3. Recent advances in understanding the pathophysiological mechanisms of ARDS

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Acute respiratory distress syndrome (ARDS) is now undoubtedly considered as the local manifestation of a generalized autodestructive inflammatory reaction. It can originate from direct lung injury (lung contusion, pneumonia, near drowning, aspiration…), but also from indirect injury (multiple trauma, sepsis, acute pancreatitis…). The onset and development of ARDS present several aspects, which correspond to the different initial causes, but ARDS remains characterized by the same pulmonary response, with the same or similar clinical sings and syndromes. The definition of ARDS has recently be the subject of a consensus conference : ARDS is now defined as the most severe form of acute lung injury (ALI) with impaired oxygenation ($Pa_{O_2}/FI_{O_2} < 200$ mmHg) appearing together with bilateral infiltration of the lungs and a wedge pressure < 18 mmHg. The modern version of ARDS implicates that, when the syndrome develops progressively (particulary when the origin of ARDS is indirect), the lung failure is often the first and the most easily observable aspect of an extended process that affects many other organs and leads to the multiple organ dysfunction syndrome (MODS), responsible for a high death rate, which is thus not the consequence of hypoxemia and lung failure.

Several phases can be observed in the evolution of ARDS. The first one, appearing in the first hours, is characterized by dyspnea and tachypnea without pulmonary alterations or clear pathophysiological changes. After 12 to 24 hours, the lung damage becomes visible, with modification of the permeability of lung capillaries with fluid infiltration, oedema and hypoxemia. The inflammatory response is already present, particularly when sepsis is simultaneously observed : neutrophils are increasingly marginated in lung capillaries and migrate into the interstitium and alveoli. Fibrin and platelets aggregates also accumulate in capillaries and the pulmonary surfactant is damaged or decreased. In this phase, ARDS remains reversible, with a mortality of 20 to 40%. In the next phase, lung failure progresses, leading to a necessary mechanical ventilation and an increase in FI_{O_2}. Particulaly when sepsis is present, a hyperdynamic state occurs, with an increase in cardiac output and oxygen need, and a decrease in systemic vascular resistance and oxygen extraction. The invasion of lungs by cells increases, inflammatory exsudate persists, and type II cells proliferate. In this phase, the mortality is above 50%, but ARDS still remains reversible. In the last phase, the lung failue becomes complete with pulmonary fibrosis (and loss of compliance) and/or recurrent pneumonia, which occurs in more than 50% of late ARDS. This fibrosis, triggered and amplified by an excessive production of growth factors, is accompanied by increasing evidence of barotrauma and is characterized by an increasing production and deposition of inelas-

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tic collagen in distal interstitium. The mortality rate reaches 80% or greater, and is a consequence of MODS rather than hypoxia.

The basic pathophysiological mechanism of ARDS is thus a pulmonary inflammatory reaction, progressing from lung to the other organs or reaching lung from distal sources by the way of humoral and cellular mediators. Among these inflammatory mediators, the cytokines, the activated oxygen species, the bioactive lipids and the proteases are the most studied and the main targets of a possible pharmacological treatment. These inflammatory mediators were firstly searched and measured in plasma in an attempt to identify specific and early markers of ARDS, allowing early treatment of the disease, before the development of MODS. It is now admitted that there are no specific early makers of ARDS in plasma. However, it increasingly appears that the monitoring of the cellular composition and inflammatory mediators concentrations of broncho-alveolar lavage fluids (BAL) is important since BAL fluid better reflects the evolution of the syndrome than plasma.

The cytokines are intercellular messengers, modulating and regulating the inflammatory response as well as the immunologic defense of the host. In ARDS, the most active (and the best known) of these cytokines are the pro-inflammatory TNF and IL 1, 6 and 8, this last interleukin being a powerful chemo-attractant for neutrophils. These cytokines are active on many types of cell and particularly on the surface expression of adhesion receptors by these cells, which increase the interaction of neutrophils with endothelium. However, it is now clear that many other cytokines are involved in ARDS, some of them, such as IL 10 and IL 12 with anti-inflammatory properties. This leads to new therapeutic possibilities. The activated oxygen species, which are essentially the products of stimulated phagocytes, are responsible for lipoperoxidation leading to the destruction of the ccellular membranes with further increase in permeability and oedema. Their excessive production results in the disturbance of the oxidant-antioxidant balance of the plasma by the consumption of plasma antioxidants such as vitamin E. It also appears that their uncontrolled release and the oxidant stress it causes lead to an activation of intracellular signals of transduction, starting the synthesis of new proteins (eg heat shock proteins), the consequence of this being largely unknown in ARDS. But, the inhibition of these active oxygen species is far from being easy and, to be effective, must be achieved very early in the disease process. Cyclooxygenase and lipoxygenase products (the bioactive lipid metabolites of arachidonic acid), without being primary initiators of ARDS, play a supporting role in this disease by augmenting inflammation and cell-induced injury, by their action on vascular tone and bronchoconstriction as well as by their chemotactic activity. Proteases, released by the cells stimulated by the complement and coagulation cascades, also increase the inflammatory reaction by the release of active peptides and by tissue destruction. However, these mediators have reciprocal interactions, the activity of one of them resulting often in the enhanced production of the other mediators by cellular recruitment and stimulation.

The treatment of ARDS is firstly respiratory support. Mechanical ventilation using conventional tidal volume and generating high airway pressure to normalize gas exchange induces pulmonary damage (VILI or Ventilator Induced Lung Injury) better called volotrauma rather than barotrauma. In animals, conventional ventilation can itself induce acute lung inflammation. It could be an aggravating factor in acute lung injury, by streching residual nor-

mal lung parenchyma or already damaged lung tissue. A new approach called the "open lung approach" with low distending pressures tends to reduce volotrauma, but leads to increased Pa_{CO_2} (permissive hypercapnea). Other means like NO inhalation (with iv almitrine to reinforce pulmonary vasoconstriction), prone positioning, tracheal gas insufflation, allow the intensivist to reduce the F_{IO_2} (<0.6) and pulmonary distending pressures. This treatment approach, called lung protective ventilation, is a compromise. Its purpose is to prevent further lung damage due to hyperoxia and mechanical injury while maintaining acceptable Pa_{O_2} and tolerating increased Pa_{CO_2} (providing arterial pH remains higher than 7.2).

The second aspect of ARDS therapy tries to limit the inflammatory reaction by inhibition of the production or by limiting the effects of mediators, by modulating cellular activity. But the complexity of the interactions between cell activity and mediators explains the lack of efficacy of this kind of therapy. The new pharmacological approaches of ARDS control at the cellular level are however promising. An essential step in the progress of ARDS therapy remains the early detection of important inflammatory mediators, most promising by BAL and understanding the physiological and biochemical mechanisms occuring in patients at risk of ARDS, who do not go on to develop the syndrome.

During the last 25 years, ARDS mortality has remained unacceptably high despite progress in the understanding of its pathophysiological mechanisms and in ICU patient management. During the last 5 years, better results have been observed, related more to better ICU care (including less aggressive lung ventilation) than to modulating the inflammatory response (an exception may be the treatment of late ARDS with low dose corticosteroids). Hopefully further progress will come from better understanding of the pathophysiological mechanisms (lung inflammation and repair) and from gene therapy.