

Luciano Gattinoni  
Antonio Pesenti

## The concept of “baby lung”

Received: 2 March 2005  
Accepted: 15 March 2005  
Published online: 6 April 2005  
© Springer-Verlag 2005

L. Gattinoni (✉)  
Istituto di Anestesia e Rianimazione,  
Fondazione IRCCS,  
Ospedale Maggiore Policlinico,  
Mangiagalli, Regina Elena di Milano,  
Università degli Studi,  
Via Francesco Sforza 35, 20122 Milan,  
Italy  
e-mail: gattinon@policlinico.mi.it  
Tel.: +39-02-55033232 ext 3231  
Fax: +39-02-55033230

A. Pesenti  
Dipartimento di Medicina Perioperatoria e  
Terapia Intensiva, A.O. Ospedale S.Gerardo  
Monza,  
Università degli Studi,  
Milan-Bicocca, Italy

**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<sub>2</sub>O, all patients were hypoxemic, and PCO<sub>2</sub> 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  $\text{PCO}_2$  and  $\text{PO}_2$ . Maintaining normal  $\text{PCO}_2$  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  $\text{PaO}_2$  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  $\text{cmH}_2\text{O}$  in ten patients with ARDS. PEEP improved  $\text{PaO}_2$  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  $\text{PaO}_2$  but the best oxygen transport (cardiac output  $\times$  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  $\text{cmH}_2\text{O}$  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  $\text{PCO}_2$  high volume and pressure ventilation was required, and to ensure normal oxygenation high  $\text{FIO}_2$  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  $\text{FIO}_2$ .

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  $\text{FIO}_2$  in the group receiving extracorporeal membrane oxygenation.

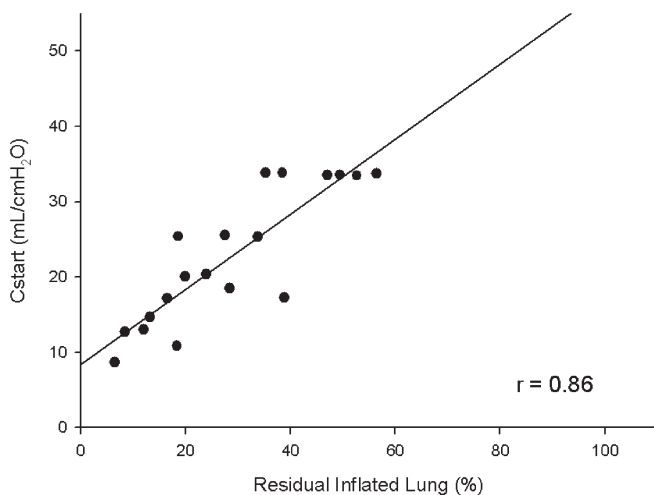
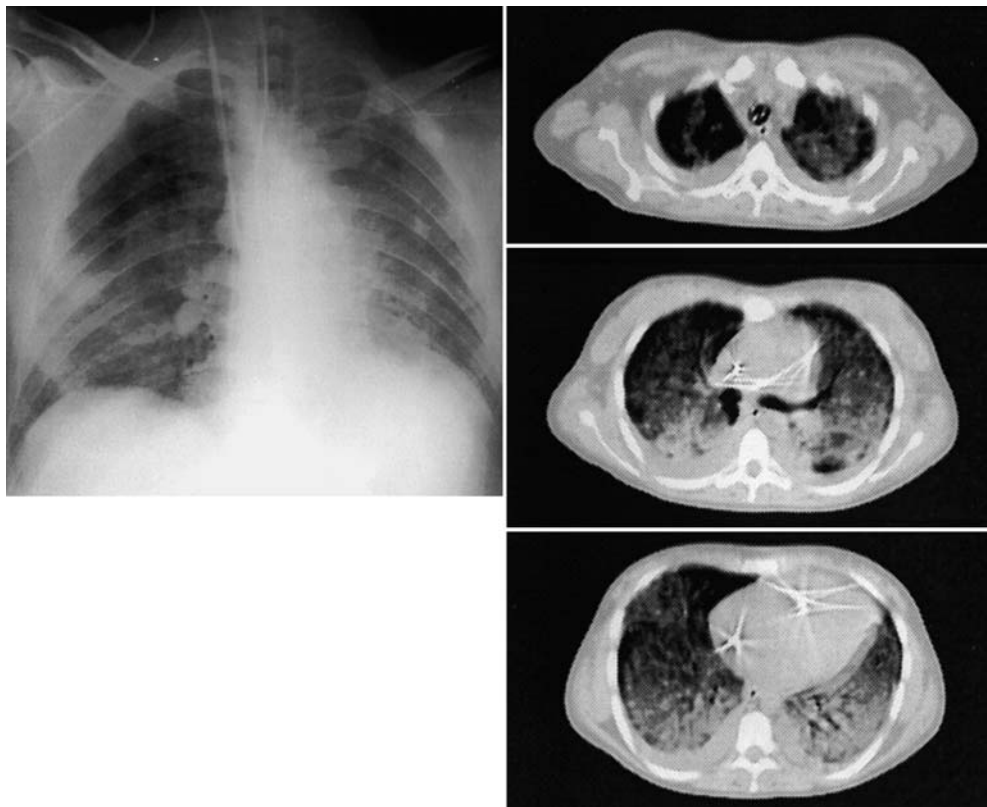
At about the same time, after extensive experimental work showing that it was possible to control breathing by extracorporeal removal of  $\text{CO}_2$  [12, 13, 14], we began to treat severe ARDS patients with this technique [15], the aim being to provide "lung rest" avoiding high-volume/pressure mechanical ventilation [16]. With this technique we could dissociate  $\text{CO}_2$  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  $\text{CO}_2$  removal the gas exchange targets were again, as in the early 1970s, normal  $\text{PCO}_2$  and normal  $\text{PO}_2$ .

## 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<sub>2</sub>O 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])

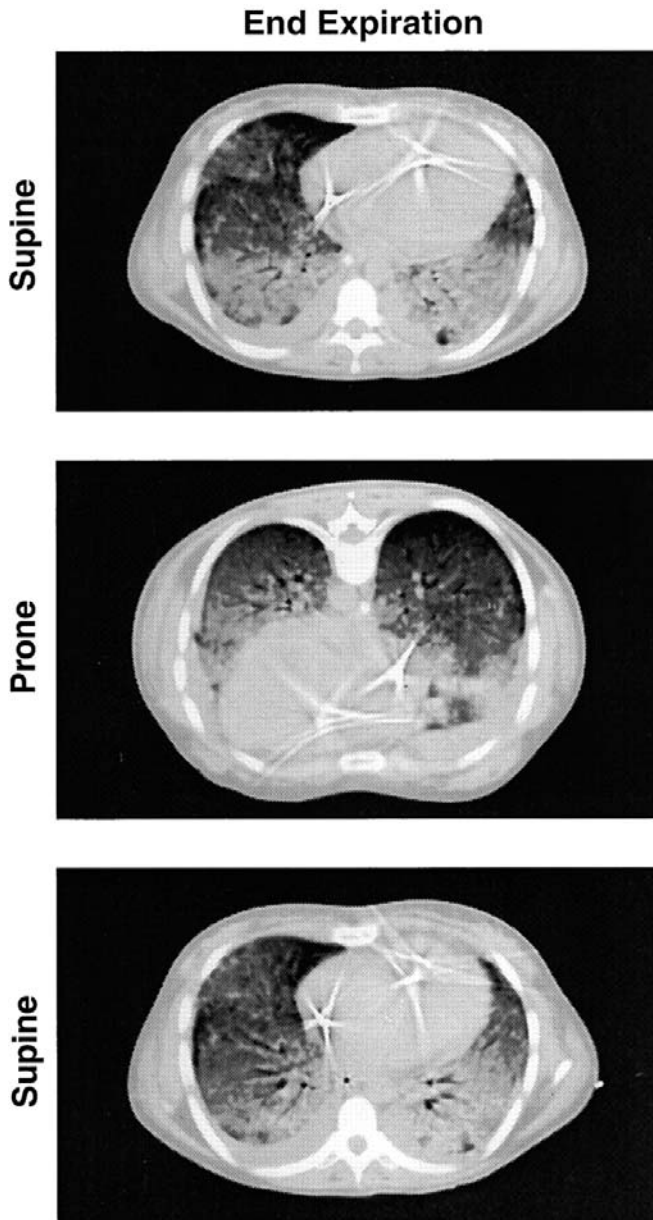


**Fig. 2** Starting compliance ( $C_{start}$ ) as a function of residual inflated lung expressed as percentage of the expected normal lung volume. (Redrawn from Gattinoni et al. [22])

[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<sub>2</sub>O (“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<sub>2</sub>O 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].

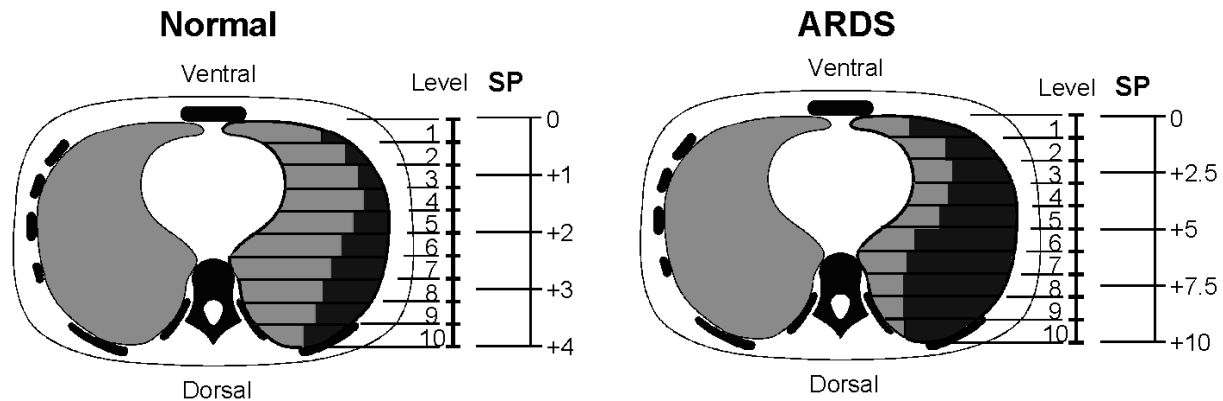
This model, which Bone [34] called “sponge lung,” accounts, although not completely, for the redistribution of the lung densities in prone position: the superimposed hydrostatic pressure is reversed, and the ventral regions instead of the dorsal are compressed [35]. The sponge lung also partly explains 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 ( $SP$ ;  $\text{cmH}_2\text{O}$ ), which in turn leads to a “gas squeezing” from the most dependent lung regions. Superimposed pressure is expressed as  $\text{cmH}_2\text{O}$ . (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  $\text{cmH}_2\text{O}$  of airway pressure. Some lung regions, however—usually the most dependent—may require opening pressure up to 45  $\text{cmH}_2\text{O}$ . It follows that during inspiration new tissue continuously opens to the plateau pressure. Of course, if the plateau pressure is limited, say, to 25  $\text{cmH}_2\text{O}$ , 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

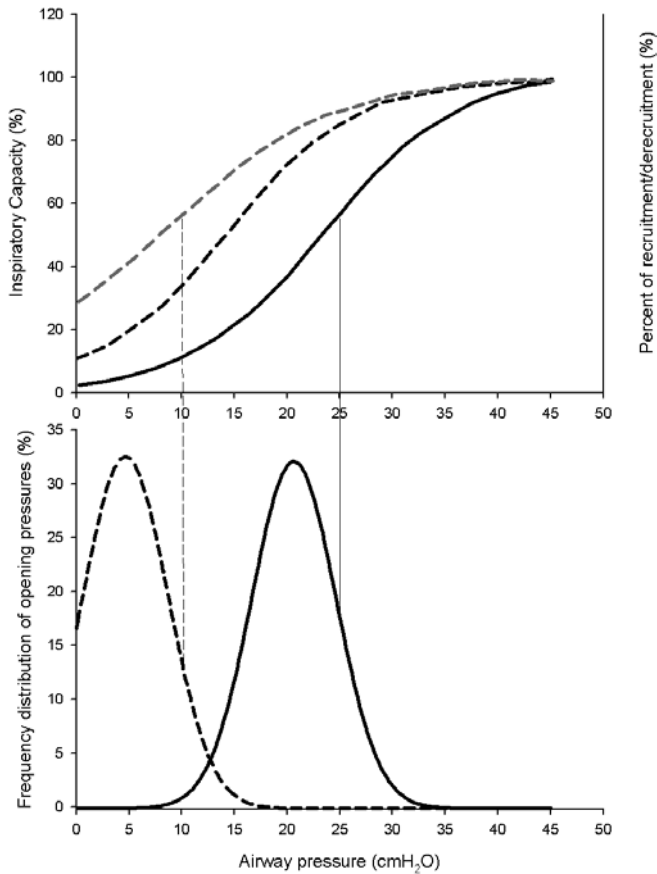
As discussed above, the concept of “baby lung” fully justified the goal of lung rest. With extracorporeal  $\text{CO}_2$  removal we were able to fully provide lung rest, but at the price of the side effects of extracorporeal circulation (primarily bleeding). In the 1990s Hickling et al. [46] introduced 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  $\text{PCO}_2$  [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<sub>2</sub>O (solid line) and PEEP 10 cmH<sub>2</sub>O (dashed line). At 25 cmH<sub>2</sub>O airway pressure nearly 60% inspiratory capacity, 40% of lung units are still closed. At 10 cmH<sub>2</sub>O 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 ( $\Delta L$ ) 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:  $stress = K \times strain$ , 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”

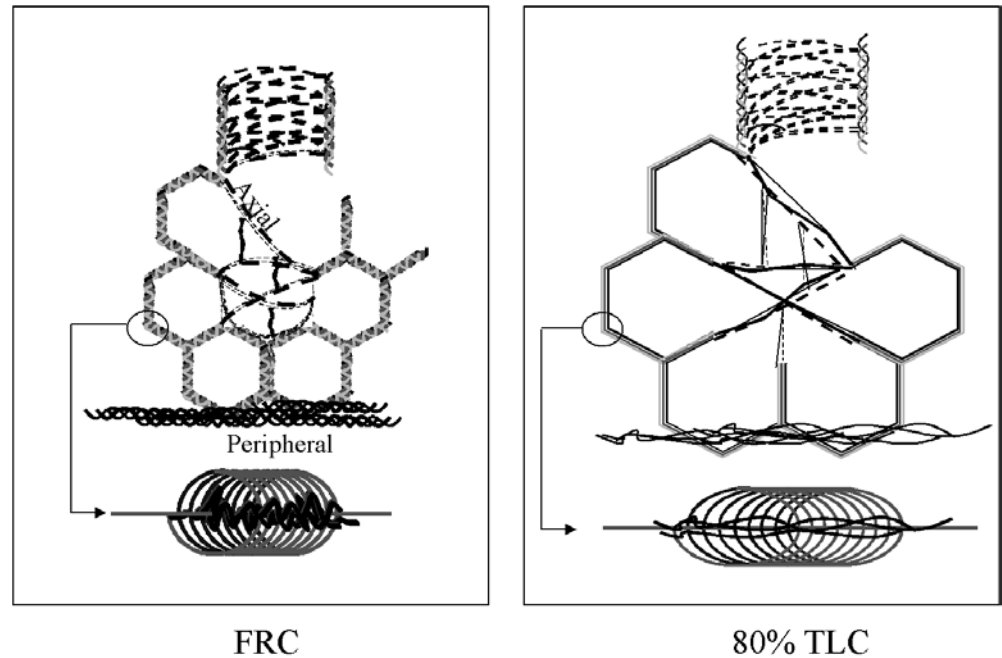
From this perspective, VILI is nothing more than the global/regional excessive stress and strain applied to the “baby lung.” The rough equivalent of the stress in the whole lung is the PL, while the equivalent of the strain is the change in the size of the lung from its resting position, i.e., the ratio of  $V_T$  to the size of the “baby lung” at end-expiration (ZEEP):  $PL$  (i.e. stress) =  $K \times [(V_T/baby\ lung)]$  (i.e. strain). The link between stress and strain,  $K$ , is the specific lung elastance ( $E_{spec} = PL/V_T \times “baby\ lung”$ ), 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 ( $V_T/\text{end-expiratory lung volume} = 1$ ) most of the collagen fibers are unfolded, and PL equals the specific elastance, which is normally 12.5 cmH<sub>2</sub>O. 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<sub>2</sub>O).

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<sub>2</sub>O and 2.1], [13.1 cmH<sub>2</sub>O 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<sub>2</sub>O 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:  $PL = E_{spec} \times (V_T / \text{baby lung})$ . The final message is straightforward: Treat the “baby lung” gently. Low PL, low  $V_T$ , and prone position are the means to hand today.

**Acknowledgements** We cannot list individually, but we are deeply indebted to the hundreds of incredible persons who have worked, contributed, and discussed with us over the past 30 years. Without them we could not have reached any result, great or small. Intensive care is founded not only on a “great idea” but on near-paranoid attention to detail and understanding of the minute-by-minute changes in patients’ physiology.

## References

1. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE (1967) Acute respiratory distress in adults. *Lancet* II:319–323
2. Gattinoni L, Pesenti A (1987) ARDS: the non-homogeneous lung; facts and hypothesis. *Intensive Crit Care Dig* 6:1–4
3. Pontoppidan H, Geffin B, Lowenstein E (1972) Acute respiratory failure in the adult. III. *N Engl J Med* 287:799–806
4. Kumar A, Pontoppidan H, Falke KJ et al (1973) Pulmonary barotrauma during mechanical ventilation. *Crit Care Med* 1:181–186
5. Baeza OR, Wagner RB, Lowery BD (1975) Pulmonary hyperinflation. A form of barotrauma during mechanical ventilation. *J Thorac Cardiovasc Surg* 70:790–805

6. Falke KJ, Pontoppidan H, Kumar A et al (1972) Ventilation with end-expiratory pressure in acute lung disease. *J Clin Invest* 51:2315–2323
7. Suter PM, Fairley B, Isenberg MD (1975) Optimum end-expiratory airway pressure in patients with acute pulmonary failure. *N Engl J Med* 292:284–289
8. Lemaire F, Harf A, Simonneau G et al (1981) [Gas exchange, static pressure-volume curve and positive-pressure ventilation at the end of expiration. Study of 16 cases of acute respiratory insufficiency in adults]. *Ann Anesthesiol Fr* 22:435–441
9. Kirby RR, Downs JB, Civetta JM et al (1975) High level positive end expiratory pressure (PEEP) in acute respiratory insufficiency. *Chest* 67:156–163
10. Hill JD, O'Brien TG, Murray JJ et al (1972) Prolonged extracorporeal oxygenation for acute post-traumatic respiratory failure (shock-lung syndrome). Use of the Bramson membrane lung. *N Engl J Med* 286:629–634
11. Zapol WM, Snider MT, Hill JD et al (1979) Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomized prospective study. *JAMA* 242:2193–2196
12. Kolobow T, Gattinoni L, Tomlinson TA, Pierce JE (1977) Control of breathing using an extracorporeal membrane lung. *Anesthesiology* 46:138–141
13. Kolobow T, Gattinoni L, Tomlinson T, Pierce JE (1978) An alternative to breathing. *J Thorac Cardiovasc Surg* 75:261–266
14. Gattinoni L, Kolobow T, Tomlinson T et al (1978) Control of intermittent positive pressure breathing (IPPB) by extracorporeal removal of carbon dioxide. *Br J Anaesth* 50:753–758
15. Gattinoni L, Agostoni A, Pesenti A et al (1980) Treatment of acute respiratory failure with low-frequency positive-pressure ventilation and extracorporeal removal of CO<sub>2</sub>. *Lancet* II:292–294
16. Gattinoni L, Pesenti A, Mascheroni D et al (1986) Low-frequency positive-pressure ventilation with extracorporeal CO<sub>2</sub> removal in severe acute respiratory failure. *JAMA* 256:881–886
17. Rommelsheim K, Lackner K, Westhofen P et al (1983) [Respiratory distress syndrome of the adult in the computer tomograph]. *Anasth Intensivther Notfallmed* 18:59–64
18. Maunder RJ, Shuman WP, McHugh JW et al (1986) Preservation of normal lung regions in the adult respiratory distress syndrome. Analysis by computed tomography. *JAMA* 255:2463–2465
19. Gattinoni L, Mascheroni D, Torresin A et al (1986) Morphological response to positive end expiratory pressure in acute respiratory failure. Computerized tomography study. *Intensive Care Med* 12:137–142
20. Gattinoni L, Caironi P, Pelosi P, Goodman LR (2001) What has computed tomography taught us about the acute respiratory distress syndrome? *Am J Respir Crit Care Med* 164:1701–1711
21. Gattinoni L, Pesenti A, Avalli L et al (1987) Pressure-volume curve of total respiratory system in acute respiratory failure. Computed tomographic scan study. *Am Rev Respir Dis* 136:730–736
22. Gattinoni L, Pesenti A, Baglioni S et al (1988) Inflammatory pulmonary edema and positive end-expiratory pressure: correlations between imaging and physiologic studies. *J Thorac Imaging* 3:59–64
23. Gattinoni L, D'Andrea L, Pelosi P et al (1993) Regional effects and mechanism of positive end-expiratory pressure in early adult respiratory distress syndrome. *JAMA* 269:2122–2127
24. Dreyfuss D, Soler P, Basset G, Saumon G (1988) High inflation pressure pulmonary edema. Respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. *Am Rev Respir Dis* 137:1159–1164
25. Langer M, Mascheroni D, Marcolin R, Gattinoni L (1988) The prone position in ARDS patients. A clinical study. *Chest* 94:103–107
26. Gattinoni L, Pelosi P, Vitale G et al (1991) Body position changes redistribute lung computed-tomographic density in patients with acute respiratory failure. *Anesthesiology* 74:15–23
27. Pelosi P, D'Andrea L, Vitale G et al (1994) Vertical gradient of regional lung inflation in adult respiratory distress syndrome. *Am J Respir Crit Care Med* 149:8–13
28. Jones T, Jones HA, Rhodes CG et al (1976) Distribution of extravascular fluid volumes in isolated perfused lungs measured with H<sub>2</sub>15O. *J Clin Invest* 57:706–713
29. Hales CA, Kanarek DJ, Ahluwalia B et al (1981) Regional edema formation in isolated perfused dog lungs. *Circ Res* 48:121–127
30. Sandiford P, Province MA, Schuster DP (1995) Distribution of regional density and vascular permeability in the adult respiratory distress syndrome. *Am J Respir Crit Care Med* 151:737–742
31. Quintel M, Pelosi P, Caironi P et al (2004) An increase of abdominal pressure increases pulmonary edema in oleic acid-induced lung injury. *Am J Respir Crit Care Med* 169:534–541
32. Albert RK, Hubmayr RD (2000) The prone position eliminates compression of the lungs by the heart. *Am J Respir Crit Care Med* 161:1660–1665
33. Malbouissin LM, Busch CJ, Puybasset L et al (2000) Role of the heart in the loss of aeration characterizing lower lobes in acute respiratory distress syndrome. CT Scan ARDS Study Group. *Am J Respir Crit Care Med* 161:2005–2012
34. Bone RC (1993) The ARDS lung. New insights from computed tomography. *JAMA* 269:2134–2135
35. Gattinoni L, Pelosi P, Valenza F, Mascheroni D (1994) Patient positioning in acute respiratory failure. In: Tobin MJ (ed) *Principle and practice of mechanical ventilation*. McGraw-Hill, New York, pp 1067–1076
36. Pelosi P, Goldner M, McKibben A et al (2001) Recruitment and derecruitment during acute respiratory failure: an experimental study. *Am J Respir Crit Care Med* 164:122–130
37. Martynowicz MA, Minor TA, Walters BJ, Hubmayr RD (1999) Regional expansion of oleic acid-injured lungs. *Am J Respir Crit Care Med* 160:250–258
38. Wilson TA, Anafi RC, Hubmayr RD (2001) Mechanics of edematous lungs. *J Appl Physiol* 90:2088–2093
39. Gattinoni L, Pelosi P, Suter PM et al (1998) Acute respiratory distress syndrome caused by pulmonary and extrapulmonary disease. Different syndromes? *Am J Respir Crit Care Med* 158:3–11
40. Ranieri VM, Brienza N, Santostasi S et al (1997) Impairment of lung and chest wall mechanics in patients with acute respiratory distress syndrome: role of abdominal distension. *Am J Respir Crit Care Med* 156:1082–1091
41. Goodman LR, Fumagalli R, Tagliabue P et al (1999) Adult respiratory distress syndrome due to pulmonary and extrapulmonary causes: CT, clinical, and functional correlations. *Radiology* 213:545–552
42. Desai SR, Wells AU, Suntharalingam G et al (2001) Acute respiratory distress syndrome caused by pulmonary and extrapulmonary injury: a comparative CT study. *Radiology* 218:689–693
43. Gattinoni L, Pelosi P, Crotti S, Valenza F (1995) Effects of positive end-expiratory pressure on regional distribution of tidal volume and recruitment in adult respiratory distress syndrome. *Am J Respir Crit Care Med* 151:1807–1814
44. Crotti S, Mascheroni D, Caironi P et al (2001) Recruitment and derecruitment during acute respiratory failure: a clinical study. *Am J Respir Crit Care Med* 164:131–140



45. Jonson B, Richard JC, Straus C et al (1999) Pressure-volume curves and compliance in acute lung injury: evidence of recruitment above the lower inflection point. *Am J Respir Crit Care Med* 159:1172–1178
46. Hickling KG, Henderson SJ, Jackson R (1990) Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome. *Intensive Care Med* 16:372–377
47. Darioli R, Perret C (1984) Mechanical controlled hypoventilation in status asthmaticus. *Am Rev Respir Dis* 129:385–387
48. Pesenti A (1990) Target blood gases during ARDS ventilatory management. *Intensive Care Med* 16:349–351
49. Gattinoni L, Carlesso E, Cadringher P et al (2003) Physical and biological triggers of ventilator-induced lung injury and its prevention. *Eur Respir J Suppl* 47:15s–25s
50. Weibel ER (1986) Functional morphology of lung parenchyma. In: American Physiological Society (ed) *Handbook of physiology a critical, comprehensive presentation of physiological knowledge and concepts*. Waverly, Baltimore, pp 89–111
51. Wilson TA (1986) Solid mechanics. In: American Physiological Society (ed) *Handbook of physiology a critical, comprehensive presentation of physiological knowledge and concepts*. Waverly, Baltimore, pp 35–39
52. Dos Santos CC, Slutsky AS (2000) Invited review: mechanisms of ventilator-induced lung injury: a perspective. *J Appl Physiol* 89:1645–1655
53. Pugin J, Dunn I, Jolliet P et al (1998) Activation of human macrophages by mechanical ventilation in vitro. *Am J Physiol* 275:L1040–L1050
54. Edwards YS (2001) Stretch stimulation: its effects on alveolar type II cell function in the lung. *Comp Biochem Physiol A Mol Integr Physiol* 129:245–260
55. Vlahakis NE, Hubmayr RD (2000) Invited review: plasma membrane stress failure in alveolar epithelial cells. *J Appl Physiol* 89:2490–2496
56. Vlahakis NE, Hubmayr RD (2003) Response of alveolar cells to mechanical stress. *Curr Opin Crit Care* 9:2–8
57. Vlahakis NE, Schroeder MA, Pagano RE, Hubmayr RD (2001) Deformation-induced lipid trafficking in alveolar epithelial cells. *Am J Physiol Lung Cell Mol Physiol* 280:L938–L946
58. Liu M, Tanswell AK, Post M (1999) Mechanical force-induced signal transduction in lung cells. *Am J Physiol* 277:L667–L683
59. Uhlig S (2002) Ventilation-induced lung injury and mechanotransduction: stretching it too far? *Am J Physiol Lung Cell Mol Physiol* 282:L892–L896
60. Pugin J (2003) Molecular mechanisms of lung cell activation induced by cyclic stretch. *Crit Care Med* 31:S200–S206
61. Haseneen NA, Vaday GG, Zucker S, Foda HD (2003) Mechanical stretch induces MMP-2 release and activation in lung endothelium: role of EMMPRIN. *Am J Physiol Lung Cell Mol Physiol* 284:L541–L547
62. Yamamoto H, Teramoto H, Uetani K et al (2002) Cyclic stretch upregulates interleukin-8 and transforming growth factor-beta1 production through a protein kinase C-dependent pathway in alveolar epithelial cells. *Respirology* 7:103–109
63. Vlahakis NE, Schroeder MA, Limper AH, Hubmayr RD (1999) Stretch induces cytokine release by alveolar epithelial cells in vitro. *Am J Physiol* 277:L167–L173
64. Belperio JA, Keane MP, Burdick MD et al (2002) Critical role for CXCR2 and CXCR2 ligands during the pathogenesis of ventilator-induced lung injury. *J Clin Invest* 110:1703–1716
65. Acute Respiratory Distress Syndrome Network (2000) Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 342:1301–1308
66. Valenza F, Guglielmi M, Maffioletti M et al (2005) Prone position delays the progression of ventilator-induced lung injury in rats: does lung strain distribution play a role? *Crit Care Med* 33:361–367
67. Weibel ER (1984) *The pathway for oxygen structure and function in the mammalian respiratory system*. Harvard University Press, Cambridge