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SEMINAL STUDY

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The concept of "baby lung"

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Abstract *Background:* The "baby lung" concept originated as an offspring of computed tomography examinations which showed in most patients with acute lung injury/acute respiratory distress syndrome that the normally aerated tissue has the dimensions of the lung of a 5- to 6-year-old child (300–500 g aerated tissue). *Discussion:* The respiratory system compliance is linearly related to the "baby lung" dimensions, suggesting that the acute respiratory distress syndrome lung is not "stiff" but instead small, with nearly normal intrinsic elasticity. Initially we taught that the "baby lung" is a distinct anatomical structure, in the nondependent lung regions. However, the density redistribution in prone position shows that the "baby lung" is a functional and not an anatomical concept. This provides a rational for "gentle lung treatment" and a background to explain concepts such as baro- and volutrauma. *Conclusions:* From a physiological perspective the "baby lung" helps to understand ventilator-induced lung injury. In this context, what appears dangerous is not the V_T/kg ratio but instead the V_T/"baby lung" ratio. The practical message is straightforward: the smaller the "baby lung," the greater is the potential for unsafe mechanical ventilation.

Keywords Acute respiratory distress syndrome · Baby lung · Baro-/volutrauma · Mechanical ventilation · Respiratory system compliance · Ventilator-induced lung injury

Introduction

Adult respiratory distress syndrome (ARDS) was first described in 1967 [1]. It is worth rereading the original paper as it clearly outlines the basic physiopathology and management problems which continue to be a matter of scientific debate. The 12 patients described there had ARDS of pulmonary and extrapulmonary origin, some with fluid overload and shock. Positive end-expiratory pressure (PEEP) was applied in five of them (three survived) and zero end-expiratory pressure (ZEEP) in the remaining seven (two survived). Respiratory system compliance ranged from 5 to 16 ml/cmH_2O, all patients were hypoxemic, and PCO_2 ranged from 22 to 69 mmHg. At autopsy the lungs were heavy (average 2110 g), and microscopic examination revealed areas of alveolar atelectasis, interstitial and alveolar hemorrhage and edema, dilated and congested capillaries. Interestingly, PEEP was described as a "buying time maneuver," preventing alveolar collapse at end-expiration.

How does the "baby lung" fit into this framework? The concept was introduced in the middle 1980s [2], but before discussing its place a brief history of the ARDS physiopathology and treatment is necessary. Some of the "new" concepts are nothing more than rediscoveries. Often, as new knowledge progresses, old knowledge is abandoned or forgotten.

From the 1970s to the middle 1980s

To understand the progress of research in this period it is important to realize that the ultimate, undisputed target in ARDS patients was to maintain normal arterial PCO_2 and PO_2. Maintaining normal PCO_2 was not considered a problem, as it was common to use high pressure and volume ventilation, with tidal volume (V_T) even exceeding 20 ml/kg. Actually the recommended standard care was V_T between 12 and 15 ml/kg [3]. The most common side effects were pneumothorax and pulmonary hyperinflation, collectively termed barotrauma [4, 5].

To improve PaO_2 the key maneuver, after the report by Ashbaugh et al. [1], was to apply PEEP. To investigate its mechanism Falke et al. [6] first tested the effect of increasing PEEP from 0 to 15 cmH_2O in ten patients with ARDS. PEEP improved PaO_2 linearly, and the putative mechanism was the prevention of alveolar end-expiratory collapse and/or airway closure. That study reported a decrease in lung compliance with high PEEP and variable hemodynamic responses, as in some patients cardiac output rose and in others it fell. It is important to recall that at that time the major concern with PEEP was the possible hemodynamic impairment caused by the increase in intrathoracic pressure.

In 1975 Suter et al. [7] published their investigation on the "optimum PEEP." For the first time the relationship between lung mechanics and hemodynamics was approached in a structured fashion. Defining optimum PEEP as that which achieves not the best PaO_2 but the best oxygen transport (cardiac output × oxygen content), they found it to be associated with the highest compliance of the respiratory system. The hypothesis that was successfully tested, explicitly stated by the authors, is that the best compliance indicates that recruitment prevails over alveolar overdistension.

It is impossible to cite all the subsequent reports dealing with this concept, but in our opinion those that have introduced a new view of the problem were the ones by Lemaire et al. [8] and Kirby et al. [9] Lemaire et al. [8] suggested that the "minimal PEEP" to keep the lung open is 2 cmH_2O higher than the lower inflection point on the inflation limb of the volume pressure curve [8]. At the other end of the spectrum stood Kirby et al. [9] who proposed the "super PEEP" concept, defined as the pressure that maximally reduces shunt (down to 20% at 20 torr) [9]. For many years beginning in the middle 1970s the overall picture can be summarized as follows: ARDS lungs were regarded as homogeneously heavy and stiff. To achieve normal PCO_2 high volume and pressure ventilation was required, and to ensure normal oxygenation high FIO_2 and PEEP were necessary, although the criteria for selecting PEEP were elusive. At that time the recognized side effects were ventilation-induced barotrauma, and the major concern was the hemodynamic impairment due to PEEP and high FIO_2.

A new perspective was opened by Hill et al. [10] who described the successful treatment of a young trauma patient with long-term membrane lung oxygenation. This led the National Institutes of Health in the United States to sponsor the first multicenter randomized trial on ARDS [11]: 42 patients were randomized to extracorporeal membrane oxygenation (ECMO) and 48 to conventional care. Overall mortality in both groups was near 90%. To highlight the thinking at that time it is worth noting that both groups were treated with high-volume/pressure ventilation, and that the only difference was the lower FIO_2 in the group receiving extracorporeal membrane oxygenation.

At about the same time, after extensive experimental work showing that it was possible to control breathing by extracorporeal removal of CO_2 [12, 13, 14], we began to treat severe ARDS patients with this technique [15], the aim being to provide "lung rest" avoiding high-volume/pressure mechanical ventilation [16]. With this technique we could dissociate CO_2 removal and oxygenation; the first was achieved with a low-flow venovenous extracorporeal membrane lung and the second by apneic oxygenation through the natural lungs which were kept substantially immobile, being ventilated with only 3/5 bpm. At that time we had no scientific rationale for the "lung rest," except for the clinical observation of severe traumatic damage induced by high-volume/pressure ventilation. With extracorporeal CO_2 removal the gas exchange targets were again, as in the early 1970s, normal PCO_2 and normal PO_2.

Middle 1980s: the "baby lung" concept

Surprisingly the first reports on computed tomography (CT) examinations appeared only in the middle 1980s [17, 18, 19]. CT dramatically changed our view of ARDS [20]. What was considered a "homogeneous lung," as usually shown by anteroposterior radiography, appeared non-homogeneous on CT, with the densities concentrated primarily in the most dependent regions (Fig. 1). When we began a quantitative assessment of CT images, which measures the amount of normally aerated, poorly aerated, overinflated, and nonaerated tissue, we found that the amount of normally aerated tissue, measured at end-expiration, was in the order of 200–500 g in severe ARDS, i.e., roughly equivalent to the normally aerated tissue of a healthy boy of 5/6 years. From this finding came the concept of "baby lung," as an offspring of CT examinations [2].

As expected, the amount of nonaerated tissue was correlated with the degree of hypoxemia, the shunt fraction, and pulmonary hypertension. What was absolutely new, however, was the finding that respiratory compliance was well correlated only with the amount of normally aerated tissue and not with the amount of nonaerated tissue

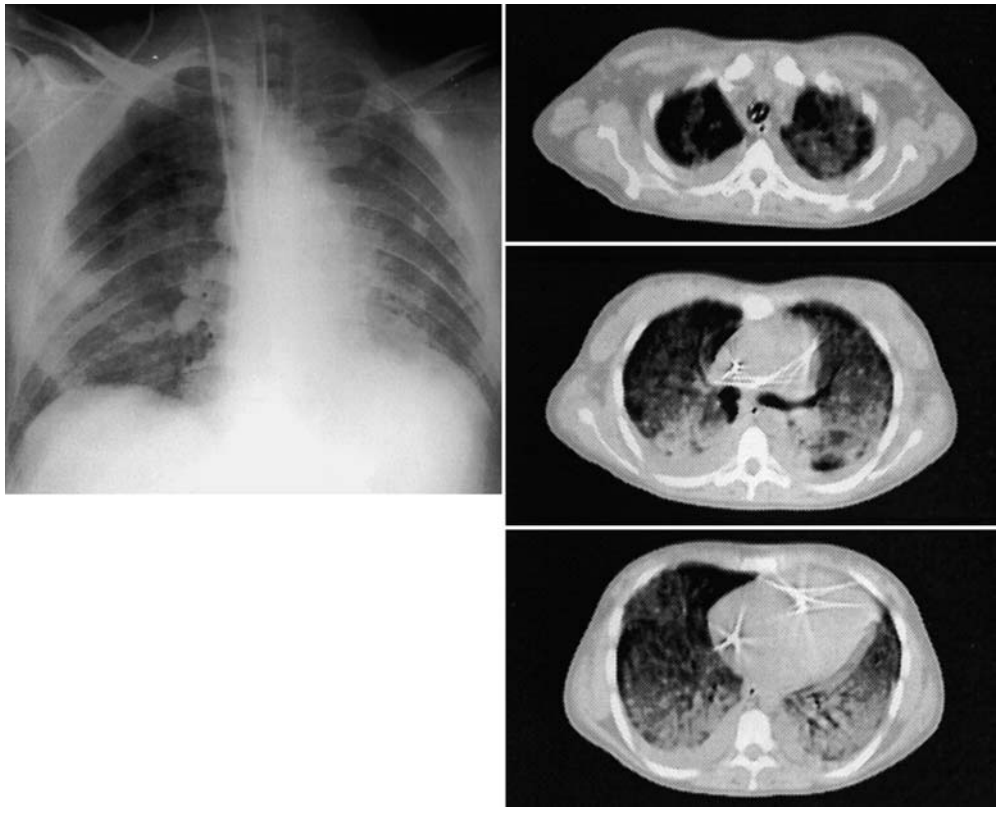

Fig. 1 Anteroposterior chest radiography (*right*) and CT—apex, hilum, and base—(*left*) in ARDS from sepsis, taken at 5 cmH_2O end-expiratory pressure. Chest radiography shows diffuse ground glass opacification, sparing the right upper lung. CT shows inhomogeneous disease and both the craniocaudal and sternovertebral gradients. (From Gattinoni et al. [20])

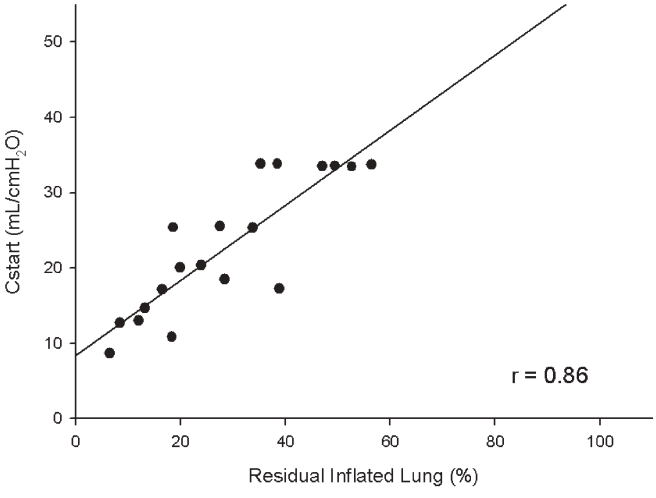

Fig. 2 Starting compliance (*Cstart*) as a function of residual inflated lung expressed as percentage of the expected normal lung volume. (Redrawn from Gattinoni et al. [22])

[21]. In other words, compliance appears to "measure" the dimension of the "baby lung" [22] (Fig. 2). We then discovered that the ARDS lung is not "stiff" at all, but small, and that the elasticity of the residual inflated lung is nearly normal, as indicated by the specific tissue compliance (compliance/normally aerated tissue) [21, 23].

When we first elaborated these concepts, we believed that the "baby lung" was a healthy anatomical structure, located in the nondependent regions of the original lungs. This model helped account for the disaster observed during high-volume and pressure mechanical ventilation. It was easily understandable that ventilating the lung of a healthy child with, for example, 1000 ml V_T, would destroy it. The relationship between the "baby lung" size and compliance explained why, on quite a large ARDS population with similar gas exchange impairment (referred to our hospital for extracorporeal support), only the patients with compliance below 20 ml/cmH_2O ("baby lung" approx. 20% of the original lung) actually received extracorporeal assistance while the others, with similar gas exchange but better compliance, could be treated with alternative methods [16]. Moreover, the "baby lung" concept fitted neatly with the concept of volutrauma (straining of the "baby lung") introduced by Dreyfuss et al. [24]. This helped provide a solid rational basis for trying to achieve "lung rest."

As soon as we realized that the "baby lung" was located primarily in the nondependent lung regions, we started to use the prone position. The goal was to improve oxygenation by increasing perfusion of the anatomical "baby lung," which was expected to be dependent in the prone position. Oxygenation did actually improve in the majority of patients. However, when we examined CT images in the prone position to confirm the theory [25], we found that the

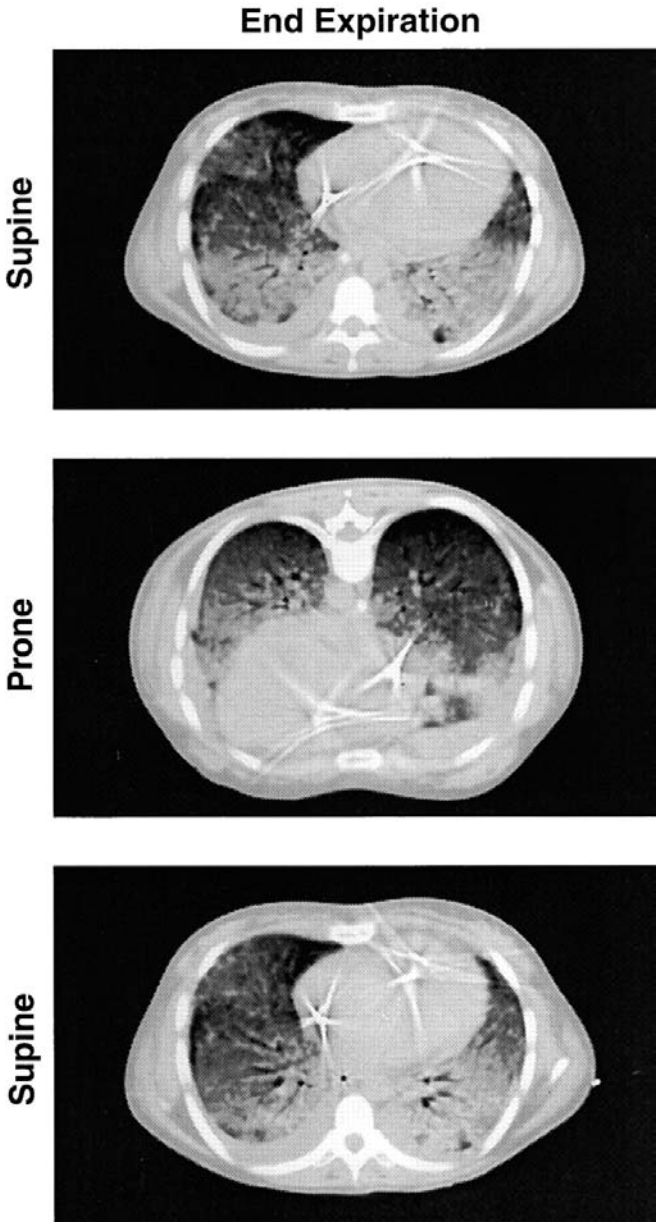

Fig. 3 CT of ARDS lung in supine (*upper*), prone (*middle*), and return to supine position (*lower*). The images were taken at end expiration and 10 cmH_2O PEEP. Note how gravity-dependent densities shift from dorsal to ventral within minutes when the patient is turned prone. (From Gattinoni et al. [20])

densities were redistributed in the dependent lung [26], thus demolishing the notion of the "baby lung" as a discrete, healthy anatomical structure (Fig. 3).

From "baby lung" to "sponge lung"

To understand the mechanism of lung density redistribution in the prone position we applied regional analysis, studying the lung composition along the sternum-vertebral axis [26, 27]. The main findings can be summarized as follows: all the lung parenchyma in ARDS is involved by the disease process, and the edema is evenly distributed from the sternum to the vertebra, i.e., not gravitationally, as observed previously [28, 29] and after [30, 31] ex vivo and in experimental animals. The increased lung weight, due to the accumulated edema, raises the hydrostatic pressures transmitted throughout the lung, which we called superimposed pressure. Consequently the gas in the dependent lung regions is squeezed out by the heavy lung parenchyma above (Fig. 4). The densities in the dependent lung regions are in fact due not to an increase in the amount of edema but to a loss of alveolar gases, as the result of the compressive gravitational forces, including the heart weight [32, 33].

This model, which Bone [34] called "sponge lung," accounts, although not completely, for the redistribution of the lung densities in prone position: the superimposed hydrostatic pressure is reversed, and the ventral regions instead of the dorsal are compressed [35]. The sponge lung also partly explains the mechanism of PEEP: to keep open the most dependent lung regions PEEP must be greater than the superimposed pressure [23]. Unfortunately, this unavoidably leads to overdistension of the lung regions with lower superimposed pressure (Fig. 4). That superimposed pressure is the main cause of collapse was inferred from the human studies cited above and, years later, was directly confirmed experimentally in animals [36] although this view was challenged [37, 38]. In the context of "sponge lung" the "baby lung" still has value if considered from a functional, not an anatomical, perspective. In a broad sense the "baby lung" concept can be applied to any kind of ARDS as every patient has a reduced amount of normally aerated tissue.

The sponge lung model, however, implies different considerations. It assumes that the edema is evenly distributed throughout the lung parenchyma. While this is likely when the noxious stimulus leading to ARDS originates from the blood, i.e., all the lung parenchyma is exposed as in extrapulmonary ARDS, the picture may differ when the noxious stimulus comes from the airways, and distribution may possibly be nonhomogeneous (as in pulmonary ARDS) [39, 40]. This, however, remains to be verified, although CT differences between pulmonary and extrapulmonary ARDS have been reported [41, 42].

The "baby lung" at end-inspiration

New information was obtained, with further refinement of the model, when not only end-expiration but also end-inspiration was explored. We found that during inspiration part of the lung is recruited [43]. This has been shown in humans and in experimental animals both with [36, 44] and without CT [45]. These findings suggest the follow-

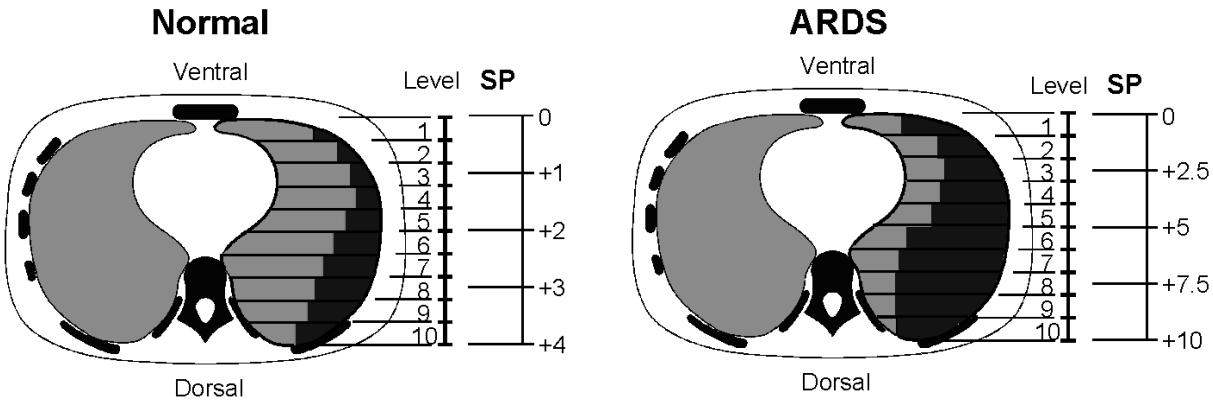

Fig. 4 Schema representation of sponge model. In ARDS the "tissue," likely edema in the early phase, is almost doubled in each lung level compared with normal, indicating the nongravitational distribution of edema. The increased mass, however, causes an increased superimposed pressure (*SP*; cmH_2O), which in turn leads to a "gas squeezing" from the most dependent lung regions. Superimposed pressure is expressed as cmH_2O. (The values are taken from Pelosi et al. [27])

ing scheme (Fig. 5): the opening pressures are widely and normally distributed throughout the lung parenchyma both in humans and in experimental models, with the mode between 20 and 25 cmH_2O of airway pressure. Some lung regions, however—usually the most dependent—may require opening pressure up to 45 cmH_2O. It follows that during inspiration new tissue continuously opens to the plateau pressure. Of course, if the plateau pressure is limited, say, to 25 cmH_2O, all collapsed tissue with a higher opening pressure stays closed throughout the entire respiratory cycle. At end-expiration the PEEP, if adequate, can keep open only the lung regions that were already opened by the plateau pressure [36, 44].

CT examinations at end-inspiration did in fact clearly focus the relationship between the end-expiratory and end-inspiratory pressures, which may be relevant and are discussed below in the context of the lung protective strategy. During inspiration the "baby lung" augments its own parenchyma through newly recruited tissue up to the inspiratory plateau pressure. This complicates the interpretation of the pressure/volume curve. In fact the amount of tissue explored between end-expiration and end-inspiration in ARDS is not the same as in the normal lung which simply inflates. In ARDS during inspiration the "baby lung" gains both gas and tissue, and the gas volume/pressure curve is similar to the recruitment/pressure curve [20].

The "baby lung" and the protective lung strategy: changing the goals

As discussed above, the concept of "baby lung" fully justified the goal of lung rest. With extracorporeal CO_2 removal we were able to fully provide lung rest, but at the price of the side effects of extracorporeal circulation (primarily bleeding). In the 1990s Hickling et al. [46] introduced low V_T ventilation to "rest the lung." This technique, referred to as "permissive hypercapnia," to underline the price paid for resting the lung, had been used with success in asthma patients [47]. In our opinion, however, *the real "revolution" was not the use of low tidal volume but the change of the goal*. For nearly 20 years this had been normal gas exchange, but from the 1990s the accepted target became gentle lung treatment while maintaining adequate oxygenation and accepting high PCO_2 [48].

The "baby lung" and "VILI"

Anatomical and physiological basis of ventilator-induced lung injury

We recently reviewed the physical and biological triggers of ventilator-induced lung injury (VILI) [49] and briefly discuss them now in relation to the "baby lung." The lung's fibrous skeleton is the structure that bears the forces applied by mechanical ventilation. The skeleton consists of two fiber systems: an axial system which is anchored to the hilum and runs along the branching airways down to the alveolar ducts, and a peripheral system which is anchored to the visceral pleural that goes centripetally down into the lung to the acini. The two systems are linked at the level of the alveoli and form a continuum, the lung skeleton [50]. The anatomical units of the system are extensible elastin and inextensible collagen which is "folded" in the lung resting position (Fig. 6, left panel). The lung cells (epithelial and endothelial) do not bear the force directly but are anchored (via integrins) to the fibrous skeleton and must accommodate their shape when the skeleton is distended. The limits of distension are of course dictated by the inextensible collagen fibers, which work as a "stop-length" system. When the collagen fibers are fully unfolded, the lungs reach their maximal volume (total lung capacity) and further elongation is

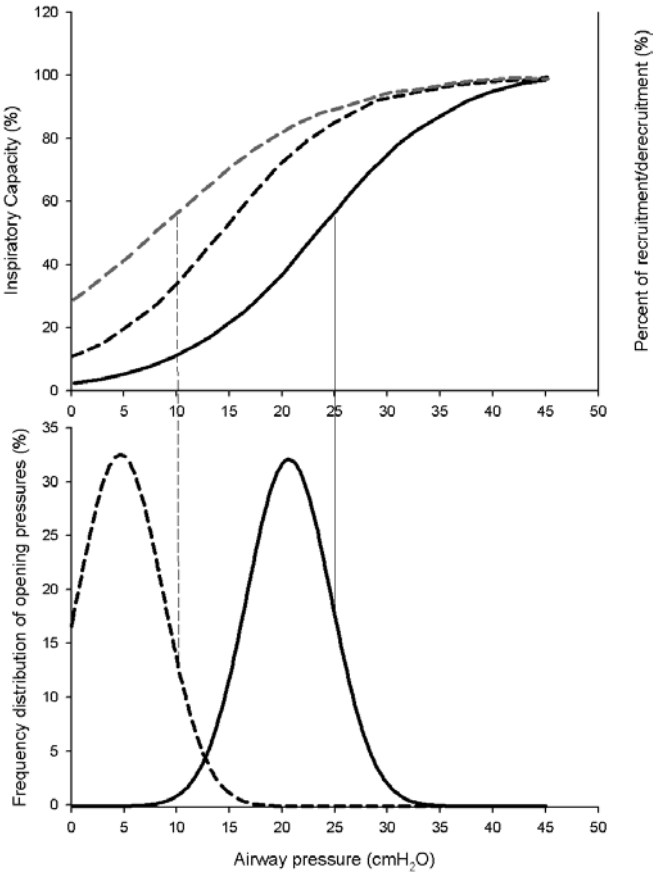

Fig. 5 *Upper* Percentage of inspiratory capacity (*black lines*; *solid black line* also percentage of recruitment) and percentage of derecruitment (*dashed gray line*) as function of airway pressure. *Lower* Frequency distribution of opening pressure as function of airway pressure (*solid line*) and of closing pressure (*dashed line*). *Vertical lines* Example of airway pressures used during mechanical ventilation, plateau pressure 25 cmH_2O (*solid line*) and PEEP 10 cmH_2O (*dashed line*). At 25 cmH2O airway pressure nearly 60% inspiratory capacity, 40% of lung units are still closed. At 10 cmH_2O PEEP nearly 35% undergoes opening and closing. (Data from Crotti et al. [44])

prevented (Fig. 6, right panel). This is true for the whole lung as well as for each lung region, which has its own "total regional maximal capacity."

When a force is applied by the ventilator, the fibers of the lung skeleton develop an internal tension (spatial molecular rearrangement), equal to but opposite the pressure applied to the fibers. The applied pressure is not the airway pressure but the transpulmonary pressure (PL), i.e., the airway pressure minus the pleural pressure. The fiber tension is called "stress." In an elastic structure such as the lung skeleton, the stress is associated with elongation (ΔL) of the fibers from their resting position (L_0), and this is called "strain" ($\Delta L/L_0$). Stress and strain, indeed, are two faces of the same coin, and are linked as follows: *stress=K* × *strain*, where K is Young's module of the material [51].

If the stress exceeds the tensile properties of the collagen fibers up to "stress at rupture," the lung undergoes the classical "barotrauma." When the strain, without reaching the levels of physical rupture, is unphysiological (volutrauma), the macrophages, endothelial, and epithelial cells anchored to the lung skeleton are stretched abnormally [52, 53, 54, 55, 56, 57], the mechanosensors are activated [58, 59, 60], cytokines are produced [61, 62, 63], and full-blown inflammation develops [64].

Stress and strain in the "baby lung"

From this perspective, VILI is nothing more than the global/regional excessive stress and strain applied to the "baby lung." The rough equivalent of the stress in the whole lung is the PL, while the equivalent of the strain is the change in the size of the lung from its resting position, i.e., the ratio of V_T to the size of the "baby lung" at end-expiration (ZEEP): *PL(i.e. stress)=K* × *[(V_T/baby lung)] (i.e. strain)*. The link between stress and strain, K, is the specific lung elastance (E_{spec}=*PL*/V_T × *"baby lung"*), which is the pressure at which the "baby lung" (end-expiratory lung volume) doubles in size, i.e., when V_T/"baby lung"=1.

The issue is more complicated (but the overall concept does not change) when PEEP is applied. In fact, the effects of PEEP are twofold. On the one hand, PEEP may overdistend the already open lung, increasing stress and strain (i.e., the numerator of above equation increases). On the other hand, PEEP may keep open new lung portions, increasing the resting end expiratory lung volume (i.e., the denominator of the above equation increases, stress/strain decreases). The final effect should be detected in every patient, who may show varying amounts of recruitable lung.

We do not know the safe limits of mechanical ventilation, but they can be discussed against a physiological and anatomical background. In the normal lung doubling the resting volume occurs at approx. 80% of total lung capacity, and at this level of strain (V_T/end-expiratory lung volume=1) most of the collagen fibers are unfolded, and PL equals the specific elastance, which is normally 12.5 cmH_2O. We found that specific elastance in the "baby lung" is near normal [21, 23]. If so, considering the upper limits of physiological strain between 0.8 and 1 as "safe" (although we do not know), the "safe" PL should not exceed the specific elastance (approx. 12–13 cmH_2O).

To prevent VILI, by applying stress and strain within physiological limits, we must take the V_T/"baby lung" ratio, not the V_T/kg ratio. For example, in a 70-kg ARDS patient the "baby lung" dimension may be highly variable, say 200, 400, or even 800 ml. A 6 ml/kg V_T [65] applied to these different "baby lungs" would result in three different sets of global [stress and strain], i.e., [26.3 cmH_2O and 2.1], [13.1 cmH_2O and 1.1],

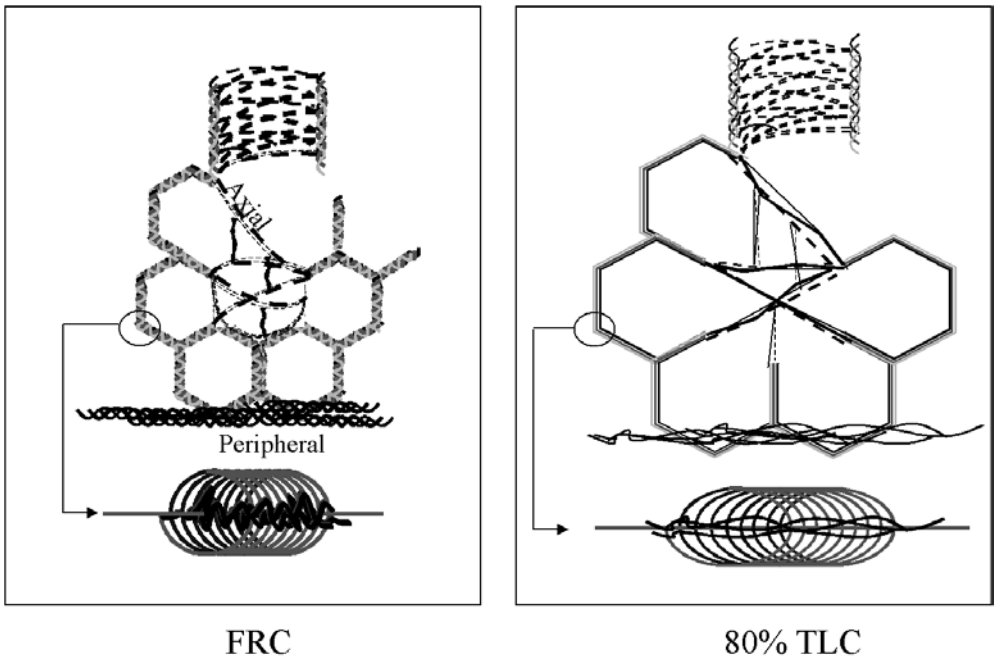

Fig. 6 Disposition of fibers in an acinus. The particular shows the association of elastic fibers (spring) and collagen fibers (string). *Left* Relaxed state (*FRC*); *right* 80% TLC state. (Modified from Weibel [67])

[6.6 cmH_2O and 0.5] respectively. Only the third set is within physiological limits.

If we eventually verify (work is in progress) that E_{spec} is constant or within narrow limits in ARDS, knowing either the PL or the "baby lung" dimension will be sufficient to tailor stress and strain, so that they remain within physiological limits. Unfortunately, none of the variables needed to estimate stress and strain are measured routinely in the ICU.

So far we have considered PL as a single value, but in fact it changes along the vertical axis of the lung. In supine position the PL gradient is steeper than in prone position [26]. This suggests that strain and stress are distributed more evenly in the prone position, and this is the rationale for its application in ARDS, independently of gas exchange, as we recently observed experimentally [66].

Conclusion

The "baby lung" is a model, with all the limits inherent to models. However, it is useful for the interpretation of both physiopathology and treatment. The "baby lung" is actually the "small" lung open at end-expiration; it may become larger during inspiration due to newly recruited tissue, according to the recruitment-pressure curve and the opening pressure distribution. The "baby lung" is not healthy but it is aerated. Its specific elastance, however, is usually near-normal. The smaller the "baby lung," the greater the potential for VILI. Barotrauma (PL, stress) and the volutrauma-biotrauma (V_T/end-expiratory lung volume, strain) are linked to the "baby lung" by the following relationship, which clearly indicates that the smaller the "baby lung" the greater the stress/strain: $PL=E_{spec}\times(V_T/baby\ lung)$. The final message is straightforward: Treat the "baby lung" gently. Low PL, low V_T, and prone position are the means to hand today.

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