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Abstract
Background The principal features of elastic pressure-volume curves of lungs or the respiratory system (P_{el}/V curves) recorded during reexpansion of collapsed lungs and subsequent deflation have been known since the 1950s. In acute respiratory failure and acute respiratory distress syndrome such curves have recently attracted increasing interest because new knowledge can be acquired from them, and because such curves may be useful as guidelines in setting the ventilator so as to avoid ventilator-induced lung injury. *Discussion* This article reviews recording methods, underlying physiology and utility of P_{el}/V curves in research and clinical work.

Introduction

The relationship between elastic recoil pressure and volume (P_{el}/V) when a collapsed isolated lung in health is reinflated was studied as early as the 1950s by Mead et al. [*1*] and Radford [*2*]. They observed that lung units "pop open" during the irregular reexpansion of the lung, and that the elastic recoil pressure during inflation with air is much higher than during emptying (Fig. 1). Emptying occurred more uniformly over the lung. They explained that one reason for the higher elastic pressure during insufflation is that a particular volume was shared by fewer open lung units than emptying. When the lung was inflated with saline, no hysteresis was observed. Obviously surface forces have a large influence on the P_{el}/V curves, a fact that was later misinterpreted, as is discussed below. The seminal study by Mead et al. [*1*] demonstrates that some basic concepts relating to collapse/recruitment of lung units and the P_{el}/V loop were known and understood as early as the 1950s! Development with respect to measurement technique and mathematical analysis, understanding of physiology, and clinical utility of the P_{el}/V curve has progressed since that time, as is described in this review.
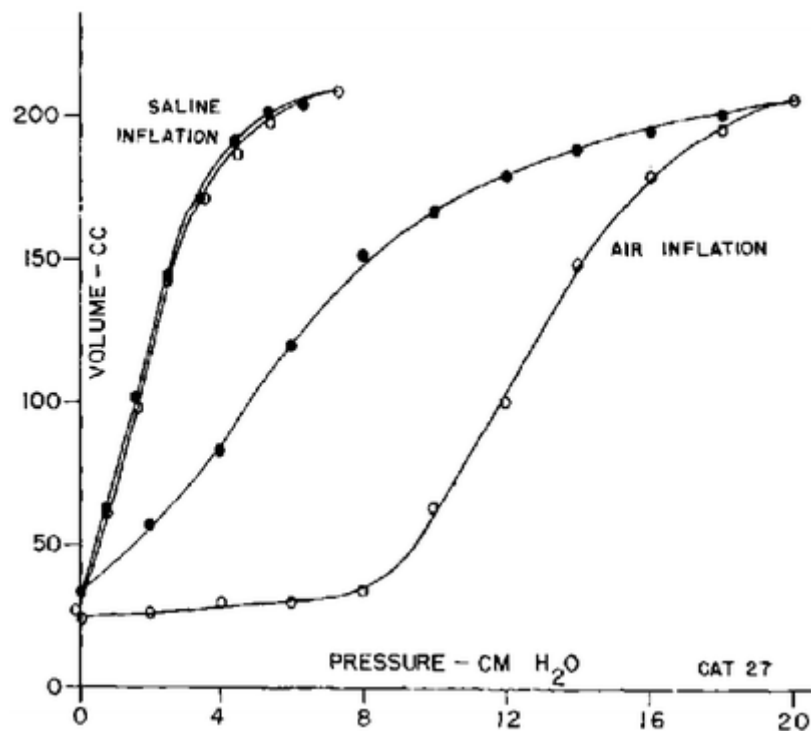
Fig. 1 Pressure-volume loops from an isolated cat lung that was reinflated from a degassed state, with air and with saline [*2*]

Technical development with respect to intensive care medicine

The development of the specialty of intensive care medicine that took off in the early 1970s was closely linked to new facilities for recording physiological events. Dynamic pressure volume loops were recorded in patients with acute severe respiratory failure in a study by Falke et al. in 1972 [*3*]. The supersyringe introduced by Harf et al. [*4*] in 1975 was an innovation of great significance and enabled more detailed studies of static P_{el}/V loops. The ServoVentilator 900 first marketed in 1971 comprised transducers for airway pressure and flow allowing studies of mechanics without disconnection of the patient from the ventilator [*5*]. Much later this facility was used for recording static P_{el}/V curves based upon the flow interruption method [*6*, *7*, *8*, *9*]. This method uses interruption of study breaths at varying volume. The study breaths are separated by some ordinary breaths and are followed by a pause during which static P_{el} is measured. A potential problem with this method is the assumption that end-expiratory volume remains constant following each exhalation. Recruitment during the larger breaths causes an error if the recruited volume is not lost during the interposed normal breaths.

The constant inspiratory flow or the pulse method for recording inspiratory P_{el}/V curves was introduced by Suratt and Owens [*10*] in 1980. Compliance of the respiratory system was accurately calculated by dividing the constant flow rate (L/s) by the rate of pressure increase (cmH$_2$O/s). A low inspiratory flow rate minimized the importance of resistance. By applying the complementary principle to measure resistance and subtracting the resistive pressure to obtain P_{el} Servillo et al. [*11*] showed that dynamic P_{el}/V curves, which are equivalent to static P_{el}/V curves, could be determined in a few seconds in critically sick patients. Finally,

implementing sinusoidal flow modulation a computer-controlled ServoVentilator 900 (ServoVentilator 900C, Siemens-Elema, Solna) allowed fully automated recording of inspiratory and now also expiratory P_{el}/V curves in less than 0.5 min [*12*, *13*, *14*].

Gas exchange may cause artifacts in P_{el}/V recordings [*15*]. During insufflation the CO_2 and O_2 exchanged roughly balance each other. During recording of expiratory P_{el}/V curves only O_2 uptake continues. This leads to a volume loss not detected by integration of flow rate at airway opening. To reduce the artifact caused by gas exchange the time for expiration should be minimized. This is carried out both with the flow interruption technique for static curves and with the low flow modulation technique for dynamic curves. Gattinoni et al. [*16*] have underlined how artifacts may affect P_{el}/V recordings, and how they may be corrected. Still the exchange of O_2, CO_2, heat, and humidity can be avoided completely only using body plethysmography, which is applicable only in experimental work [*8*].

During recording of dynamic expiratory P_{el}/V curves flow limitation often occurs towards the end of expiration down to the elastic equilibrium volume. Then resistance depends upon driving pressure and increases towards infinity at low volumes. When resistance has no defined value, the subtraction of resistive pressure is not feasible. If flow rate is reduced to very low values, flow limitation occurs only very late during expiration. However, problems related to gas exchange increase if expiration is exceedingly prolonged.

A mathematical description of the P_{el}/V curve facilitates objective analysis of results. A model by Venegas et al. [*17*] describes with four parameters a sigmoid that is symmetrical with respect to one upper and one lower curvilinear segment without a liner segment between them. However, an inspiratory P_{el}/V curve is often characterized by a linear segment between the upper and lower nonlinear segments (Fig. 2). Furthermore, the upper and lower segments represent different physiological phenomena. There is hardly any reason to assume that they are symmetrical, and in reality they are not. The algorithm of Venegas et al. can be improved by adding one more coefficient to allow nonsymmetrical upper and lower segments [*18*]. A six-parameter model was developed to allow a comprehensive description of a nonsymmetrical curve with a middle, strictly linear segment [*19*, *20*]. Four parameters describe the coordinates of the linear segment and the two others the minimum and maximum volumes at which compliance of the extrapolated curve would fall to zero. The parameters of the noncontinuous, nonlinear equation are calculated with a numerical method available, for example, in Excel (Microsoft, Redmond, Wash., USA). A precise mathematical description of the curve is normally obtained (Fig. 2)
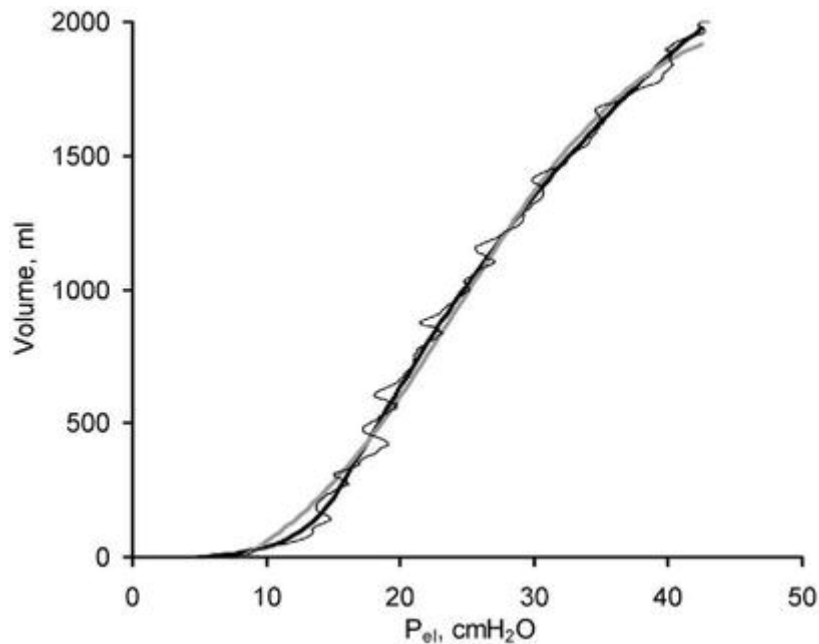
Fig. 2 *Thin line* Elastic P_{el}/V curve recorded with the low flow inflation method; *smooth black line* curve according to Svantesson et al. [*19*, *20*]; *gray line* curve according to Venegas et al. [*17*] The symmetrical nature of the latter implies that the curvature is exaggerated in the upper segment and underestimated in the lower. Obviously both fits have very high R^2 values

In contexts in which the detailed shape of the P_{el}/V curve is an issue the six-parameter model has obvious advantages. In other situations the four-parameter model may well serve its purpose. In spite of an excellent fit one needs to be warned against uncritical physiological interpretation of the parameters of any equation. Although the parameters were originally based upon physiological concepts, the values, for example, for lower (LIP) and upper (UIP) inflection points have complex physiological significance, as is discussed below.

Physiology

In the pioneering study by Falke et al. [*3*] dynamic P_{el}/V loops from different levels of positive end-expiratory pressure (PEEP) showed that recruitment was maintained by PEEP. Furthermore, increasing compliance during insufflation, later referred to as the LIP, was considered to represent recruitment of terminal airspaces. When PEEP was increased from 10 to 15 cmH$_2$O, compliance fell as a sign of "overdistension of open alveoli."

Using the supersyringe Matamis et al. [*21*] in 1984 presented static P_{el}/V loops from patients at varying stages of acute respiratory failure and acute lung injury/acute respiratory distress syndrome (ALI/ARDS; Fig. *3*). In acute stages high hysteresis indicated alveolar flooding. A pressure higher than LIP and above the zone of inflection was suggested as a guideline to set PEEP on the basis of observations of improved oxygenation when this was implemented. In late stages compliance and hysteresis were low and LIP was no longer evident; fibrotic changes had occurred. These observations and the interpretations are still of great significance.

Fig. 3 Inspiratory P_{el}/V curves from patients with nearly normal chest radiography (*1*), early progressive ALI/ARDS (*2*, *3*), and late-stage ARDS (*4*). (From Matamis et al. [*21*])

As early as 1975 Suter et al. [22] suggested that by choosing an optimum PEEP the tidal volume could be confined within the part of the P_{el}/V curve with highest compliance. This was later underlined by Roupie et al. [23]. The rationale would be to avoid derecruitment of lung below the LIP and overdistension above the UIP. In the first controlled study showing that lung-protective ventilation was associated with increased survival in ARDS patients PEEP was set above the pressure at LIP to avoid derecruitment while plateau pressure was not higher than PEEP plus 20 cmH$_2$O in order to avoid hyperinflation and barotrauma [24].

A basic concept in today's lung-protective ventilation goes back to 1970 when Mead et al. [25] and later Jonson [26] and explained that shear leads to extremely high local forces when a collapsed lung zone is recruited (Fig. 4).

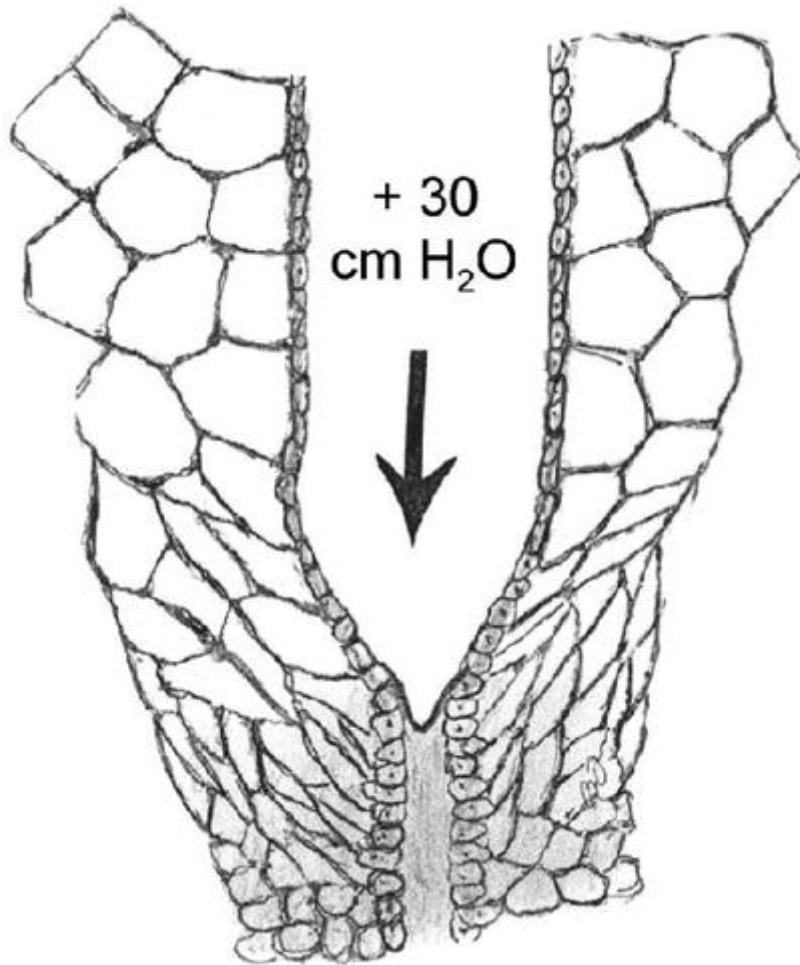**Fig. 4** Illustration of shear forces in the zone of lung opening, caused by stretching of densely distributed alveolar membranes, obliquely attached to bronchiolar basal membranes [26]. "At a transpulmonary pressure of 30 cmH$_2$O the pressure tending to expand an atelectatic region surrounded by a fully expanded lung would be approximately 140 cmH$_2$O" [25]

In ALI/ARDS it has repeatedly been shown that recruitment is not limited to a narrow zone of pressure. Rather, it is a phenomenon that continues to high transpulmonary pressures [27, 28, 29, 30, 31]. The notation by Frazer et al. [29] that sequential opening of the lung contributes to an increased value of the slope of the inspiratory P$_{el}$/V curve was later underpinned in theoretical studies [32, 33, 34]. Obviously volume change in a lung that undergoes recruitment reflects both distension of open units and recruitment of previously closed lung units when they "pop open": $\Delta V = (\Delta V_{distension} + \Delta V_{recruitment})$. Accordingly, recruitment contributes to compliance, C: $C = (\Delta V_{distension} + \Delta V_{recruitment})/\Delta P_{el}$. It is noteworthy that a concept established by Mead et al. [1] in 1957 and so clearly demonstrated in the prominent articles referred to needed to be reiterated. Elegant experimental and clinical computed tomography studies have recently confirmed finally that recruitment is a process that continues throughout the insufflation to high airway pressures [28, 30]. The effect of continuing recruitment makes a single P$_{el}$/V curve difficult to interpret. The LIP reflects rather the onset of recruitment. The UIP may indicate the gradual cessation of recruitment rather than overdistension of the lung. It is worth pointing out that in patients with early severe acute lung injury the particularly high compliance corresponding to the steep part of the pressure-volume curve probably represents ongoing recruitment rather than an open lung. Titration of best PEEP should not be determined from compliance read from inspiratory P$_{el}$/V curves.

In ARDS the P_{el}/V curve is dependent upon the volume history immediately preceding the recording [35]. Also in health this may be the case particularly in swine [36, 37]. Also in healthy anesthetized and paralyzed humans derecruitment of lung units occurring at zero airway pressure is reversed by a deep insufflation [38, 39]. P_{el}/V curves performed before and after a recruitment maneuver are suitable for studying such phenomena. On the other hand, a standardized volume history, for example, a recruitment maneuver, is recommended to allow comparisons of P_{el}/V curves observed in different groups or situations.

Enhanced information has since long been obtained by recording multiple P_{el}/V curves at different levels of PEEP [3, 40]. The 1973 studies by Glaister et al. [40] of isolated dog lungs illustrate important principles which are actually applied in clinical studies (Fig. 5) [41]. In a study of ARDS by Ranieri et al. [42] showed in 1994 that recruitment at different PEEP levels can be studied using multiple inspiratory P_{el}/V curves.
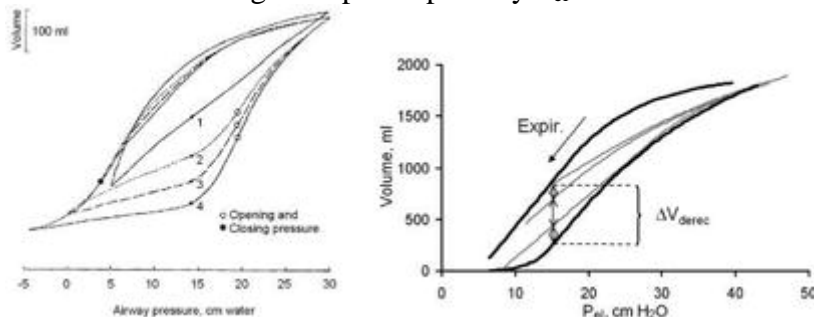

Fig. 5 It took 30 years to go from dog lungs [40] to ARDS patients [41]. A family of inspiratory P_{el}/V curves shows derecruitment at low expiratory airway pressure (ΔV_{derec}). The inspiratory curves merge at high pressures because of recruitment. Expiratory curves follow a common trajectory

Jonson et al. [13] studied a group of patients with ALI using the computer-controlled ventilator in a mode that allows alignment of successive pressure-volume curves to the elastic equilibrium volume. Full recovery of volume loss caused by derecruitment during a single expiration at zero PEEP occurred during the following insufflation only after pressure was higher than 35 cmH$_2$O. It was confirmed that the LIP indicated nothing more than onset of recruitment, and that compliance was increased during the process of recruitment.

The progressive derecruitment for each step of lower PEEP below 15 cmH$_2$O was quantified by recording a family of inspiratory P_{el}/V curves in ALI/ARDS [20, 43]. In the modestly large groups of patients derecruitment was about equally large for each step of lower PEEP. Later a larger series indicated that this is not always the case (unpublished). Figure 5 shows an example in which derecruitment occurred mainly between 5 and 10 cmH$_2$O. As is commonly observed, the merging inspiratory curves show that recruitment continued to about 40 cmH$_2$O.

In dogs with oleic acid induced ARDS Pelosi et al. [30] gave a solid demonstration of the relationship between the inspiratory P_{el}/V curve and recruitment as observed with computed tomography. Recruitment had just started at the LIP; it was prominent over the linear part of the P_{el}/V curve and continued to pressures above 40 cmH$_2$O. In an accompanying study of ARDS patients the same group showed a similarly wide range of opening pressure [28]. Closing pressures were widely distributed, but closing occurred in general at much lower pressures than opening. These data confirm previous conclusions drawn on the basis of P_{el}/V curve recordings. Accordingly, the information obtained from an inspiratory curve recorded from zero pressure is limited, while a family of P_{el}/V curves indicates the distribution of both

opening and closing pressures of the lungs. This information is attainable at the bedside without any other equipment than a computer-controlled ventilator.

Recording of expiratory P_{el}/V curves is an alternative way to enhance information. The physiological significance of an expiratory P_{el}/V curve recorded from a pressure high enough to recruit the lung must then be considered. In its upper segment, before derecruitment has begun, it reflects elastic properties of the respiratory system. At lower pressures, when derecruitment has started, it is also influenced by expulsion of gas from collapsing lung units. Accordingly, the expiratory P_{el}/V curve is in principle affected by the same physiological factors as the inspiratory curve. Furthermore, in its lower part dynamic airway compression and flow limitation are sometimes additional factors making analysis of dynamic expiratory P_{el}/V curves difficult. In any case, as collapse of lung units and flow limitation affects mainly the lower part of the expiratory curve, this curve gives a better indication of elastic properties than the inspiratory curve.

Various characteristics reflecting shape of the expiratory P_{el}/V curve have been suggested as indicators of closure of lung units and even as guidelines for setting PEEP [29, 40, 44]. However, this curve reflects a physiology as complex as the inspiratory curve. Overinterpretation, as that of the inspiratory LIP, should not be repeated.

Another aspect is that the expiratory P_{el}/V curve recorded from a pressure high enough to recruit the lung shows the highest volume that can be maintained at each pressure level. It may accordingly be regarded as a reference for other P_{el}/V curves. Benito et al. [45] showed as early as 1985 how expiratory compliance increases when measured after insufflations to higher and higher volumes. The hypothesis was confirmed that opening of previously closed units continues to occur, and that the increase in compliance reflects sequential opening of more units. Rimensberger et al. [46, 47] showed the usefulness of the expiratory curve recorded from a high pressure as a reference for P_{el}/V loops recorded under tidal volume ventilation (Fig. 6). While the inspiratory P_{el}/V curve is affected by continuing recruitment over a wide range of pressure, the expiratory P_{el}/V curve is affected by alveolar collapse only in its lower part. This was very recently emphasized in an elegant study by Downie et al. [48].
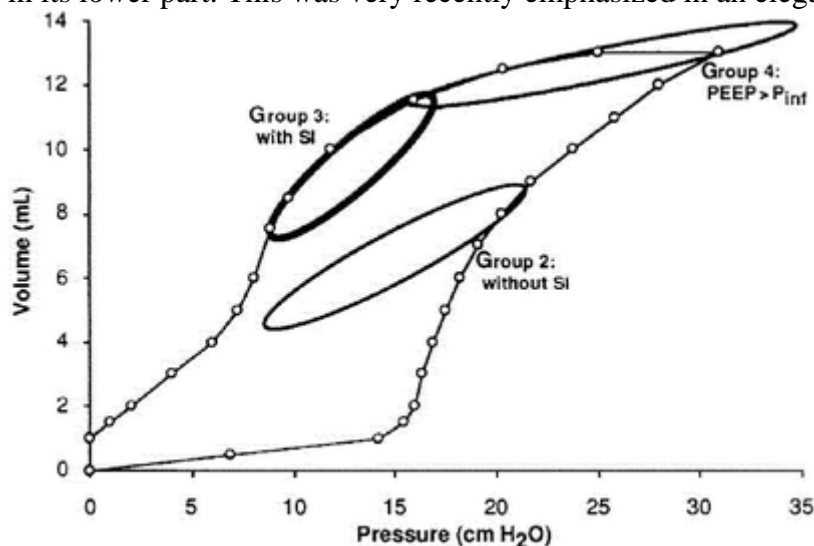

Fig. 6 Schematic drawing illustrating how in an ARDS animal model a large P_{el}/V loop was recorded from zero to 35 cmH$_2$O. *Group 3* Ventilated at moderate PEEP after a recruitment maneuver, showing less damage than other groups. The P_{el}/V loop over the tidal volume was in this group situated at the expiratory limb of the large loop. (From [46])

As shown in Fig. 5, the inspiratory curve recorded from the highest PEEP level falls closest to the expiratory curve. However, even the P_{el}/V curve recorded from a PEEP of 15 cmH$_2$O falls below the expiratory curve recorded from 50 cmH$_2$O. This may reflect collapse of some lung units above this pressure or by other factors (see below).

In ARDS the hysteresis of P_{el}/Vloops is reduced by PEEP because it attenuates collapse of lung units [49]. Static P_{el}/V loops show minimal hysteresis under conditions when lung closure and reopening does not occur, either in health [6, 8, 12] or in disease [50]. These observations motivate reassessment of the common model of lung surfactant film hysteresis as an important source of P_{el}/V hysteresis of the lung. An even greater misconception related to surfactant and closure of lung units involves Laplace's law of elastic spheres. As Prange [51] notes, "The Y-tube model of alveolar inflation and the bunch-of-grapes model of alveolar anatomy deserves a place, not in our minds and textbooks, but in the museum of wrong ideas."

Hysteresis of dynamic P_{el}/V curves is caused in a complex way by resistance, viscoelastic behavior, and differences between closing and opening pressure of lung units. Even at low flow rates during recording of dynamic P_{el}/V loops and after subtraction of resistive pressure dynamic and static loops differ slightly because of viscoelastic phenomena in healthy pigs [12]. More data from patient studies are needed for proper interpretation of hysteresis of dynamic loops.

Utility of P_{el}/V curves in research and in the clinic

For about 50 years the recording of P_{el}/V curves has contributed to the understanding of the physiology of healthy and diseased lungs. At present we have come to the knowledge that a family of P_{el}/V curves estimate how much volume is lost by derecruitment for each step of lower PEEP, and how recruitment successively occurs with increasing pressures during insufflation (Fig. 5). Accordingly, P_{el}/V curves have given us substantial knowledge about the pathophysiology in ALI/ARDS with regards to the phenomenon of lung collapse and reopening. As this phenomenon is probably linked to ventilator-induced lung injury, the knowledge obtained through P_{el}/V curves is one of the keys to improved treatment of patients with ALI/ARDS. Studies based upon recording of P_{el}/V curves have demonstrated how the maintenance of recruitment depends upon PEEP, tidal volume, and recruitment maneuvers [42, 52, 53]. Thus the lungs may be well recruited even at low tidal volume ventilation if PEEP is adequately high. In a proper context therefore PEEP is a major component of the open lung concept. How should this knowledge be applied to a particular patient?

In patients with ALI/ARDS a distinct LIP of an inspiratory P_{el}/V curve recorded from zero pressure indicates that derecruitment and recruitment are a threat with respect to ventilator-associated lung injury. PEEP should then be used and set at some value above the pressure at LIP. This strategy has long been applied [21, 23, 42] but has only recently been associated with improved outcome in a controlled study by Amato et al. [24]. As in the latter study, the setting of PEEP in relation to the LIP was not the only component of the tested strategy; a role of the P_{el}/V curve may be argued. Experimental evidence suggest that the role of PEEP in a lung protective strategy is important [54]. The P_{el}/V curve is used in only rather few centers, mainly in those with scientific interest in the topic. To tailor ventilation to the changing

pathophysiology of the individual patient with respect to tidal volume, respiratory rate, and PEEP one would need the detailed information of multiple P_{el}/V curves or loops aligned to a common volume axis. In ALI/ARDS this should be repeatedly obtained to follow the course of the disease. Studies in both animal models and in patients show that this is feasible using computer-controlled ventilators [*13*, *14*, *47*, *55*]. The recently released Hamilton Galileo Gold Ventilator represents a step forward (Hamilton Medical, Rhäzüns, Switzerland). When systems fulfilling the demands on versatility become generally available, it will be possible to develop new strategies and test them in large series of patients in multicenter studies. Only then it will be possible to define the optimal use of P_{el}/V curves for improving ventilation so as to avoid ventilator-induced lung damage.

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