

Pulmonary and Extrapulmonary Forms of Acute Respiratory Distress Syndrome

Paolo Pelosi, M.D.,¹ Pietro Caironi, M.D.,² and Luciano Gattinoni, M.D.²

ABSTRACT

Acute respiratory distress syndrome (ARDS) is usually viewed as the functional and morphological expression of a similar underlying lung injury caused by a variety of insults. However, the distinction between ARDS due to a *direct* (ARDS_p) versus an *indirect* (ARDS_{exp}) lung injury is gaining more attention as a means of better comprehending the pathophysiology of ARDS and for modifying ventilatory management. From the few published studies, we can summarize that: (1) the prevalent damage in early stages of a direct insult is intra-alveolar, whereas in indirect injury it is the interstitial edema. It is possible that the two insults may coexist (i.e., one lung with direct injury (as in pneumonia) and the other with indirect injury, through mediator release from the contralateral pneumonia); (2) the radiological pattern, by chest x-ray or computed tomography (CT), is different in ARDS_p (characterized by prominent consolidation) and ARDS_{exp} (characterized by prominent ground-glass opacification); (3) in ARDS_p lung elastance is more markedly increased than in ARDS_{exp}, where the main abnormality is the increase in chest wall elastance, due to abnormally high intra-abdominal pressure; (4) positive end-expiratory pressure (PEEP), inspiratory recruitment, and prone position are more effective to improve respiratory mechanics, alveolar recruitment, and gas-exchange in ARDS_{exp}. Further studies are warranted to better define if the distinction between ARDS of different origins can improve clinical management and survival.

KEYWORDS: Acute respiratory distress syndrome, pulmonary pneumonia, extrapulmonary pneumonia

Objectives: Upon completion of this article, the reader will be able to (1) define pulmonary and extrapulmonary ARDS; (2) describe and discuss possible differences in pathophysiology, lung morphology, and respiratory mechanics between pulmonary and extrapulmonary ARDS; and (3) discuss possible differences in clinical and ventilatory management of ARDS of different origins.

Accreditation: The University of Michigan is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

Credit: The University of Michigan designates this educational activity for a maximum of 1.0 hours in category one credit toward the AMA Physicians Recognition Award.

Seminars in Respiratory and Critical Care Medicine, volume 22, number 3, 2001. Reprint requests: Paolo Pelosi, M.D., Dipartimento di Scienze Cliniche e Biologiche, Università degli Studi dell'Insubria, viale Borri 57, 21100, Varese, Italy. E-mail: paolopelosi@hotmail.com. ¹Dipartimento di Scienze Cliniche e Biologiche, Università degli Studi dell'Insubria, Varese; Ospedale di Circolo, Fondazione Macchi, Varese, Italy; ²Istituto di Anestesia e Rianimazione, Università degli Studi di Milano, Ospedale Maggiore di Milano - IRCCS, Milano, Italy. Copyright © 2001 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel: +1(212) 584-4662. 1069-3424,p;2001,22,03,259,268,ftx,en; srm00079x.

Since its initial description, the acute respiratory distress syndrome (ARDS) has been considered a morphological and functional expression of a similar underlying lung injury caused by a variety of insults. In fact, Ashbaugh and colleagues¹ in defining this syndrome stated that "[. . .] The aetiology of this respiratory-distress syndrome remains obscure. Despite a variety of physical and possibly biochemical insults, the response of the lung was similar in all 12 patients. [. . .] In view of the similar response of the lung to a variety of stimuli, a common mechanism of injury may be postulated. [. . .]"

These observations used the term *syndrome* to refer to "a group of symptoms and signs of disordered function related to one another by means of some anatomic, physiologic, or biochemical peculiarity."²

In 1994, the American-European Consensus Conference³ defined two pathogenetic pathways leading to ARDS: a *direct* ("primary" or "pulmonary") insult, that directly affects lung parenchyma, and an *indirect* ("secondary" or "extrapulmonary") insult, that results from an acute systemic inflammatory response. The differentiation between direct and indirect insult is often straightforward as for primary diffuse pneumonia or ARDS originating from intra-abdominal sepsis. In other situations, the precise identification of the pathogenetic pathway is somewhat questionable, as for trauma, cardiac surgery, and the like. The distinction, however, was mainly speculative until Gattinoni and colleagues⁴ reported possible differences in the underlying pathology, respiratory mechanics, and response to positive end-expiratory pressure (PEEP) in pulmonary ARDS (ARDS_p, primarily pneumonia) and extrapulmonary ARDS (ARDS_{exp}, primarily from abdominal disease). Since then, the distinction between ARDS_p and ARDS_{exp} has garnered attention, and an increasing number of papers on this subject have appeared in the scientific literature.⁵⁻⁸

In this review, we summarize what we know about the possible differences in the (1) pathophysiology, (2) lung morphology, (3) respiratory mechanics, and (4) response to different mechanical ventilation strategies (PEEP, alveolar recruitment, and prone position) in ARDS of different origins.

EPIDEMIOLOGY

ARDS occurs following a variety of risk factors.⁹ The strongest evidence supporting a cause-and-effect relationship between ARDS and a risk factor was identified for sepsis, trauma, multiple transfusions, aspiration of gastric contents, pulmonary contusion, pneumonia, and smoke inhalation. The weakest evidence was identified for disseminated intravascular coagulation, fat embolism, and cardiopulmonary bypass. Very few studies have investigated the prevalence and mortality using the categories ARDS_p and ARDS_{exp}. In the majority of available studies the prevalence of ARDS_p was higher and the mortal-

ity similar in both groups.^{5,6,10-12} Other studies reported an increased prevalence¹³⁻¹⁵ and mortality¹⁴ of ARDS_{exp}. Moreover, it has been reported that pulmonary trauma was associated with higher survival rate, whereas opportunistic pneumonia had a lower survival rate.^{13,14} Among complications, acute renal failure, pulmonary infection, and bacteremia seem to be independent factors associated with increased mortality.¹⁶ The lack of agreement among various studies can be explained by differences in (1) baseline status, (2) the prevalence of the disease precipitating ARDS in each center, (3) the impact of therapy, and (4) the overall distribution of these factors in the studied population. Thus, we do not know if a different clinical management and ventilatory treatment modified in accord with different pathophysiological characteristics could improve outcome. In our opinion, the distinction between ARDS_p and ARDS_{exp} should not be focused, at the moment, on possible differences in morbidity and mortality. It is more important to first understand if this distinction is truly large and carries major implications for clinical management. If it does, further studies on morbidity and mortality would be reasonable once differences in clinical strategy were clarified.

PATHOPHYSIOLOGY

The alveolar-capillary barrier is formed by two different structures, the vascular endothelium and the alveolar epithelium. Traditionally, it has been thought that insults applied to the lung, through the airways or the circulation, result in diffuse alveolar damage. Although many insults may converge in the late stage of ARDS, we wonder if, in early stages, a direct or indirect insult to the lung may have different manifestations.¹⁷

Direct Insult

A direct insult has been studied in experimental models by using intratracheal instillation of endotoxin,¹⁸ complement,¹⁹ tumor necrosis factor,²⁰ or bacteria.²¹ After a direct insult, the primary structure injured is the alveolar epithelium. This causes an activation of alveolar macrophages and of the inflammatory network, leading to intrapulmonary inflammation. The prevalence of the epithelial damage determines a localization of the pathological abnormality in the intra-alveolar space, with alveolar filling by edema, fibrin, collagen, neutrophilic aggregates, and/or blood, and is often described as pulmonary consolidation. Possible clinical causes of direct lung injury are shown in Table 1.

Indirect Insult

An indirect insult has been studied in experimental models by intravenous²² or intraperitoneal²³ toxic injection. After an indirect insult, the lung injury originates

from the action of inflammatory mediators released from extrapulmonary foci into the systemic circulation. In this case, the first target of damage is the pulmonary vascular endothelial cell, with an increase of vascular permeability and recruitment of monocytes, polymorphonuclear leukocytes, platelets, and other cells. Thus, the pathological alteration due to an indirect insult is primarily microvascular congestion and interstitial edema, with relative sparing of the intra-alveolar spaces. Possible clinical causes of indirect lung injury are shown in Table 1.

These experimental findings suggest that damage in the early stage of direct insults is primarily intra-alveolar, whereas in indirect injuries interstitial edema is most prominent. However, it is worth noting the possible coexistence of the two insults: one lung with direct injury (as pneumonia) and the other with indirect injury (through mediator release from the original pneumonia).²⁴

MORPHOLOGICAL ASPECTS

In recent years, a number of studies have identified differences by chest x-ray and computed tomography (CT) between ARDSp and ARDSexp.

Chest X-ray

We retrospectively scored the chest x-rays, performed in a standardized way, in 21 ARDS patients (9 ARDSp and 12 ARDSexp), to identify the amount of "hazy" and "diffuse" lung densities—likely representing interstitial

edema and compression atelectasis—and "patchy" densities—likely representing pulmonary consolidations.⁵ Patients with ARDSp presented an increased amount of patchy densities compared with patients with ARDSexp, whereas the amount of hazy and extensive densities was similar in both groups. No significant differences were found between the right and the left lung. Overall the lung injury severity scores were significantly higher in patients with ARDSp.

CT Scan

Several studies have analyzed lung morphology by CT evaluation of part of the lung^{6,25-27} or the whole lung.²⁸ As a reference, we present representative lung CT scans, taken at end-expiration at 0 cmH₂O PEEP, of a normal subject spontaneously breathing (Fig. 1) and during general anesthesia and paralysis (Fig. 2). In these settings, the appearance of limited densities in the dependent part of the lung is quite limited.

Goodman and colleagues⁶ studied 33 ARDS patients (22 ARDSp and 11 ARDSexp) by performing three representative scans at the apex (top of the upper aortic arch), at the hilum (first section below the carina), and at the base (2 cm above the highest diaphragm). The ventilatory setting was not standardized during scans. The lung was scored as follows: "normal lung," "ground-glass opacification" (mild increased attenuation with visible vessels), and "consolidation" (markedly increased attenuation with no visible vessels). They found that in ARDSexp, ground-glass opacification was more than twice as extensive as consolidation (Fig. 3). This contrasted markedly with ARDSp, in which there was an even balance between ground-glass

Table 1 Major Categories of Pulmonary and Extrapulmonary ARDS

- | |
|---|
| I. Direct injury (pulmonary ARDS) |
| A. Aspiration |
| B. Diffuse pulmonary infection (i.e. bacterial, viral, <i>Pneumocystis</i> , others) |
| C. Near-drowning |
| D. Toxic inhalation |
| E. Lung contusion |
| II. Indirect injury (extrapulmonary ARDS) |
| A. Sepsis syndrome, with or without clinically significant hypotension, with or without evidence of infection outside the lung. |
| B. Severe non-thoracic trauma as indicated by: |
| 1) Clinical description |
| 2) Scoring systems such as the injury severity score (ISS) or Apache II/III |
| 3) Treatment interventions, such as the Treatment Intervention Scoring System (TISS) |
| C. Hypertransfusion for emergency resuscitation |
| D. Cardiopulmonary bypass (rare) |
| E. Pancreatitis |

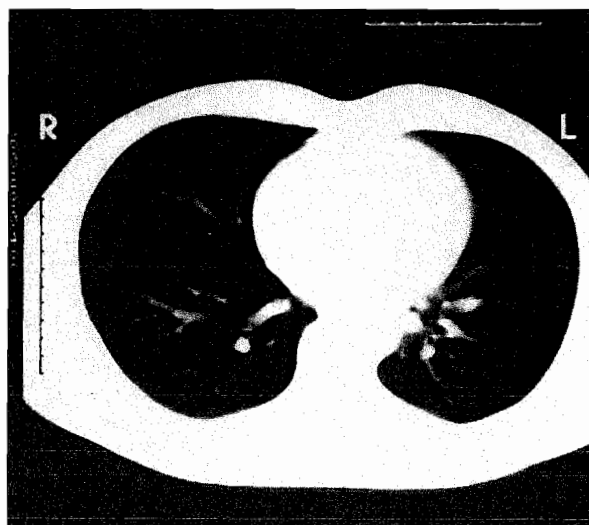


Figure 1 Representative lung computed tomography scan, at end-expiration, of a normal subject breathing spontaneously. Note the fully aerated lung and the absence of any densities throughout the parenchyma.

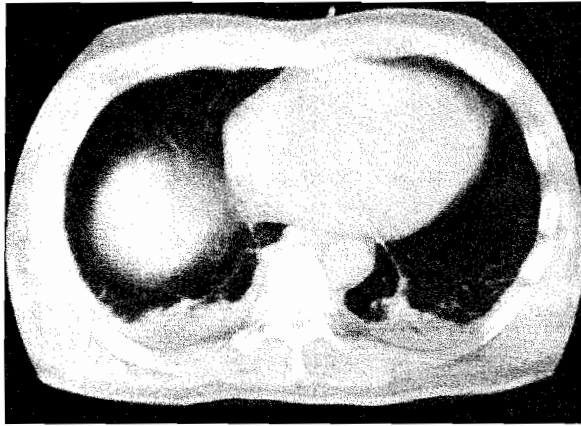


Figure 2 Representative lung computed tomography scan, at end-expiration, of a normal subject during general anesthesia and paralysis. Note the presence of small densities in the dependent part of the lung.

opacification and consolidation (Fig. 4). When the type of opacification between the two groups was compared, the patients with ARDSexp had 40% more ground-glass opacification than did those with ARDSp. Conversely, the ARDSp patients had over 50% more consolidation than did those with ARDSexp. The authors found also differences in the regional distribution of the densities. In ARDSexp ground-glass opacification was greater in the central (hilar) third of the lung than in the sternal or vertebral third. There was no significant craniocaudal predominance for ground-glass opacification or consolidation, but consolidation showed a preference for the vertebral position over the sternal and central positions. In ARDSexp ground-glass opacification was evenly distributed in both the craniocaudal and sternal-vertebral directions. Consolidation tended to favor the middle and basal levels, but also favored the vertebral

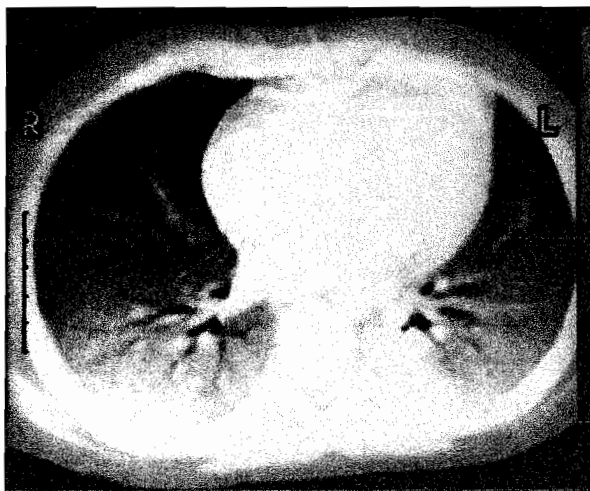


Figure 3 Representative lung computed tomography scan, at end-expiration, of a patient with ARDSexp due to sepsis. There is a predominantly ground-glass opacification.

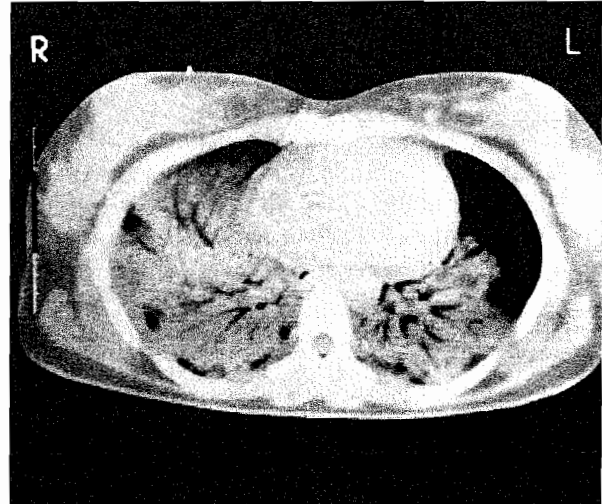


Figure 4 Representative lung computed tomography scan, at end-expiration, of a patient with ARDSp, due to community-acquired streptococcus pneumonia, showing extensive consolidation, with an approximately equal amount of normal lung and ground-glass opacification and air bronchograms.

position. The total lung disease was almost evenly distributed between the left and right lungs in both ARDSp and ARDSexp. However, grossly asymmetric disease was always due to asymmetric consolidation. Moreover, the presence of air bronchograms and pneumomediastinum were prevalent in ARDSp, while emphysema-like lesions (bullae) were comparable in both groups.

Unfortunately, it appears that the word *consolidation* may have different meanings in different contexts. In radiology, consolidation simply means a "marked increase in lung attenuation with no visible vessels," and it may derive from alveolar atelectasis as well as alveolar filling. In pathology, consolidation refers only to alveolar filling.

Similar findings were reported by other authors. D'Angelo and colleagues²⁵ reported homogeneous diffuse interstitial and alveolar infiltration, without evidence of atelectasis, in eight patients with ARDSp due to *Pneumocystis carinii* (Fig. 5), whereas Winer-Muram and colleagues²⁶ found that dependent atelectasis was more common in patients with early ARDSexp compared with ARDSp.

Recently, we investigated by CT scan the morphological lung alterations in 10 patients with head injury, of traumatic and nontraumatic origin, developing severe respiratory insufficiency ($\text{PaO}_2/\text{FiO}_2$ lower than 200 and bilateral infiltrates) within the first week of mechanical ventilation (early onset pneumonia).²⁷ Patients with head injury have been shown to be at particularly high risk of ventilator-associated pneumonia.²⁸ Its incidence is estimated to reach 40 to 50%. The most frequent etiologic agents includes *Staphylococcus aureus*, and less frequently, *Streptococcus pneumoniae* and *Hemophilus in-*



Figure 5 Representative lung computed tomography scan, at end-expiration, of a patient with ARDSp, due to community-acquired *Pneumocystis carinii* pneumonia, with a homogeneous diffuse interstitial and alveolar infiltration, without evidence of atelectasis.

fluenzae.²⁹ The early onset of pulmonary infection and the peculiar microbial pattern may be due to oropharyngeal or gastric colonization followed by high inoculum aspiration of oropharyngeal secretions. Patients may aspirate oropharyngeal secretions shortly after brain injury, during resuscitation, or as a consequence of intubation.³⁰ This represents an excellent "in vivo" model of direct pneumonia (i.e., ARDSp) in humans. The CT scans were classified as by Goodman and colleagues.⁶ We found that all the patients showed consolidation opacities in the dependent part of the lung (Fig. 6A). However, unlike ARDSp originating from community-acquired pneumonia, as in the Goodman study, in nosocomial pneumonia the amount of ground-glass opacification was negligible and the overall disease scores were markedly lower. Thus, it is possible to hypothesize that the patho-

physiology and the lung morphology in ARDSp may be different in community-acquired pneumonia and in nosocomial pneumonia. It is possible that the period of time from the infection and the development of severe respiratory failure (usually within 1 week), can favor some initial diffusion of inflammatory agents, which can explain the presence of moderate amounts of ground-glass opacification in ARDSp from community-acquired pneumonia.³¹ Moreover, the aggressive therapeutic management in nosocomial pneumonia, and thus a potential reduction in release of inflammatory agents in the peripheral circulation, may limit the radiological pattern to consolidation.

Different observations were obtained by Rouby and colleagues in 69 ARDS patients (49 ARDSp and 20 ARDSexp) in whom a CT scan of the whole lung was performed.³² CT densities were classified as consolidations of ground-glass opacification. Consolidation was defined as a homogeneous increase in pulmonary parenchymal attenuation that obscures the margins of the vessels and airway walls. Ground-glass opacities were defined as hazy, increased attenuations of the lung but with preservation of bronchiolar and vascular margins. The patient was classified as having a "lobar" pattern if areas of lung attenuation had a lobar or segmental distribution established on the recognition of anatomical structures such as the major fissure or the interlobular septa, a "diffuse" pattern if lung attenuations were diffusely distributed throughout the lungs, and "patchy" pattern if there were lobar or segmental areas of lung attenuation in some parts of the lungs but lung attenuations without recognized anatomical limits in others. They found that ARDSp was more frequent among patients with diffuse and patchy attenuation,

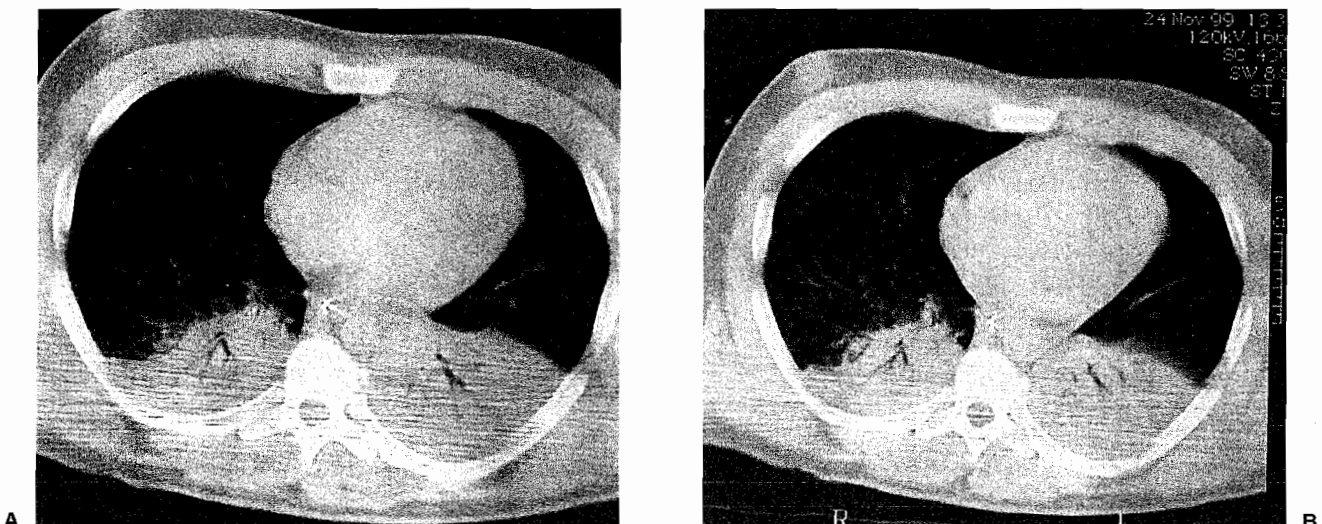


Figure 6 Representative lung computed tomography scan, at end-expiration, at 0 cmH₂O positive end-expiration pressure (PEEP) (A) and at 15 cmH₂O PEEP (B) of a neuro-injured patient with ARDSp due to a nosocomial pneumonia caused by *Pseudomonas aeruginosa*. The lung parenchyma is characterized by extensive consolidations, with air bronchograms in the dependent regions, with normally aerated nondependent ones. Application of PEEP did not result in any alveolar recruitment.

whereas ARDS_{exp} was more common in patients with lobar attenuation.

With all the limits and somewhat arbitrary classification of patients and interpretation of morphological observations, these findings support the hypothesis that the radiological pattern is different in ARDS_p and ARDS_{exp}. We can conclude that (1) in ARDS, the increase in the lung densities is most prominent in the dependent lung regions in the supine position but may, in a minority of patients, be more homogeneously distributed throughout the lung parenchyma; (2) in ARDS_p, due to community-acquired pneumonia, two prevalent patterns have been described: (a) extensive consolidation and air bronchograms in the dependent part of the lung together with ground-glass opacification, or (b) homogeneous diffuse interstitial and alveolar infiltration, without evidence of atelectasis; (3) in ARDS_p, due to nosocomial pneumonia, clear consolidation of the dependent part of the lung is seen, with the remaining lung substantially normal; and (4) in ARDS_{exp}, there is a predominantly ground-glass opacification.

RESPIRATORY MECHANICS

Traditionally, the mechanical alterations of the respiratory system observed during ARDS were attributed to the lung because the chest wall elastance was considered nearly normal.³³ Studies in which respiratory system, lung, and chest wall mechanics were partitioned, have proved this assumption wrong. We consistently found that the elastance of the respiratory system was similar in ARDS_p and ARDS_{exp}, but the elastance of the lung was higher in ARDS_p, indicating a stiffer lung (Fig. 7).⁴ Conversely, the elastance of the chest wall was more than twofold higher in ARDS_{exp} than in ARDS_p, indicating a stiffer chest wall. The increase in the elastance of the chest wall was related to an increase in the intra-abdominal pressure, which was threefold greater in ARDS_{exp}. In critically ill patients, data on intra-abdominal pressure are surprisingly scanty. In most of our patients, the elevated values could be explained by primary abdominal disease or edema of the gastrointestinal tract. Figure 8 shows the sonographic findings of the abdomen in a normal spontaneously breathing subject (A), in a patient with ARDS_{exp} due to abdominal sepsis (B), and in a patient with ARDS_p due to *Legionella pneumonia* (C). In the normal subject it is difficult to recognize the abdominal wall and the gut anatomical structures. In the patient with ARDS_{exp} and related abdominal problems, the increased dimensions and thickness of the gut, with intraluminal debris and fluid and with reduced peristaltic movements, are visible. In the patient with ARDS_p, the dimensions of the gut are slightly increased while the gut wall thickness is not increased, without any consistent debris or

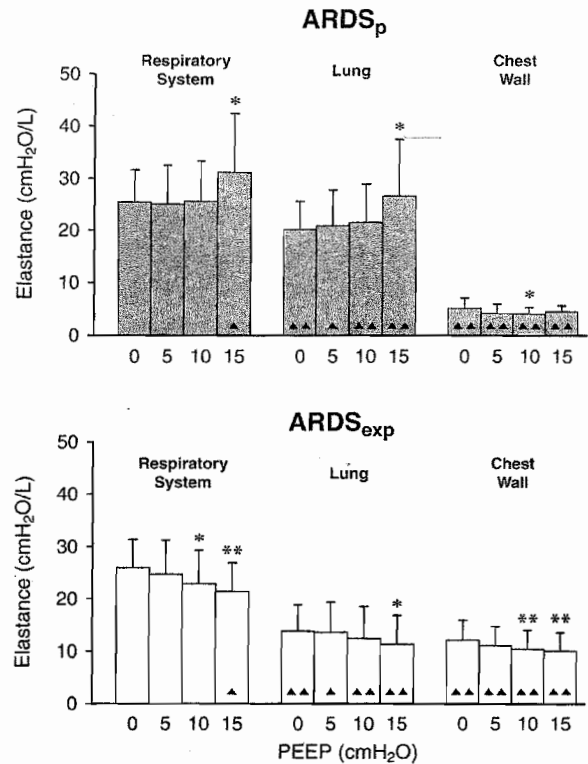


Figure 7 Static elastances of the total respiratory system, lung, and chest wall and their modifications with positive end-expiratory pressure (PEEP) in patients with ARDS_p and ARDS_{exp} (modified from⁴).

fluid. Thus, it is evident that patients with abdominal problems present important anatomical alterations of the gut, which can explain the increased intra-abdominal pressure. Thus these findings suggest that in ARDS the increased elastance of the respiratory system is produced by two different mechanisms: in ARDS_p a high elastance of the lung is the major component, whereas in ARDS_{exp} increased elastance of the lung and of the chest wall equally contributed to the high elastance of the respiratory system. Moreover, we found that respiratory resistance, partitioned into its airway and viscoelastic components, was comparable in ARDS_p and ARDS_{exp}. However, the resistance of the chest wall was also elevated in ARDS_{exp} and significantly correlated to intra-abdominal pressure, suggesting that intra-abdominal pressure can affect the viscoelastic properties of the thoracoabdominal region.

Altered lung elastance with relatively normal chest wall elastance was also found in patients affected by severe *Pneumocystis carinii* pneumonia,²⁵ and in patients with nosocomial pneumonia²⁷ that usually present the same histopathology as ARDS_p.

All these data suggest, in agreement with recent work,^{34,35} the importance of respiratory partitioning for a better characterization of the pathology underlying ARDS and an improvement in clinical management.

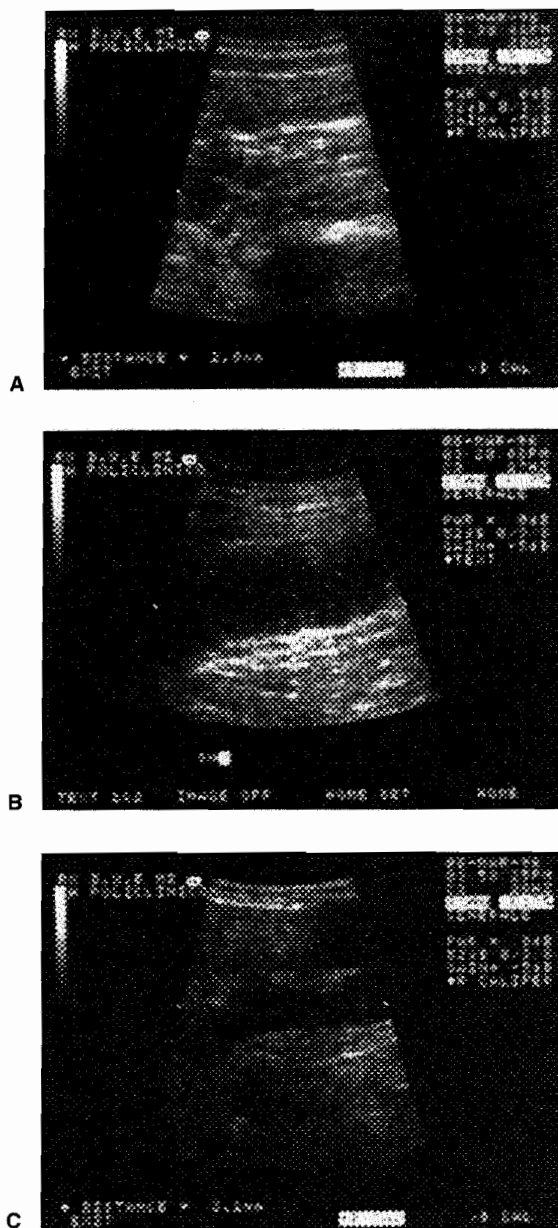


Figure 8 Sonographic findings of the abdomen in a healthy subject spontaneously breathing (A), in a patient with ARDSexp (B), and in a patient with ARDSp (C). In the normal subject it is difficult to recognize the abdominal wall and the gut anatomical structures. In the patient with ARDSexp and abdominal pathology, the increased dimensions and the increased thickness of the gut, with intraluminal debris and fluid with reduced peristaltic movements, are shown. In the patient with ARDSp, the dimensions of the gut are slightly increased whereas the gut wall thickness is not increased, without any consistent intralumina, debris or fluid.

VENTILATORY STRATEGIES

The most important consequence of the different respiratory mechanics in ARDSp and ARDSexp is that for a given applied airway pressure, the transpulmonary pres-

sure (i.e., the distending pressure of the lungs), is higher in ARDSp than in ARDSexp. Indeed, the main differences between ARDSp and ARDSexp seems to be (1) a different underlying pathology (prevalent consolidation vs prevalent collapse) and (2) a different transpulmonary pressure for the same applied airway pressure.

PEEP and Recruitment

The differences in underlying pathology and respiratory mechanics may have clinical consequences. In fact, the potential for recruitment is higher in alveolar collapse and lower in alveolar consolidation. On the other hand the applied opening pressures for lung recruitment may lead to different transpulmonary pressures according to chest wall elastance. This hypothesis is supported by the finding that in ARDSp, increasing PEEP mainly induced overstretching, while in ARDSexp PEEP mainly induced recruitment. Gattinoni and colleagues found that an increase of PEEP leads to opposite effects on elastance.⁴ In ARDSp, increasing PEEP caused an increase of the elastance of the total respiratory system due to an increase in lung elastance with no change in chest wall elastance. Conversely, in ARDSexp the application of PEEP caused a reduction of the elastance of the total respiratory system, mainly due to a reduction in lung elastance and chest wall elastance. See Figure 7. Moreover, although an increased PEEP led to an elevation of end-expiratory lung volume in both ARDSp and ARDSexp, it resulted in alveolar recruitment primarily in ARDSexp (Fig. 9A, B). In line with these results, the beneficial effects of sighs on oxygenation and recruitment are more pronounced in ARDSexp, suggesting the sigh is more likely to cause transpulmonary pressure sufficient for lung opening in ARDSexp.⁷ In neuroinjured patients with "pure" nosocomial pneumonia and severe respiratory insufficiency, we found no beneficial effects on respiratory mechanics, alveolar recruitment, or gas exchange with PEEP or recruitment maneuvers (Fig. 6A, B).²⁷

These clinical findings are in line with the results obtained in pathological studies and animal experiments. In a very elegant morphological study, Lamy and colleagues found that in patients in whom gas exchange did not improve with PEEP in early ARDS, severe lung tissue damage resulted, with alteration of alveolar spaces by hemorrhage and purulent exudate, whereas the responders to PEEP had less severe lung damage but diffuse congestion, microatelectasis, and some alveolar damage.³⁶ However, it is possible that different responses to PEEP disappear in late ARDS where the lung structure undergoes important changes such as remodeling and fibrosis.³⁷ Comparing three different experimental models of acute lung injury during recruitment maneuvers, Van der Kloot and colleagues found that more alveolar recruitment oc-

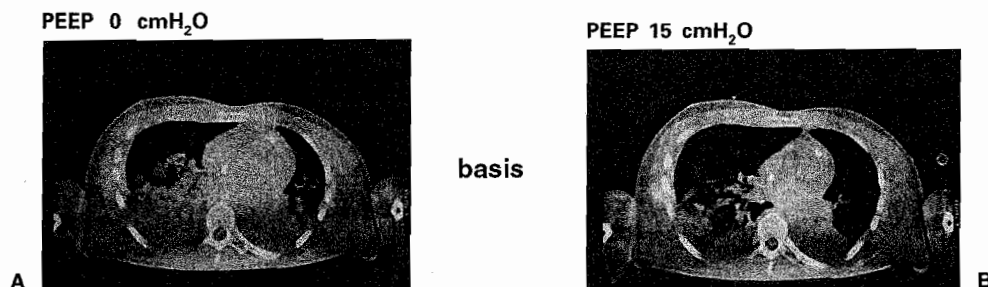


Figure 9 Representative lung computed tomography (CT) scan at base, at end-expiration, at 0 cmH₂O positive end-expiratory pressure (PEEP) (A), and at 15 cmH₂O PEEP (B) of a patient with ARDSexp due to sepsis. The lung parenchyma is characterized by ground-glass opacities, which are clearly reduced with application of PEEP, resulting in alveolar recruitment.

curred in an oleic acid model, similar to ARDSexp, compared with the model of intratracheal instillation of bacterial pneumonia, more similar to ARDSp.³⁸ Other authors have observed that PEEP is less effective in localized lung diseases like pneumonia.³⁹

Inconsistent with these findings, Puybasset and colleagues found a similar response to PEEP in alveolar recruitment and oxygenation in patients with ARDSp and ARDSexp.⁸ This could reflect differences in the clinical characteristics of the population investigated or in the ventilatory and clinical management at the moment of the study.

In sum, these data indicate that in the presence of "pure" pulmonary consolidation, increases of both inspiratory and expiratory pressures are less beneficial and, sometimes, even deleterious.

Prone Position

If chest wall mechanics, intra-abdominal pressures, and underlying pathology are different in ARDSp and ARDSexp, it is not surprising that the response to prone position may also be different. In fact, several factors that are different between ARDSp and ARDSexp (i.e., chest wall elastance and regional transpulmonary pressure), are likely involved in determining the response to prone position.⁴⁰

Two recent studies investigated the possible differences in the response in oxygenation to prone position in ARDSp and ARDSexp.^{12,41} Lim and colleagues, in a 2-hour physiological study, investigated 47 patients (31 ARDSp and 16 ARDSexp).⁴¹ They showed that the effect of prone positioning on respiratory function appears to be different in patients with early ARDSp and ARDSexp. Briefly they found that in prone position (1) the response in oxygenation (defined as an increase of PaO₂/FiO₂ greater than 40% from baseline) was more marked in ARDSexp compared with ARDSp (63% vs 23% at 0.5 h, and 63% vs 29% at 2 h, respectively); (2) the rate of increase in oxygenation was slower in ARDSp; (3) the decrease of respiratory system compliance was greater in ARDSexp; (4) the densities, deter-

mined on the chest x-ray, decreased to a greater degree in ARDSexp.

Pelosi and colleagues performed a large prospective trial in 73 patients (51 ARDSp and 22 ARDSexp) with bilateral chest infiltrates, a PaO₂/FiO₂ ratio lower than 200 with PEEP higher or equal to 5 cmH₂O, and no evidence of cardiac problems.¹² Patients were evaluated daily for a 10-day period for the presence of respiratory failure criteria (the same as entry criteria). Patients who met these criteria were placed in a prone position for 6 hours once a day. The improvement in oxygenation was greater in ARDSexp compared with ARDSp, although the overall mortality was not different between the two groups.

The different time course of oxygenation according to the etiology of ARDS suggests that the mechanisms of oxygenation in the prone position may be multifactorial or time-dependent, or both. An attenuation of the vertical gradients of the pleural pressure, or an increased effective transpulmonary pressure at the dependent lung regions, is obtained immediately as the patients are turned to the prone position. This mechanical benefit could then result in the reversal of compressive atelectasis in ARDSexp, but would not bring about an immediate change in the consolidated lung units in ARDSp. The greater decrease in consolidation densities in the prone position of ARDSexp as compared with ARDSp suggests that the effects of position and the mechanisms through which it may improve respiratory function can be different in ARDSp and ARDSexp. In ARDSexp, in which collapse and compression atelectasis together with an increase of intra-abdominal pressure play a major role in inducing hypoxia,⁴² the redistribution of atelectasis from dorsal to ventral⁴³ and possibly the changes in regional transpulmonary pressure⁴⁴ may induce an immediate improvement of oxygenation. In ARDSp, in which collapse is likely less relevant, the same mechanism may operate to a lesser degree and possibly the redistribution of ventilation may play an additional role.

These two studies reinforce the hypothesis that the mechanisms by which prone position improves oxy-

generation may be different or may operate to different degrees in ARDS_p and ARDS_{exp}.

CONCLUSIONS

ARDS_p and ARDS_{exp} are characterized by different pathophysiological, radiological, and mechanical patterns: (1) in ARDS_p, the prevalent damage in early stages is likely intra-alveolar, whereas in ARDS_{exp} it is interstitial edema. Sometimes the differentiation between ARDS_p and ARDS_{exp} is not so evident, possibly because of the coexistence of the two insults (i.e., one lung with direct injury (as pneumonia) and the other with indirect injury, through mediator release from the original pneumonia); (2) the radiological pattern, from chest x-ray or CT, is different in ARDS_p (characterized by prevalent consolidation) and ARDS_{exp} (characterized by prevalent ground-glass opacification); (3) in ARDS_p lung elastance is more markedly increased than in ARDS_{exp}, where the main abnormality is the increase in chest wall elastance, due to abnormal intra-abdominal pressure; (4) PEEP, inspiratory recruitment, and prone position more effectively improve respiratory mechanics, alveolar recruitment, and gas-exchange in ARDS_{exp}. Further studies are warranted to better define whether the distinction between ARDS of different origins can improve clinical management and survival.

REFERENCES

- Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. *Lancet* 1967;2:319-323
- Fauci AS, Braunwald E, Isselbacher KJ, et al. The practice medicine. In: Fauci AS, Braunwald E, Isselbacher KJ, et al, eds. *Harrison's Principles of Internal Medicine*. New York: McGraw-Hill; 1998:1-6
- Bernard GR, Artigas A, Brigham KL, et al, and the Consensus Committee. The American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994;149:818-824
- Gattinoni L, Pelosi P, Suter PM, Pedoto A, Vercesi P, Lissoni A. Acute respiratory distress syndrome caused by pulmonary and extrapulmonary disease: different syndromes? *Am J Respir Crit Care Med* 1998;158:3-11
- Pelosi P, Brazzi L, Gattinoni L. Diagnostic imaging in acute respiratory distress syndrome. *Current Opinion in Critical Care* 1999;5:9-16
- Goodman LR, Fumagalli R, Tagliabue P, et al. Adult respiratory distress syndrome due to pulmonary and extrapulmonary causes: CT, clinical, and functional correlations. *Radiology* 1999;213:545-552
- Pelosi P, Cadringer P, Bottino N, et al. Sigh in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1999;159:872-880
- Puybasset L, Gusman P, Muller JC, Cluzel P, Coriat P, Rouby JJ, and the CT Scan ARDS Study Group. Regional distribution of gas and tissue in acute respiratory distress syndrome. III: Consequences for the effects of positive end-expiratory pressure. *Intensive Care Med* 2000;26:1215-1227
- Hudson LD, Milberg JA, Anardi D, Maunder RJ. Clinical risks for development of the acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1995;151:293-301
- Villar J, Perez-Mendez L, Kacmarek RM. Current definitions of acute respiratory distress syndrome do not reflect their true severity and outcome. *Intensive Care Med* 1999;25:930-935
- Jardin F, Fellahi JL, Beauchet A, Vieillard-Baron A, Loubieres Y, Page B. Improved prognosis of acute respiratory distress syndrome 15 years on. *Intensive Care Med* 1999;25:936-941
- Pelosi P, Brazzi L, Gattinoni L. Prone position in acute respiratory distress syndrome. *Eur Respir J* 2001; (in press)
- Squara P, Dhainout JF, Artigas A, Carlet J. Hemodynamic profile in severe ARDS: results of the European Collaborative ARDS study. *Intensive Care Med* 1998;24:1018-1028
- Suchyta M, Clemmer T, Elliot C, Orme J, Weaver L. The adult respiratory distress syndrome: a report of survival and modifying factors. *Chest* 1992;101:1074-1079
- Arigas A, Le Gall JK, Chastang CL, Carlet J, Blanch L, Fernandez R. Clinical presentation, prognostic factors, and outcome of ARDS in the European Collaborative study: a preliminary report. In: Zapol WM, Lemaire F, eds. *Adult Respiratory Distress Syndrome*. New York: Marcel Dekker; 1991:37-63
- Montgomery B, Stager M, Carrico C, Hudson L. Cause of mortality in patients with the adult respiratory distress syndrome. *Am Rev Respir Dis* 1985;32:485-489
- Pugin J, Verghese G, Widmer MC, Matthay MA. The alveolar space is the site of intense inflammatory and profibrotic reactions in the early phase of acute respiratory distress syndrome. *Crit Care Med* 1999;27:304-312
- Terashima T, Kanazawa M, Sayama K. Granulocyte colony-stimulating factor exacerbates acute lung injury induced by intratracheal endotoxin in guinea pigs. *Am J Respir Crit Care Med* 1994;149:1295-1303
- Shaw JO, Henson PM, Henson J, Webster RO. Lung inflammation induced by complement derived chemotactic fragments in the alveolus. *Lab Invest* 1980;42:547-558
- Tutor JD, Mason CM, Dobard E, Beckerman C, Summer WR, Nelson S. Loss of compartmentalization of alveolar tumor necrosis factor after lung injury. *Am J Respir Crit Care Med* 1994;149:1107-1111
- Johanson WG, Higuchi JH, Woods DE, Gomez P, Coalson JJ. Dissemination of *Pseudomonas aeruginosa* during lung infection in hamsters. *Am Rev Respir Dis* 1985;132:358-361
- Muller-Leisse C, Klosterhalfen B, Hauptmann S. Computed tomography and histologic results in the early stages of endotoxin-injury lungs as a model for adult respiratory distress syndrome. *Invest Radio* 1993;28:39-45
- Seidenfeld JJ, Curtix Mullins R, Fowler SR, Johanson WG. Bacterial infection and acute lung injury in hamsters. *Am Rev Respir Dis* 1986;134:22-26
- Terashima T, Matsubara M, Nakamura M. Local *Pseudomonas* instillation induces contralateral injury and plasma cytokines. *Am J Respir Crit Care Med* 1996;153:1600-1605
- D'Angelo E, Calderini E, Robatto FM, Puccio P, Milic-Emili J. Lung and chest wall mechanics in patients with acquired immunodeficiency syndrome and severe *Pneumocystis carinii* pneumonia. *Eur Respir J* 1997;10:2343-2350
- Winer-Muran HT, Stainer RM, Gurney JW, et al. Ventilator-associated pneumonia in patients with adult respiratory

- distress syndrome: CT evaluation. *Radiology* 1998;208:193-199
27. Pelosi P, Colombo G, Gamberoni C, et al. Effects of positive end-expiratory pressure on respiratory function in head-injured patients. *Intensive Care Med* 2000;26:A450
 28. Rodriguez JL, Gibbons KJ, Bitzer LG, Dechert E, Steinberg SM, Flint M. Pneumonia: incidence, risk factors and outcome in head injured patients. *J Trauma* 1991;31:907-914
 29. Ewig S, Torres A, El-Ebiary M, et al. Bacterial pattern in mechanically ventilated patients with traumatic and medical lung injury. *Am J Respir Crit Care Med* 1999;159:188-198
 30. Torres A, El-Ebiary M, Gonzales J, Ferrer M, Puig de la Bellacasa J, Gene A, Martos A, Rodriguez-Roisin R. Gastric and pharyngeal flora in nosocomial pneumonia acquired during mechanical ventilation. *Am Rev Respir Dis* 1993;148:352-357
 31. Ranieri VM, Suter PM, Tortorella C, et al. Effects of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 1999;282:54-61
 32. Rouby JJ, Puybasset L, Cluziel P, Richecoeur J, Lu Q, Grenier P. Regional distribution of gas and tissue in acute respiratory distress syndrome. II: Physiological correlations and definition of an ARDS severity score. *Intensive Care Med* 2000;26:1046-1056
 33. Polese G, Rossi A, Appendini L, Brandi G, Bates JHT, Brandolese R. Partitioning of respiratory mechanics in mechanically ventilated patients. *J Appl Physiol* 1991;71:2425-2433
 34. Mergoni M, Martelli A, Volpi S, Primavera S, Zucchi P, Rossi A. Impact of positive end-expiratory pressure on chest wall and lung pressure-volume curve in acute respiratory failure. *Am J Respir Crit Care Med* 1997;156:846-854
 35. Ranieri VM, Brienza N, Santostasi S, et al. Impairment of lung and chest wall mechanics in patients with acute respiratory distress syndrome: role of abdominal distension. *Am J Respir Crit Care Med* 1997;156:1082-1091
 36. Lamy M, Fallat RJ, Koeniger E. Pathologic features and mechanisms of hypoxemia in adult respiratory distress syndrome. *Am Rev Respir Dis* 1976;114:267-284
 37. Gattinoni L, Bombino M, Pelosi P, Lissoni L, Pesenti A, Fumagalli R, Tagliabue M. Lung structure and function in different stages of severe adult respiratory distress syndrome. *JAMA* 1994;271:1772-1779
 38. Van der Kloot TE, Blanch L, Youngblood AM, et al. Recruitment maneuvers in three experimental models of acute lung injury: effect on lung volume and gas exchange. *Am J Respir Crit Care Med* 2000;161:1485-1494
 39. Light RB, Mink SN, Wood DM. The effect of unilateral PEEP on gas exchange and pulmonary perfusion in canine lobar pneumonia. *Anesthesiology* 1981;55:251-255
 40. Pelosi P, Tubiolo D, Mascheroni D, et al. Effects of the prone position on respiratory mechanics and gas exchange during acute lung injury. *Am J Respir Crit Care Med* 1998;157:387-393
 41. Lim CM, Kim EK, Lee JS, et al. Comparison of the response to the prone position between pulmonary and extrapulmonary acute respiratory distress syndrome. *Intensive Care Med* 2001;27:477-485
 42. Pelosi P, Ravagnan I, Giurati G, et al. Positive end-expiratory pressure improves respiratory function in obese but not in normal subjects during anesthesia and paralysis. *Anesthesiology* 1999;91:1221-1231
 43. Gattinoni L, Pelosi P, Vitale G, Pesenti P, D'Andrea L, Mascheroni D. Body position changes redistribute lung computed tomographic density in patients with respiratory failure. *Anesthesiology* 1991;74:15-23
 44. Mure M, Glenny RW, Domino KB, Hlastala MP. Pulmonary gas exchange improves in the prone position with abdominal distension. *Am J Respir Crit Care Med* 1998;157:1785-1790