970) and leads to PAI.

Clinical implications of PAI

In open-chest anaesthetised rabbits, mechanical ventilation (MV) without positive end-expiratory pressure (PEEP) elicited within 3–4 h a significant PAI, characterised *hystologically* by denuded epithelium, rupture of alveolar-airway attachments, and increased number of polymorphonuclear leucocytes in the alveolar walls, and *functionally* by a persistent increase in airway resistance (D'Angelo et al. 2002). These abnormalities were attributed to tidal AC. In the open-chest rabbits, PAI was distributed uniformly throughout the lung because P_{pl} was uniform and hence the alveolar expansion and distribution of ventilation should also be essentially uniform (Faridy et al. 1967; Katsura et al. 1970). With closed chest, however, tidal AC tends to occur preferentially in the dependent lung zones which are exposed to more positive P_{pl} (Kaneko et al. 1966; Milic-Emili 1974). The same is valid for tidal EFL. Thus AC and EFL are always first present in the supine position and next in the prone, semirecumbent, and sitting posture. Initially, these potential sources of PAI may be, therefore, present only supine but, with increased severity of the lung disorder, they will eventually occur also sitting (Eltayara et al. 1996; Leblanc et al. 1970). In some subjects, by simply changing body posture, the tidal AC and EFL may either vanish or are distributed to other lung regions reducing the intensity of the PAI strain and giving time for repair and/or remodelling of the peripheral airways. In this context it should be stressed that during daily life the body posture is continuously changing, lowering the intensity of PAI strain in any given locus of the lung. However, there are conditions in which the body posture may remain fixed for periods long enough to result in overt PAI. In this connection, it should be noted that open-chest rabbits developed significant PAI within relatively short periods of MV at low lung volume (3–4 h). Such periods of MV at fixed body position may occur during surgery, in mechanically

ventilated patients in intensive care units, and in patients who are immobile because of neuromuscular disease. Clearly this topic is of clinical interest because PAI may be avoided by simply applying PEEP sufficient to increase the EELV above CC, or by periodically changing the body posture. In fact there is experimental evidence indicating that morbidly obese patients exhibit PAI after 3–4 h surgical interventions without PEEP, while with PEEP there is no evidence of PAI (Koutsoukou et al. 2004). Similarly, in brain damaged patients with initially normal lung mechanics, airway resistance increased and lung compliance decreased after 5 days of MV without PEEP (Koutsoukou et al. 2006). With PEEP there was no evidence of lung damage after 5 days of MV.

Since tidal AC and EFL are present in many patients, particularly those with advanced age (see Functional implications), the potential clinical impact of PAI is staggering. In fact, it has been suggested that PAI may play a pivotal role in the genesis of COPD in smokers (Milic-Emili 2004), and the same should be valid for many other conditions such as asthma, chronic heart failure, and neuromuscular disorders, in which AC, and possibly EFL, are present during tidal breathing. Obese patients are probably a special risk-group. Indeed in normal sheep it has been shown that ''low lung volume'' breathing alters the contractile properties of the airway smooth muscle (McClean et al. 2003). Similarly, in normal subjects, chest wall strapping increases airway responsiveness probably because it involves ''low lung volume'' breathing with concurrent functional or structural alterations of smooth muscle (Torchio et al. 2006c). This type of PAI may explain the high prevalence of asthma in obesity (Chinn 2005).

The rabbit experiments of D'Angelo et al. (2002, 2005, 2006), which have provided insight into the nature of PAI, have been carried out using both pathophysiological and molecular biology methods. Indeed, it is by gently weaving molecular biology into the delicate supporting fabric of pathophysiology, that substantial advances can be made. Studies based solely on molecular biology techniques will often result in unsupported, caducous ''Deus ex machina'' conclusions.

Conclusions

In animal studies, tidal airway closure has been shown to cause peripheral airway injury, characterised *histologically* by rupture of the alveolar-airways attachments, denuded epithelium, and increased number of polymorphonuclear leucocytes in the alveolar walls, and *functionally* by increased airway resistance. In addition, it has been shown that under these conditions there may be disruption of the airway smooth muscle. Since tidal AC and/or tidal EFL are common, PAI may be a common unrecognised complication. In mechanically ventilated subjects, PAI can be avoided by application of small levels of PEEP. Though the incidence and magnitude of PAI in spontaneously breathing patients is as yet undefined, it is likely that PAI plays a major role in the genesis of COPD and other respiratory disorders. Shifting of body posture is a simple modality to moderate PAI due to tidal AC and/or EFL. Finally, measurement of the OC instead of closing capacity is proposed because it is less demanding both in terms of task performance and equipment.

References

Abernethy JD, Maurizi JJ, Farhi LE (1967) Diurnal variations in urinary-alveolar N2 difference and effects of recumbency. J Appl Physiol 23:875–879

Anthonisen NR, Bass H, Oriol A, Place RE, Bates DV (1968) Regional lung function in patients with chronic bronchitis. Clin Sci Dec 35:495–511

Anthonisen NR, Danson J, Robertson PC, Ross WR (1970) Airway closure as a function of age. Respir Physiol 8:58–65

Anthonisen NR, Engel L, Grassino A, Zidulka A, Bode F, Dosman J, Martin RR, Macklem PT (1974) The clinical significance of measurements of closing volume. Scand J Respir Dis 85:245–250

Bake B, Fugl-Meyer AR, Grimby G (1972) Breathing patterns and regional ventilation distribution in tetraplegic patients and in normal subjects. Clin Sci 42:117–128

Basch S von (1887) ''Ueber eine Function des Capillardruckes in den Lungen Alveoli''. Wien Med Blatter 10:465–467

Bilek AM, Dee KC, Gaver DP III (2003) Mechanisms of surface-tension-induced epithelial cell damage in a model of pulmonary airway reopening. J Appl Physiol 94:770–783

Bjure J, Grimby G, Kasalicky J, Lindh M, Nachemson A (1970) Respiratory impairment and airway closure in patients with untreated idiopathic scoliosis. Thorax 25:451–456

Bouhuys A (1964) Distribution of inspired gas in the lungs. In: Fenn WO and Rahn H (eds) Handbook of physiology. Section 3. Respiration vol 1, American Physiological Society, Washington, pp 715–735

Buist SA, Ross BB (1973) Predicted values for closing volumes using a modified single breath test. Am Rev Respir Dis 107:744–752

Calverley PM, Koulouris NG (2004) Flow limitation and dynamic hyperinflation: key concepts in modern respiratory physiology. Eur Respir J 25:186–199

Carlin RE, Ferrario L, Boyd JT, Camporesi EM, McGraw DJ, Hakim TS (1997) Determinants of nitric oxide in exhaled gas in the isolated rabbit lung. Am J Respir Crit Care Med 155:922–927

Cavagna GA, Stemmler EJ, DuBois AB (1967) Alveolar resistance to atelectasis. J Appl Physiol 22:441–452

Cheng KC, Zeng H, Slutsky AS (2002) Ventilation with negative airway pressure induces a cytokine response in isolated mouse lung. Anesth Analg 94:1577–1582

Chinn S (2005) Concurrent trends in asthma and obesity. Thorax 60:3–4

Chiumello D, Pristine G, Slutsky AS (1999) Mechanical ventilation affects local and systemic cytokines in an animal model of acute respiratory distress syndrome. Am J Respir Crit Care Med 160:109–116

Cremona G, Higenbottam T, Takao M, Hall L, Bower EA (1995) Exhaled nitric oxide in isolated pig lungs. J Appl Physiol 78:59–63

D'Angelo E (1972) Local alveolar size and transpulmonary pressure in situ and in isolated lungs. Respir Physiol l4:251–266

D'Angelo E, Pecchiari M, Baraggia P, Saetta M, Balestro E, Milic-Emili J (2002) Low-volume ventilation causes peripheral airway injury and increased airway resistance in normal rabbits. J Appl Physiol 92:949–956

D'Angelo E, Pecchiari M, Saetta M, Balestro E, Milic-Emili J (2004) Dependence of lung injury on inflation rate during low-volume ventilation in normal open-chest rabbits. J Appl Physiol 97:260–268

D'Angelo E, Pecchiari M, Della Valle P, Koutsoukou A, Milic-Emili J (2005) Effects of mechanical ventilation at low lung volume on respiratory mechanics and nitric oxide exhalation in normal rabbits. J Appl Physiol 99:433–444

D'Angelo E, Pecchiari M, Gentile G (2006) Dependence of lung injury on surface tension during low-volume ventilation in normal open-chest rabbits. J Appl Physiol

Delgado M, Munoz-Elias EJ, Gomariz RP, Ganea D (1999) Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide prevent inducible nitric oxide synthase transcription in macrophages by inhibiting NF-kB and IFN regulatory factor 1 activation. J Immunol 162:4685–4696

De Troyer A, Estenne M (1995) The respiratory system in neuromuscular disorders. In: Roussos Ch (ed) The thorax. Marcel Dekker Inc., New York, pp 2177–2212

Dollfuss RE, Milic-Emili J, Bates DV (1967) Regional ventilation of the lung studied with boluses of 133 Xenon. Respir Physiol 2:234–246

Dos Santos CC, Slutsky AS (2000) Cellular responses to mechanical stress. Invited Review: Mechanisms of ventilator-induced lung injury: a perspective. J Appl Physiol 89:1645–1655

Dosman J, Bode F, Urbanetti J, Martin R, Macklem PT (1975) The use of a helium-oxygen mixture during maximum expiratory flow to demonstrate obstruction in small airways in smokers. J Clin Invest 55:1090–1099

Dreyfuss D, Saumon G (1998) Ventilator-induced lung injury: lessons from experimental studies. Am J Respir Crit Care Med 157:294–323

Eltayara L, Becklake MR, Volta CA, Milic-Emili J (1996) Relationship between chronic dyspnea and expiratory flow limitation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 154:1726–1734

Faridy EE, Kidd R, Milic-Emili J (1967) Topographical distribution of inspired gas in excised lobes of dogs. J Appl Physiol 22:760–766

Ferretti A, Giampiccolo P, Cavalli A, Milic-Emili J, Tantucci C (2001) Expiratory flow limitation and orthopnea in massively obese subjects. Chest 119:1401–1408

Fowler WS (1952) Intrapulmonary distribution of inspired gas. Physiol Rev 32:1–20

Frank NR (1959) Influence of acute pulmonary congestion on recoiling force of excised cat's lung. J Appl Physiol 14:905–908

Gaver DP III, Samsel RW, Solway J (1990) Effect of surface tension and viscosity on airway reopening. J Appl Physiol 69:74–85

Glaister DH, Schroter RC, Sudlow MF, Milic-Emili J (1973a) Bulk elastic properties of excised lungs and the effect of a transpulmonary pressure gradient. Respir Physiol 17:347–364

Glaister DH, Schroter RC, Sudlow MF, Milic-Emili J (1973b) Transpulmonary pressure gradient and ventilation distribution in excised lungs. Respir Physiol 17:365–385

Goerke J, Clements JA (1986) Alveolar surface tension and lung surfactant. In: Macklem PT, Mead J (eds) Handbook of physiology: the respiratory system; mechanics of breathing. Part 1, Am Physiol Soc, Bethesda, Maryland, pp 247–261

Hedenstierna G (2003) Alveolar collapse and closure of airways: regular effects of anaesthesia. Clin Physiol Funct Imaging 23:123–129

Hogg JC, Macklem PT, Thurlbeck WM (1968) Site and nature of airway obstruction in chronic obstructive lung disease. N Engl J Med 278:1355–1360

Holland J, Milic-Emili J, Macklem PT, Bates DV (1968) Regional distribution of pulmonary ventilation and perfusion in elderly subjects. J Clin Invest 47:81–92

Holley HS, Milic-Emili J, Becklake MR, Bates DV (1967) Regional distribution of pulmonary ventilation and perfusion in obesity. J Clin Invest 46:475–481

Hoppin FG (1999) Sources of lung recoil. In: Milic Emili J (ed) Respiratory mechanics, vol 12. Eur Respir Monograph, pp 33–53

Hsu SH, Strohl KP, Jamieson AM (1994) Role of viscoelasticity in tube model of airway reopening I. Nonnewtonian sols. J Appl Physiol 76:2481–2489

Hughes JMB, Rosenzweig DY, Kivitz PB (1970) Site of airway closure in excised dog lungs: histologic demonstration. J Appl Physiol 29:340–344

Hughes JMB, Hoppin FG Jr, Mead J (1972) Effect of lung inflation on bronchial length and diameter in excised lungs. J Appl Physiol 32:25–35

Hunt JF, Fang K, Malik R, Snyder A, Malhotra N, Platts-Mills TAE, Gaston B (2000) Endogenous airway acidification. Am J Respir Crit Care Med 161:694–699

Hutchinson J (1846–1852) In: Thorax. Todd Encyclop Anat & Physiol, p 1059

Ingram RH, O'Cain CF, Fridy WW (1974) Simultaneous quasistatic lung pressure-volume curves and ''closing volume'' measurements. J Appl Physiol 36:135–141

Kaneko K, Milic-Emili J, Dolovich MB, Dawson A, Bates DV (1966) Regional distribution of ventilation and perfusion as a function of body position. J Appl Physiol 21:767–777

Katsura T, Rosenzwaig R, Sutherland PW, Hogg JC, Milic-Emili J (1970) Effect of external support on regional alveolar expansion in excised dog lungs. J Appl PhysioI 25:133–137

Kharitonov SA, Sapienza MM, Chung KF, Barnes PJ (1999) Prostaglandins mediate bradykinin-induced reduction of exhaled nitric oxide in asthma. Eur Respir J 14:1023–1027

Keith A (1909) The mechanisms of respiration in man. In: Hill L (eds) Further advances in physiology. Longmans, Green, and Co, New York, pp 182–207

Kleinmann LE, Puolos DA, Siebens AA (1964) Minimal air in dogs. J Appl Physiol 19:204–206

Knudson RJ, Lebowitz MD, Burton AP, Knudson DE (1977) The closing volume test: evaluation of nitrogen and bolus methods in a random population. Am Rev Respir Dis 115:423–434

Knudson RJ (1991) Physiology of the ageing lung. In: Crystal RG, West JB et al (eds) The lung: scientific foundations. Raven Press Ltd, New York, pp 1749–1759

Koutsoukou A, Koulouris N, Bekos B, Sotiropoulou C, Kosmas E, Papadima K, Roussos C (2004) Expiratory flow limitation in morbidly obese postoperative mechanically ventilated patients. Acta Anaesthesiol Scand 48:1080–1088

Koutsoukou A, Perraki H, Raftopoulo A, Koulouris N, Sotiropoulou C, Kotanidou A, Stylianos O, Roussos C (2006) Respiratory mechanics in brain damaged patients. Intensive Care Med 32:1947–1954

Leblanc P, Ruff F, Milic-Emili J (1970) Effects of age and body position on ''airway closure'' in man. J Appl Physiol 28:448–451

Linn WS, Hackney JD (1973) Nitrogen and helium ''closing volumes'': simultaneous measurement and reproducibility. J Appl Physiol 34:396–399

Maniscalco M, Vatrella A, Cremona G, Carratù L, Sofia M (2001) Exhaled nitric oxide after inhalation of isotonic and hypotonic solutions in healthy subjects. Clin Sci 101:645–650

McCarthy D, Milic-Emili J (1973) Closing volume in asymptomatic asthma. Am Rev Respir Dis 107:559–570

McCarthy DS, Spencer R, Creene R, Milic-Emili J (1972) Measurement of ''closing volume'' as a simple and sensitive test for early detection of small airway disease. Am J Med 52:747–753

McClean MA, Matheson MJ, McKay K, Johnson PR, Rynell AC, Ammit AJ, Black JL, Berend N (2003) Low lung volume alters contractile properties of airway smooth muscle in sheep. Eur Respir J 22:50–56

Mcculloch PR, Forkert PG, Froese A (1988) Lung volume maintenance prevents lung injury during high frequency oscillatory ventilation in surfactant-deficient rabbits. Am Rev Respir Dis 137:1185–1192

Mead J, Takishima T, Leith D (1970) Stress distribution in lungs: a model of pulmonary elasticity. J Appl Physiol. 28:596–608

Mellemgard K. (1966) The alveolar-arterial oxygen difference: its size and components in normal man. Acta Physiol Scand 67:10–20

Milic-Emili (1974) Pulmonary statics. In: Widdicombe J (ed) Respiration Physiology, vol. 1, University Park Press, Baltimore, pp 105–137

Milic-Emili J (2004) Does mechanical injury of the peripheral airways play a role in the genesis of COPD in smokers? COPD 1:85–92

Milic-Emili J (2005) Ventilation distribution. In: Hamid Q, Shannon J, Martin J (eds) Physiologic basis of respiratory disease. BC Decker Inc., Hamilton, pp 133–141

Milic-Emili J, Mead J, Turner JM, Glauser EM (1964a) Improved technique for estimating pleural pressure from esophageal balloons. J Appl Physiol 19:207–211

Milic-Emili J, Mead J, Turner JM (1964b) Topography of esophageal pressure as a function of posture in man. J Appl Physiol 19:212–226

Milic-Emili J, Henderson JA, Dolovich MB, Trop D, Kaneko KMB (1966) Regional distribution of inspired gas in the lung. J Appl Physiol 21:749–759

Milic-Emili J, Koulouris N, Tantucci C (2005) Spirometric prediction of exercise limitation in patients with chronic obstructive pulmonary disease. In: Hamid Q, Shannon J, Martin J (eds) Physiologic basis of respiratory disease. BC Decker Inc., Hamilton, pp 671–687

Moncada S, Vane JR (1979) Pharmacology and endogenous roles of prostaglandin endoperoxides, thromboxane A_2 and prostacyclin. Pharmacol Rev 30:293–331

Muscedere JG, Mullen JBM, Gan K, Bryan AC, Slutsky AS (1994) Tidal ventilation at low airway pressure can augment lung injury. Am J Respir Crit Care Med 149:1327–1334

Nadel JA (1990) Decreased neutral endopeptidases: possible role in inflammatory diseases of airways. Lung 168:123–127

Naire S, Jensen OE (2005) Epithelial cell deformation during surfactant-mediated airway reopening: a theoretical model. J Appl Physiol 99:458–471

Niewoehner DE, Kleinerman J, Rice DB (1974) Pathologic changes in the peripheral airways of young cigarette smokers. N Engl J Med 291:755–758

Nucci G, Suki B, Lutchen K (2003) Modeling airflow related shear stress during heterogeneous constriction and mechanical ventilation. J Appl Physiol 95:348–356

Olofsson J, Bake B, Svärdsudd K, Skoogh BE (1986) The single breath N_2-test predicts the rate of decline in FEV_1. The study of men born in 1913 and 1923. Eur J Respir Dis 69:46–56

Otis DR Jr, Petak F, Hantos Z, Fredberg JJ, Kamm R (1996) Airway closure and reopening assessed by the alveolar capsule oscillation technique. J Appl Physiol 80:2077–2084

Pankow W, Podszus T, Gutheil T, Penzel T, Peter J, Von Wichert P (1998) Expiratory flow limitation and intrinsic positive end-expiratory pressure in obesity. J Appl Physiol 85:1236–1243

Persson MG, Wiklund NP, Gustafsson LE (1993) Endogenous nitric oxide in single exhalations and the change during exercise. Am J Respir Crit Care Med 148:1210–1214

Proud D (1997) Kinins as mediators of lung disease. In: Crystal RG, West JB, Weibel ER, Barnes PJ (eds) The lung. Lippincott-Raven, Philadelphia, Chap 7, pp 89–101

Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC (1993) Lung volumes and forced ventilatory flows. Report Working Party ''Standardization of Lung Function Tests''. European Coal and Steel Community. Eur Resp J 6:5–40

Radford EP (1964) Static mechanical properties of mammalian lungs. In: Fenn WO, Rahn H (eds) Handbook of physiology. Respiration, vol II. Am Physiol Soc Washington, pp 429–449

Robertson B (1984) Lung surfactant. In: Robertson B, Van Calde L, Batenburgh J (eds) Pulmonary surfactant. Elsevier, Amsterdam

Rodarte JR, Hyatt RE, Cortese DA (1975) Influence of expiratory flow on closing capacity at low expiratory flow rates. J Appl Physiol 39:60–65

Ruff F, Wood L, Bryan AC, Milic-Emili J (1970) Effects of the augmentation of air output and of inspired gas density on the regional distribution of ventilation. J Physiol 62(s3):443

Sanderson RJ, Paul GW, Vatter AE, Filley GF (1976) Morphological and physical basis for lung surfactant action. Respir Physiol 27:379–392

Sandhar BK, Niblett DJ, Argiras EP, Dunnill MS, Sykes MK (1988) Effect of positive end-expiratory pressure on hyaline membrane formation in a rabbit model of neonatal respiratory distress syndrome. Int Care Med 14:538–546

Sorbini CA, Grassi V, Solinas E, Muiesan G (1968) Arterial oxygen tension in relation to age in healthy subjects. Respiration 25:3–13

Stanescu D, Sanna A, Veriter C, Robert A (1998) Identification of smokers susceptible to development of chronic airflow limitation: a 13-year follow-up. Chest 114:416–425

Stigol Lc, Vawter GF, Mead J (1972) Studies on elastic recoil of the lung in pediatric population. Am Rev Respir Dis 105:552–563

Strömberg S, Lönnqvist PA, Persson MG, Gustafsson LE (1997) Lung distension and carbon dioxide affect pulmonary nitric

oxide formation in the anaesthetized rabbit. Acta Physiol Scand 159:59–67
Sutherland PW, Katsura T, Milic-Emili J (1968) Previous volume history of the lung and regional distribution of gas. J Appl Physiol 25:566–574
Taskar V, John J, Evander E, Robertson B, Jonson B (1997) Surfactant dysfunction makes lungs vulnerable to repetitive collapse and reexpansion. Am J Respir Crit Care Med 155:313–320
Teculescu DB, Damel MC, Costantino E, Buhler O, Bohadana AB, Marchand M, Pham QT (1996) Computerized single-breath nitrogen washout: predicted values in a rural French community. Lung 174:43–55
Torchio R, Gulotta C, Greco-Lucchina P, Perboni A, Montagna L, Guglielmo M, Milic-Emili J (2006a) Closing capacity and gas exchange in chronic heart failure. Chest 129:1330–1336
Torchio R, Gulotta C, Greco-Lucchina P, Perboni A, Avonto L, Ghezzo H, Milic-Emili J (2006b) Orthopnea and tidal expiratory flow-limitation in chronic heart failure. Chest 130:472–479
Torchio R, Gulotta C, Ciacco C, Perboni A, Guglielmo M, Crosa F, Zerbini M, Brusasco V, Hyatt RE, Pellegrino R (2006c) Effects of chest wall strapping on mechanical response to methacholine in humans. J Appl Physiol 101:430–438
Tremblay L, Valenza F, Ribeiro S, Li J, Slutsky AS (1997) Injurious ventilatory strategies increase cytokines and c-fos m-RNA expression in an isolated rat lung model. J Clin Invest 99:944–952
Tschumperlin DJ, Oswari J, Marguleis AS (2000) Deformation-induced injury of alveolar epithelial cells. Effect of frequency, duration, and amplitude. Am J Respir Crit Care Med 162:357–362
Turner JM, Mead J, Wohl ME (1968) Elasticity of human lung in relation to age. J Appl Physiol 25:664–671
Uddman R, Sundler F, Cardell LO, Luts A (1997) Neuropeptides in the lung. In: Crystal RG, West JB, Weibel ER, Barnes PJ (eds) The lung. Lippincott-Raven, Philadelphia, Chap 8, pp 103–115
Verbanck S, Paiva M (2002) Gas washout and aerosol bolus techniques: noninvasive measures of lung structure and ventilation heterogeneity. In: Aliverti A, BrusascoV, Macklem PT, Pedotti A (eds) Mechanics of breathing. Springer, Milan, pp 129–145
Viegi G, Paoletti P, Di Pede F, Prediletto R, Carrozzi L, Pistelli G, Giuntini C (1988) Single breath nitrogen test in an epidemiologic survey in North Italy. Reliability, reference values and relationships with symptoms. Chest 93:1213–1220
Von Neergaard K (1929) Neue Auffassungen über einen Grundbegriff der Atemmechanik. Z Gesamte Exp Med 66:373–394
Ward RJ, Tolas AG, Benveniste J, Hansey M, Bonica JJ (1966) Effect of posture on normal arterial blood gas tensions in the aged. Geriatrics 21:139–143
Woolcock AJ, Vincent NJ, Macklem PT (1969) Frequency dependence of compliance as a test for obstruction in the small airways. J Clin Invest 48:1097–1106
Wyszogrodski I, Kyei-Aboagye E, Taeusch HW, Avery ME (1975) Surfactant inactivation by hyperventilation: conservation by end-expiratory pressure. J Appl Physiol 83:461–466
Young SL, Tierney DF, Clements JA (1970) Mechanisms of compliance change in excised rat lungs at low transpulmonary pressure. J Appl Physiol 29:780–785