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*Review*

# Prevention and Therapy of the Adult Respiratory Distress Syndrome

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**Abstract.** The complex pathophysiology of adult respiratory distress syndrome (ARDS) makes preventive and therapeutic concepts difficult. Ample experimental evidence indicates that ARDS can be prevented by blocking systemic inflammatory agents. Clinically, only heparin, for inhibition of coagulation phenomena, is presently used among this array of approaches. Corticosteroids have not proven to be beneficial in ARDS. Alternative antiinflammatory agents are being proposed and are under current clinical investigation (e.g. indomethacin, acetylcysteine, $\alpha_1$-proteinase inhibitor, antitumor necrosis factor, interleukin 1 receptor antagonist, platelet-activating factor antagonists). Symptomatic therapeutic strategies in early ARDS include selective pulmonary vasodilation (preferably by inhaled vasorelaxant agents) and optimal fluid balance. Transbronchial surfactant application, presently tested in pilot studies, may be available for ARDS patients in the near future and may have acute beneficial effects on gas exchange, pulmonary mechanics, and lung hemodynamics; its impact on survival cannot be predicted at the present time. Strong efforts should be taken to reduce secondary nosocomial pneumonia in ARDS patients and thus avoid the vicious circle of pneumonia, sepsis from lung infection, and perpetuation of multiple organ dysfunction syndrome. Optimal respirator therapy should be directed to ameliorate gas-exchange conditions acutely but at the same time should aim at minimizing potentially aggravating side effects of artificial ventilation (barotrauma, $O_2$ toxicity). Several new techniques of mechanical ventilation and the concept of permissive hypercapnia address these aspects. Approaches with extracorporeal $CO_2$ removal and oxygenation are being used in specialized centers.

**Key words:** Adult respiratory distress syndrome—Antiinflammatory therapy—Vasodilator inhalation—Surfactant application—Artificial ventilation.

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## Introduction

The adult respiratory distress syndrome (ARDS) was characterized first in 1967 by Ashbaugh et al., who linked its clinical pattern to the respiratory distress syndrome in premature infants [1]. ARDS is characterized by an acute disturbance of gas exchange, which may occur without any preceding lung disease, in the absence of individual predispositions. Pneumonia, as a localized lung infection causing acute gas-exchange disturbances, is a separate entity, which may, however, become indistinguishable from ARDS. Gas-exchange disturbances in ARDS are invariably linked with noncardiogenic lung edema and altered pulmonary hemodynamics, resulting in hypoxemia and loss of compliance. During the early stages of its pathogenesis, proteinaceous exudates in the interstitial and alveolar spaces resulting from the breakdown of endothelial and epithelial barrier integrity are typical findings. Abundant deposition of bronchoalveolar fibrin promotes hyaline membrane formation and subsequent alveolar fibrosis. The early stages of disease are fully reversible, whereas the processes of lung remodeling and fibrosis may persist in patients surviving the late proliferative stage. Estimation of the incidence of ARDS is difficult because different medical centers use various clinical criteria for its definition, particularly when classifying the severity of gas-exchange disturbances. With such a wide variability in diagnostic criteria, discrepancies of the annual incidence of ARDS between 3/100,000 and 74/100,000 are documented in the literature [20, 61, 132, 136]. A much higher incidence occurs in patients with predisposing diseases (high-risk collectives) such as sepsis, systemic inflammatory response syndrome (SIRS) or multiple organ dysfunction syndrome (MODS) [11, 15, 35, 97]. On the other hand, the most important sources of sepsis during ARDS are the lung and the gastrointestinal tract [3, 13].

## Different Pathogenetic Sequences in ARDS

Agents responsible for the initiation of ARDS can enter the lung parenchyma either through the intravascular space or the alveolar compartment (Fig. 1). Systemic triggering under conditions such as sepsis, polytrauma with multiple transfusions, shock, burns, and pancreatitis produces a pulmonary vascular flood of products of activated humoral cascade systems, where inflammatory cells and putatively bacterial toxins clearly assume responsibility. Transbronchial sources of ARDS are usually inhaled agents (e.g. inhalation of toxic gases) or aspirated materials (e.g. aspiration of gastric contents). Whether primarily deposited in alveoli or washed into the pulmovascular space, the effectors precipitate a second wave of perpetuating inflammation in the lung parenchyma. The description of this inflammatory process can be crudely simplified by typifying its early exudative phase and its proliferative-fibrosing late phase, which is often difficult to demarcate on clinical grounds. According to current knowledge, the course of inflammation in lung parenchyma is not characterized by a monocausal chain of inflammatory processes but rather involves a multi-

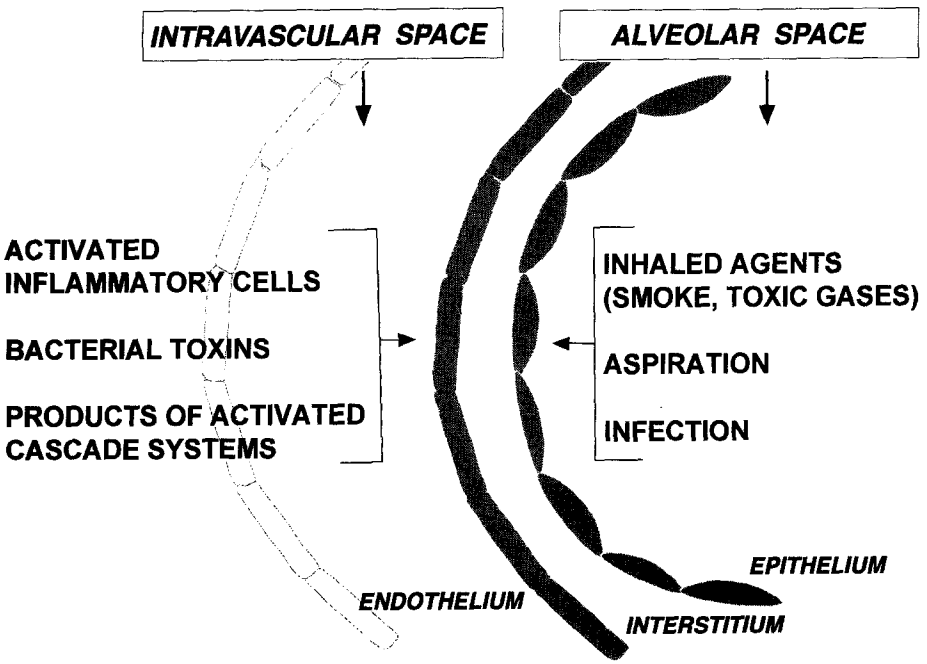


**Fig. 1.** Events initiating ARDS.

tude of humoral mediator systems, inflammatory competent cells, and bacterial toxins (overview given in Fig. 2) [98]. Evidence of neutrophilic-dominated infiltrates in histologic samples from the lungs of ARDS patients and high neutrophil counts as well as high concentrations of neutrophil degranulation products in the bronchoalveolar lavage (BAL) demonstrate the role of this cell type as a key component in the inflammatory process [94, 133]. Endotoxin-induced complement activation with subsequent priming of neutrophils may be involved in sepsis. This results in the adherence of neutrophils in the pulmonary microcirculation with subsequent degranulation (proteases, oxygen radicals, leukotriene formation).The complex interaction between neutrophils and endothelial cells causes endothelial cell damage with formation of pulmonary edema and vasomotor disturbances of the pulmonary microcirculation. In addition, endotoxin induces the formation of tumor necrosis factor (TNF) and interleukin 8 (IL-8) in various macrophages. Primary functions of IL-8 include neutrophil activation and chemotaxis [67]. TNF promotes neutrophil adherence to the endothelium and causes vasoconstriction in the pulmonary circulation. In addition, lipid mediators such as prostanoids, leukotrienes, and platelet-activating factor (PAF) influence vascular reactivity and augment inflammation. Enhanced coagulation and depressed fibrinolysis may result in alveolar fibrin deposition. Increased antifibrinolytic activity resulting from urokinase inhibitors and antiplasmins was found in BAL material from ARDS patients [7, 55]. Defective surfactant activity may result from the inhibitory

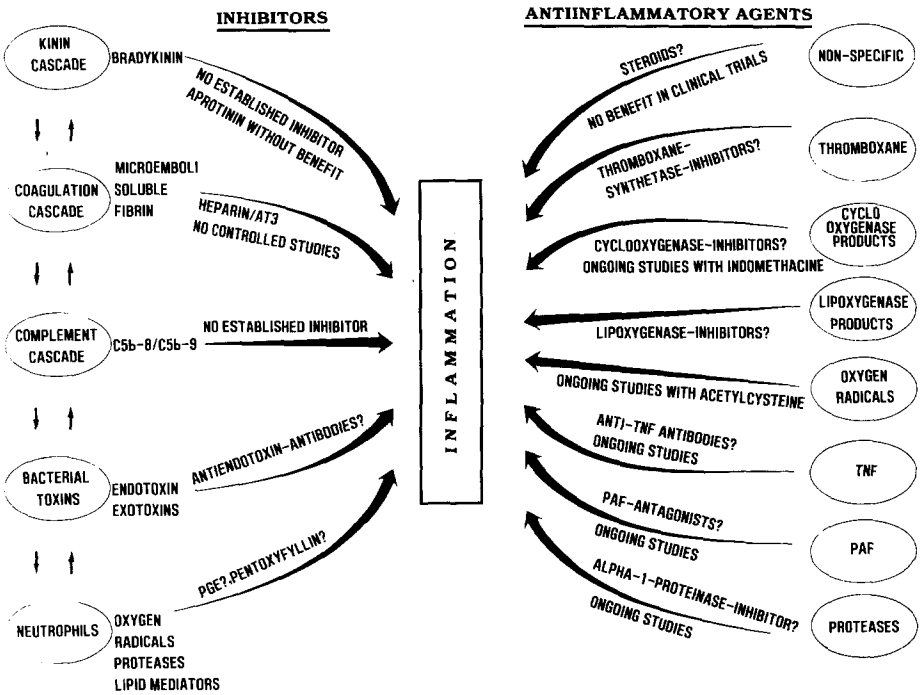


**Fig. 2.** Antiinflammatory strategies in ARDS.

capacity of plasma-derived proteins leaked into the alveolar space, oxidant attack on its lipid or apoprotein components, or type II pneumocyte injury. It is presently unclear which mediators or inflammatory cells are predominant effectors of the scenario and whether various clinical courses of ARDS are linked with different mediator or cell profiles. The perpetuating inflammation at the pulmonary gas-exchange level is responsible for the impairment of organ physiology. Typically, this includes interstitial and alveolar edema, hyaline membrane formation, development of atelectasis because of disturbed alveolar surfactant function with consequent gas-exchange impairment, and an increased pulmonary vascular resistance resulting from vasoconstriction, microembolization, and/or microthrombi.

## Multiple Pathophysiologic "Variants" of ARDS

The changes in organ physiology in ARDS may reveal different patterns. Interstitial and alveolar edema formation may predominate (particularly in the early phase), accompanied by only modest gas-exchange impairment (radiologically "white lung," but moderate hypoxemia). On the other hand, serious disturbances of gas exchange (shunt, ventilation-perfusion mismatch) may be accompanied by only moderate edema formation according to radiologic and computed tomographic (CT) criteria. The gas-exchange abnormalities may also

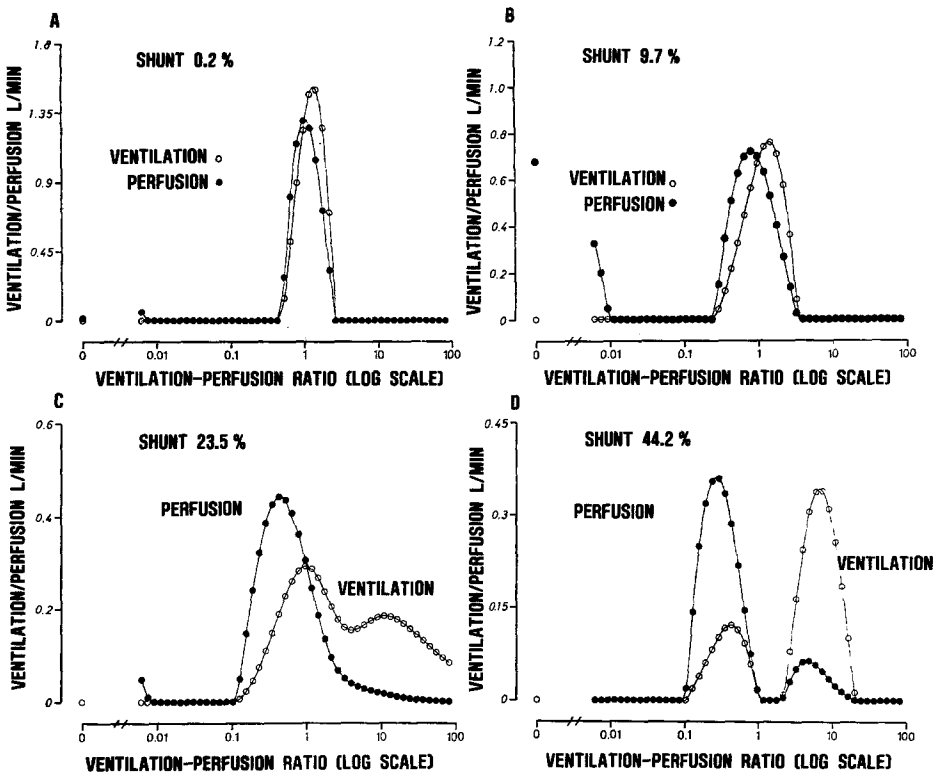


**Fig. 3.** Patterns of ventilation-perfusion ($V_A/Q$) mismatch in ARDS. $V_A/Q$ was measured by multiple inert gas analysis. **A**, healthy control; **B**, predominance of low $V_A/Q$ areas; **C**, low and high $V_A/Q$ areas, accompanied by significant shunt flow; **D**, severe respiratory failure with $V_A/Q$ mismatch and shunt flow (own unpublished results).

exhibit different profiles (examples given in Fig. 3). They may be characterized by a predominant shunt flow, whereby the ventilation-perfusion distribution in the ventilated areas remains largely intact; alternatively, they may present as a severe ventilation-perfusion mismatch. To date, no systematic investigations have been undertaken to explore whether these variants of gas-exchange disturbance are linked differently to the progression from the early exudative to the later proliferative-fibrosing stage of ARDS and whether the different patterns of lung failure predict different outcomes.

## Factors Perpetuating Inflammation and Lung Damage

The primary alterations as well as the therapeutic interventions may trigger secondary events perpetuating the inflammatory process. These interrelations can be elucidated using a few brief examples.

The host-defense mechanisms in the alveolar compartment are compromised under conditions of ARDS. In addition, ventilated patients are subjected

to a greater microbiologic load of the lungs because of microaspiration of bacteria retrogradely ascended from the gastrointestinal tract. There is a clear correlation between the duration of ARDS and increased incidence of nosocomial pneumonia, the latter being found in more than 70% of ARDS patients who have been ventilated for more than 10 days [32, 84, 110, 121]. The mortality rate rises significantly after the acquisition of secondary pneumonia [80, 108]. On the other hand, a bacterial pneumonia, primarily confined to distinct lung areas, may either spread or secondarily induce inflammatory events affecting the entire lung (parapneumonial ARDS). The transition from pneumonia to ARDS is a gradual one and therefore frequently eludes exact definition on clinical grounds.

Impaired gas-exchange function demands the use of high oxygen partial pressures to guarantee sufficient arterial oxygenation. Alveolar hyperoxia ($FiO_2 \geq 0.5$) may itself induce inflammatory processes in the lung parenchyma [58, 66]. On the other hand, microbiologic loading of the lung may prime antioxidative enzyme systems, at least under experimental conditions, thereby counterbalancing hyperoxia-induced lung injury [5, 42, 43, 59]. Presently, the extent to which the increased partial pressure of oxygen used during mechanical ventilation of ARDS patients contributes to the perpetuation of the inflammatory process remains to be determined. Experimental investigations have shown that the administration of high peak inspiratory pressure may induce increased endothelial and epithelial permeability, with subsequent development of a protein-rich edema, finally mimicking the full clinical picture of ARDS [19, 83, 123]. The lungs react in a particularly sensitive way to mechanical stress when the alveolar surfactant system has been damaged or when there are ongoing severe inflammatory processes. It is still not fully settled whether this type of microscopic barotrauma (in contrast to classical barotrauma, which includes pneumothorax and pneumomediastinum) is induced by (1) the magnitude of peak pressures during inspiration; (2) the differential between expiratory and inspiratory pressure (shear forces); (3) the integral of increased airway pressures over time; or (4) the relatively large increase in volume in the (limited) areas of the lung which are still accessible to inflation (overdistention, volutrauma) [24, 46, 70].

## Management

Two developments are decisive for the morbidity and mortality of patients with ARDS: the progression from the early exudative period to the proliferative-fibrosing late phase, and the acquisition of nosocomial pneumonia accompanying or perpetuating sepsis and multiple organ failure. Thus, prophylaxis and therapy must attempt to prevent such development, in addition to improving acute disturbances of lung function (hemodynamics, fluid balance, gas exchange). It has to be kept in mind, however, that an acute amelioration of physiologic abnormalities will not necessarily result in a reduction of morbidity (duration of ventilation, length of intensive-care unit stay) or mortality in

ARDS; even the opposite may occur. The use of very high positive end-expiratory pressure (PEEP) can, for example, result in a marked, acute reduction of shunt flow and thereby improve arterial oxygenation. However, because of increased barotrauma the development of proliferative-fibrotic changes may be favored, eventually resulting in an increase in mortality. Definite answers as to the impact of new therapeutic attempts on the morbidity and mortality of ARDS patients can only be obtained in controlled, prospective studies in large ARDS collectives. It is a primary therapeutic goal to establish early and effective medical intervention to reduce and combat all noxes directly or indirectly affecting the lung parenchyma. Sepsis and shock must be treated immediately. It is presently uncertain whether different kinds of immunoglobulin therapy (preparations rich in antilipid A IgG or IgM antibodies, monoclonal human and mouse antiendotoxin antibodies, antibodies against bacterial exotoxins) will render sepsis therapy more effective. Shock must be diagnosed early and effective medical intervention initiated to prevent secondary development of organ complication including ARDS.

### Inhibition of Plasmatic Mediator Cascades and Circulating Inflammatory Cells

The triggering of ARDS through a systemic process (e.g. sepsis) calls for an attempt to reduce the incidence and perpetuation of the disease process by inhibiting the plasmatic mediator systems and circulating inflammatory cells. The application of heparin and/or antithrombin III in disseminated intravascular coagulation (DIC) in an attempt to suppress further activation of the coagulation cascade with the generation of soluble fibrin and microemboli is accepted widely. Heparin is used even more generally as a prophylactic agent to prevent coagulation events in intensive-care patients. Concerning pulmonary circulation, the rationale of this widespread use of heparin rests upon the demonstration of vascular abnormalities and lung injury in experimental models with systemic generation of microemboli and soluble fibrin (fibrin monomer/oligomer-fibrinogen complexes) [75, 103, 106]. Moreover, intravascular deposition of coagulation products has been demonstrated repeatedly in pulmonary microcirculation when examined histologically in the early phase of ARDS. Despite such widely established use of heparin or heparin/antithrombin III, there are no controlled clinical studies proving that a suppression of the coagulation cascade in critically ill patients does reduce the incidence or severity of ARDS. In addition to its impact on the coagulation cascade, antithrombin III does possess broad antiprotease effects, and this feature has prompted clinical studies questioning the benefit of high-dose antithrombin III application in patients at high risk of developing acute respiratory failure [57]. This approach is based on a putative important role of leukocytic proteases in the pathogenetic sequence of ARDS. Results from these studies should be available in the next few years. Administering aprotinin, an antiprotease particularly effective on the kallikrein-kinin system, was not beneficial in one small study [124]. The only inhibitor of the complement system currently available for clinical appli-

cation is the C1-esterase inhibitor. Its use in a very limited number of patients with sepsis has been reported recently [38]. Controlled studies addressing the impact of this agent on the incidence and/or progression of ARDS have not yet been carried out. Therapeutic concepts for the prophylaxis and therapy of alveolar fibrin deposits are in an experimental stage and far from clinical realization [7, 41, 55]. Therapeutic approaches attempting to suppress granulocyte activation and concomitant mediator generation are of particular interest in view of the many experimental investigations concerned with the role of these inflammatory cells in the initial phase of ARDS. Besides its direct hemodynamic effects, intravenously administered prostaglandin $E_1$ ($PGE_1$) may possess such efficacy. More recent studies did, however, show that the clinically achievable plasma concentrations of $PGE_1$ and its active metabolites are not sufficient for effective inhibition of leukocytes activated via a multitude of inflammatory stimuli [29, 101]. Some very impressive experimental data have shown suppression of leukocyte activation and endotoxin-induced formation of TNF factor by pentoxifylline [105, 114, 137]. Clinical studies have been initiated to investigate the influence of pentoxifylline on the incidence and mortality of ARDS. Hopefully, valid clinical data will be forthcoming in the next few years. Other approaches to suppress granulocyte activation, diapedesis, and associated mediator generation include the use of lipid preparations rich in eicosapentaenoic acid and monoclonal antibodies against leukocytic adhesion molecules; clinical data are not yet available. At present it is, however, an open question whether the advantages of suppressing granulocyte-associated inflammatory events will outweigh the disadvantages of compromising the host-defense competence. No controlled studies address the inhibition of thrombocyte activation as a prophylactic or therapeutic concept in ARDS. The same is true with respect to monocyte and lymphocyte activation.

## Antiinflammatory Strategies

Many prophylactic and therapeutic approaches are imaginable for suppression of inflammatory processes in the lung parenchyma itself (Fig. 2). The basic problem is that these inhibitors and/or antagonists of inflammatory mediators encompass only a circumscribed part of the pathogenic process. It may, however, not be denied in advance that (at least in some variants of ARDS) distinct pathogenic sequences may predominate quantitatively in such a way that their suppression will have an overall beneficial effect. Efficacy in experimental models has been demonstrated for all antiinflammatory agents listed in Figure 2. For some of the involved mediators, increased generation in the lung tissue under conditions of ARDS has been demonstrated by analysis of the BAL fluid (e.g. leukotrienes, TNF, and oxygen radicals). Clinical studies have been initiated which address lipid mediator generation, oxygen radical formation, protease activation, and the increased generation of TNF. Interesting clinical results regarding these new therapeutic approaches are to be expected in the coming few years. At present, however, no valid data are available to justify their routine clinical application in patients at risk of ARDS or those presenting

with severe respiratory failure. This is also true for high-dose corticosteroid therapy. Steroids do suppress a variety of inflammatory mediator cascades but fail with respect to others (this applies also to the often-cited arachidonic acid lipoxygenase pathways, which are affected only in some cell types) [37]. Moreover, steroid administration interferes with the host-defense mechanisms, probably via its impact on the cytokine network. In controlled studies over the past few years, where corticosteroids were given at the earliest possible time in patients with sepsis (at risk of ARDS) or those with manifested respiratory insufficiency, no overall therapeutic benefit was noted [6, 9, 10, 74, 116, 126]. This disappointing finding contrasts to the case reports and personal clinical experience of many physicians working in intensive-care units, which suggests an acute improvement of gas exchange in response to steroid application in several patients with ARDS. Evidently, however, such an acute effect may not be translated into an increase in the survival of these patients, possibly because of rebound phenomena and compromise of host defense after the first few days of steroid application. An increased rate of secondary infection was, indeed, reported for the steroid-treated patients in some of the studies cited above. Therefore, according to present knowledge, the use of high-dose corticosteroids is not indicated in patients at high risk of ARDS or those with manifest disease. Distinct entities of ARDS may prove to be an exception; the inhalation of corticosteroids for the prevention of acute respiratory failure following smoke inhalation is clinically well established. In addition, early institution of corticosteroid administration is recommended for patients with extensive *Pneumocystis carinii* pneumonia progressing to ARDS, in order to win time for efficacy of the antimicrobial therapy [73]. Another special aspect regarding corticosteroids and ARDS was proposed recently for the late proliferative-fibrosing phase of the disease. After proving extensive mesenchymal proliferation in the absence of lung infection by open-lung biopsy in seven patients, steroid administration was started and prompted improvement of lung injury by radiologic and functional criteria [77]. Using steroids as an antiproliferative agent in the late phase of ARDS, in the absence of pulmonary infection, requires verification through controlled studies.

## Symptomatic Therapy of ARDS: Vasomotion

Vasomotor changes in ARDS include pulmonary hypertension and ventilation-perfusion mismatch. Both aspects may be influenced therapeutically (Fig. 4).

### *Almitrine*

Vasoconstriction triggered by a variety of inflammatory mediators is the predominant vasomotor change in the early exudative phase of ARDS. In parallel, however, inadequate vasodilation in nonventilated or poorly ventilated lung areas is observed regularly, synonymous with a failure of hypoxic vasoconstriction. This phenomenon is assumed to be caused by (vasodilatory) inflam-

| DRUG | VARIABLES | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | PAP | Pc | RVEF | CO | Shunt Mismatch | $PaO_2$ | $DO_2$ | $VO_2$ |
| $PGE_1$ | ↓ | (↓) | ↑ | ↑ | ↑ | ↓ | ↑ | ? |
| $PGI_2$ | ↓ | (↓) | ↑ | ↑ | ↑ | ↓ - | ↑ | ? |
| Almitrine | ↑ | - | ? | - | ↓ | ↑ | (↑) | - |
| NO Inhalation | ↓ | - | ? | - | - ↓ | - ↑ | ? | ? |
| $PGI_2$-Inhalation | ↓ | - | ? | - | - ↓ | - ↑ | ? | ? |

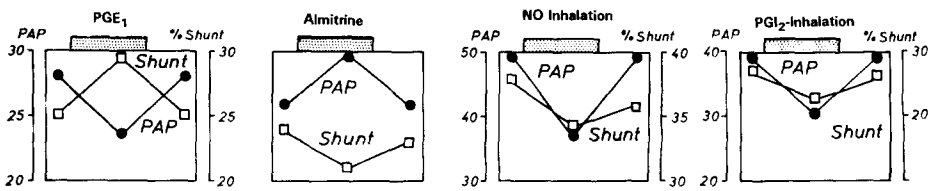


**Fig. 4.** Effects of infusion of vasodilatory prostaglandins ($PGE_1$, $PGI_2$), application of almitrine and inhalation of NO or aerosol $PGI_2$ on hemodynamics and lung function. *PAP*, pulmonary artery pressure; *Pc*, pulmonary capillary wedge pressure; *RVEF*, right ventricular ejection fraction; *CO*, cardiac output; $\dot{D}O_2$, oxygen delivery; $\dot{V}O_2$, oxygen uptake (results adapted from 88, 95, 100, 131).

matory mediators as well, and it may contribute substantially to the pulmonary shunt flow in ARDS. Almitrine has been reported previously to sensitize $O_2$ chemoreceptors, for example, in the carotid body, thereby augmenting ventilatory drive, and the substance is administered in patients with chronic obstructive pulmonary disease for this reason. It does, however, exert additional effects on intrapulmonary regulatory loops; intravenous application of almitrine in ARDS was noted to result in an acute reduction of pulmonary shunt flow, that is, an improvement of gas exchange, at the cost of some increased pulmonary artery pressure [86, 95, 96]. Most probably this efficacy is related to a similar basic effect as described for the carotid bodies: sensitization of the $O_2$-sensing mechanism, which starts the regulatory loop of hypoxic pulmonary vasoconstriction. Beyond the characterization of its short-term effects, however, no long-term investigations have been carried out with almitrine in ARDS patients, and no suggestions concerning the impact of its benefits (gas exchange) and disadvantages (pulmonary hypertension) on outcome may be given at the present time.

### *Intravascularly Applied Vasodilators*

The raised pulmonary vascular resistance in ARDS can be lowered by the infusion of $PGE_1$ or prostaglandin $I_2$ ($PGI_2$) [78, 88, 89, 110]. Their effects are dose dependent, whereby the maximum reduction in resistance approximates 30–50% in most patients. The effect diminishes within minutes after discontin-

uation of vasodilator infusion. The reduction of pulmonary vascular resistance is usually accompanied by an increase in cardiac output and right ventricular ejection fraction. Since the vasodilatory effect is not restricted to the pulmonary vasculature, a decrease in systemic vascular resistance with a drop in blood pressure is often noted. Moreover, the nonspecific vasodilation, induced in well-ventilated as well as poorly or nonventilated lung areas, may result in an increase in pulmonary shunt flow, with concomitant deterioration of arterial oxygenation. On the other hand, the increase in cardiac output results in a rise of central venous $O_2$ saturation, which diminishes the disadvantageous consequences of intrapulmonary shunt flow on arterial oxygenation and may outweigh the direct effects of the intravenous vasodilators on lung perfusion distribution. Overall, the intravenous application of prostanoid vasodilators may be beneficial in three respects.

1. The increase in cardiac output is correlated to a rise in $O_2$ delivery ($\dot{D}O_2$).
2. Vasodilatory prostanoids may reduce postcapillary vasoconstriction and thereby decrease microvascular pressure, reducing the formation of lung edema. Such efficacy has, however, not yet been demonstrated under clinical conditions.
3. Since $PGE_1$ and $PGI_2$ inhibit the activation of thrombocytes and possibly additional inflammatory-competent cells (critically dependent on the in vivo concentrations; see above), their use might offer an additional therapeutic approach to the reduction of perpetuating inflammatory mechanisms in ARDS.

In contrast to an earlier investigation [49], an improved survival rate for patients with sepsis and ARDS under continuous $PGE_1$ therapy could not be proven in two more recent controlled studies [12, 60, 102]. Thus, a general recommendation for intravenous application of $PGE_1$ or ($PGI_2$) in ARDS cannot be given at the present time. Their application may, however, be beneficial in selected patients with pronounced pulmonary hypertension and concomitant right heart failure and reduction in cardiac output. Under these conditions, the advantageous hemodynamic effect must be outweighed against a possible deterioration of arterial oxygenation.

### *Inhalation of Vasodilators*

Most recent experimental investigations have addressed the inhalation of vasoactive agents. The endothelial relaxing factor nitric oxide (NO), which is a volatile gas, was admixed to the afferent limb of the ventilator circuit under experimental conditions and in patients with ARDS [31, 100]. This intervention resulted in a rapid drop in the elevated pulmonary vascular resistance but was not accompanied by an increase in shunt flow or perfusion of poorly ventilated lung areas, and there were no systemic hemodynamic effects. The reason for this is that through its inhalational access the vasodilating agent is distributed selectively to well or at least sufficiently ventilated lung areas, exerting local

vasodilation. Redistribution of blood flow to such areas will even result in a reduction of shunt flow and an increase in arterial oxygenation. Systemic hemodynamic effects are missing, as the inhaled NO is captured immediately by hemoglobin when entering the vascular space. At present, the favorable short-term effects of inhaled NO have prompted a widespread use of this agent in ARDS patients, and most of them (but not all) respond with some reduction of pulmonary vascular resistance and improvement of arterial oxygenation. It has to be kept in mind, however, that such an effect does not necessarily result in a reduction of morbidity and mortality in these patients. Possible proinflammatory side effects of NO on the bronchial epithelium and the lung parenchyma in ARDS patients remain to be investigated in detail, and a controlled study addressing the overall efficacy of NO in patients with acute respiratory failure is needed before general use of this agent can be proposed.

In addition to NO, $PGI_2$ may be given by a transbronchial route in ARDS patients, using appropriate aerosol techniques [131]. This approach results in a reduction of elevated pulmonary artery pressure, and arterial oxygenation may be improved because of redistribution of the blood flow from shunt areas to regions with a normal ventilation-perfusion ratio. Very recently, such efficacy of aerosol $PGI_2$ was also demonstrated in patients mechanically ventilated because of acute, severe pneumonia (D. Walmrath et al., manuscript in preparation). In contrast to NO, very high doses of aerosol $PGI_2$ may cause a drop in systemic vascular resistance resulting from a spillover of this prostanoid into the systemic circulation.

Overall, it has become evident that the changes in pulmonary vasomotion during the early exudative phase of ARDS can be influenced by vasodilating agents. The transbronchial route of administration does possess particular appeal, as it addresses two different goals of therapy: a drop in pulmonary vascular pressure and improvement of ventilation-perfusion mismatch. Second, pulmonary edema formation may be reduced because of decreased capillary filtration pressure (which has not been proven yet), and the ventilator settings may be changed to avoid secondary lung injury ($O_2$ partial pressure and ventilation pressures, see below). It will be a critical future question to know the influence of inhaled vasoactive agents on mesenchymal cell activation and fibrosis as well as the host-defense competence in the alveolar compartment. In this respect, NO, $PGI_2$, and $PGE_1$ may differ substantially; in the long run it may turn out that their impact on inflammatory events, induction of fibrosis, and mechanisms of microbial clearance may be more important for the outcome of ARDS patients than (small?) differences in the direct vasoactive profile of these agents when transferred into the alveolar space via inhalation.

### Fluid Balance and Oxygen Transport

Even though the major cause of edema in ARDS is an increase in the permeability of the endothelial and epithelial barrier, pulmonary fluid balance is influenced markedly by the magnitude of microvascular pressure in the pulmonary circulation; there is an even steeper dependence on the left atrial

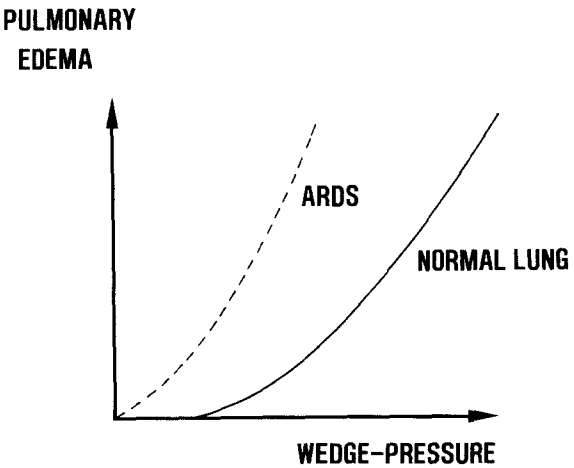


Fig. 5. Influence of pulmonary capillary wedge pressure on lung edema formation in normal lungs and in ARDS.

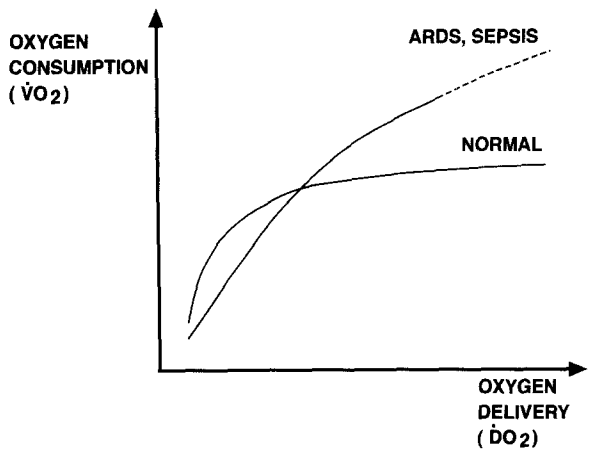


Fig. 6. Pathologic supply dependence of $\dot{V}O_2$ in sepsis and ARDS.

pressure (capillary wedge pressure) as compared with physiologic conditions (Fig. 5). A decrease of the hydrostatic pressure may thus reduce pulmonary edema formation in ARDS, although a physiologic fluid equilibrium may not be achieved because of the altered barrier characteristics. A drop in hydrostatic pressure is attainable by negative fluid balancing of the patient accompanied by reduction of central venous and left atrial pressure (e.g. diuretic therapy, continuous AV or VV filtration, hemofiltration, hemodialysis). In particular in the early exudative phase of ARDS, forced fluid removal will often result in a rapid and significant improvement of gas exchange. Clinical studies have demonstrated a reduced mortality rate in patients with ARDS in whom fluid removal and reduction of the capillary hydrostatic pressure were attainable; however, the praeter or propter of this observation is not clear at present [52, 104, 112, 113, 120]. In this regard, a therapeutic regimen guided by direct measurement of extravascular lung water may be superior to a man-

agement primarily addressing central venous and capillary wedge pressures [28, 79]. A general recommendation for the concept of volume removal in the early exudative phase of ARDS [39, 51, 71] is, however, questionable for two reasons.

1. Systemic triggering of ARDS is often accompanied by acute renal dysfunction, and drastic fluid removal under such conditions may favor the development of acute renal failure. In principle, this is reversible and may thus be accepted as a side effect, but it might also contribute to the reduction of the survival rate known to occur with increasing numbers of organ failures in sepsis and MODS.
2. Clinical investigations in patients with sepsis support the concept of a pathologic supply dependence of oxygen uptake in this patient collective (outlined schematically in Fig. 6) [18, 22, 128, 129]. Even though these results have been challenged for methodologic reasons (mathematical coupling of $\dot{V}O_2$ and $\dot{D}O_2$ calculation), they are important for pathophysiologic considerations regarding therapy of sepsis patients, in particular under conditions of lactate formation.

There is good reason to seek for high $\dot{D}O_2$ rates to guarantee sufficient or even to augment $O_2$ uptake ($\dot{V}O_2$) in peripheral organs, thereby limiting hidden $O_2$ debt. This concept can be realized by additional volume supply, optimum blood hemoglobin content, and the administration of inotropic agents (e.g. dobutamine) [8, 34, 93, 111]. In this context, systemic application of $PGE_1$ and $PGI_2$ may possibly assume new importance; when accompanied by adequate volume therapy, these vasodilatory prostanoids might reduce perfusion maldistribution in critical organs, thereby increasing regional and overall oxygen uptake [109]. As evident from the above considerations, disadvantages of systemic vasodilator therapy and generous volume supply include an increase in lung edema formation and a deterioration of gas exchange.

Hence, there is a serious therapeutic dilemma concerning volume therapy in ARDS patients. Volume removal for the reduction of pulmonary edema formation is paid for with a decrease of cardiac index and $\dot{D}O_2$ and therefore possibly with an aggravation of hidden or obvious $O_2$ debt in critical organs. Liberal volume administration, on the other hand, addresses such $O_2$ debt in patients with sepsis but may deteriorate lung function. No clinical study has as yet provided a solution to this dilemma. At present, we thus suggest a compromise, based on the accompanying conditions of ARDS. In the absence of sepsis and MODS, we favor the attempt of forced fluid removal, even at the price of a reduction of $\dot{D}O_2$ and possibly worsening renal function. We try to minimize the disadvantages of fluid removal on $O_2$ delivery by maintaining an optimum hemoglobin content. When ARDS is part of a septic multiple organ failure with metabolic acidosis and lactate formation, in particular under conditions of (septic) shock, the concept of liberal volume therapy to achieve sufficient $O_2$ delivery is given priority.

## Surfactant Replacement

Disturbances of the alveolar surfactant function in ARDS patients have been demonstrated [36, 40, 85]. According to present knowledge, an absolute lack of surface active material, as existing in the neonatal respiratory distress syndrome, is not a predominant feature in ARDS. The major determinating factors are changes in surfactant composition and metabolism as well as the inhibition of its function by the extravasation of plasma proteins [107]. Experimentally, this complex disturbance can be compensated for by transbronchial administration of sufficient amounts of functionally active surfactant. An acute reduction of atelectasis may be achieved, accompanied by a reduction of shunt flow and an increase in compliance. Experimental studies indicate that the restoration of an intact alveolar surfactant function reduces the leakage of fluid into the alveolar space. Moreover, host-defense mechanisms may be improved by the hydrophilic surfactant apoproteins (SP-A, SP-D) serving as opsonins in the alveolar compartment. Secondary pneumonia during artificial ventilation as well as aggravating inflammatory processes might be reduced. Transbronchial surfactant application has proven to be beneficial in premature infants with infantile respiratory distress syndrome (IRDS) [2, 44, 61]; arterial oxygenation and compliance are acutely improved, and the mortality rate as well as the incidence of bronchopulmonary dysplasia are reduced. It appears favorable to administer surfactant immediately after birth to premature infants who are at high risk of IRDS (preventive therapy) instead of awaiting the full formation of respiratory insufficiency (rescue therapy) [65]. To date, transbronchial application of surfactant in ARDS has only been undertaken in very few patients, mostly those who present with extreme respiratory insufficiency; impressive improvements of gas exchange have been noted in a limited number of cases [62, 68, 69, 115]. A controlled study addressing the value of transbronchial surfactant application in very severe respiratory failure has not yet been undertaken. It may, however, turn out that in analogy to the preventive application of surfactant in IRDS, transbronchial supplementation with the surface active material is even more appropriate at the very onset than after full manifestation of severe respiratory insufficiency. Moreover, instead of providing a surfactant solution via bronchoscope, appropriate aerosol techniques might be desirable. This attempt was undertaken in a recent study using a synthetic preparation. The surface activity of this material does differ largely from that of natural surfactant, and only limited amounts of surfactant were deposited in the alveolar space by this approach [92, 136]. At present, no final evaluation of this study has become available to the scientific community. A serious problem with respect to the natural surfactant compounds (extraction from animal lungs or use of recombinant apoproteins) is the limited availability of this material. This dilemma is even more aggravated by the fact that large quantities of surfactant appear to be necessary to overcome the surfactant inhibitory material present in the alveolar space in ARDS. Only after resolution of this problem can questions concerning the mode of delivery, timing of ap-

plication, and dosage be addressed in clinical studies. Until this, it remains open for speculation whether a reduction in morbidity and mortality in ARDS may be achieved by surfactant therapy.

## Respirator Therapy

Modifications of the respirator techniques in ARDS patients have received much attention in the past few years. Although not proven by controlled, prospective studies, it has to be assumed that the improvements in artificial ventilation have contributed to a decrease in the overall mortality rate of ARDS patients. None of the respirator techniques may claim to reduce lung edema formation or to suppress pulmonary inflammatory events per se. All presently used modes of artificial ventilation attempt to recruit atelectatic/edematous alveolar regions by increasing the functional residual capacity. This is mostly achieved by the use of PEEP and inverse-ratio ventilation. Disadvantages of mechanical ventilation include oxygen toxicity, baro-(volu-) trauma, as well as side effects involving hemodynamics and renal function. High $O_2$ partial pressure and ventilation with high airway pressures must be expected to aggravate inflammatory processes in the lung parenchyma, thereby favoring mesenchymal proliferation and fibrotic events. Modern concepts of respirator therapy attempt to avoid these disadvantages from the very beginning of artificial ventilation.

A proposal for the different steps in respirator therapy, as followed by the authors, is given in Figure 7. During the development of ARDS with initial use of nasal oxygen supplementation, mechanical ventilation becomes necessary when sufficient arterial oxygenation is no longer achievable ($pO_2$ below ~60 mmHg), accompanied by dyspnea, increased breathing expenditure, and clinical evidence of hypoxia. The short-term prognosis helps decision making in questionable cases; intubation and mechanical ventilation are discouraged when rapid improvement of the respiratory insufficiency is expected, but they are favored when a progressive worsening of gas-exchange conditions in the following hours is most probable. As an alternative to intubation and controlled ventilation, techniques of augmented spontaneous ventilation (with the use of face masks) may be employed at the very onset of respiratory insufficiency. In most cases, however, because of the severity of ARDS in its exudative phase, respirator therapy will start with intubation of the patient and one of the approaches indicated in phases II and III of Figure 7. From the very onset, barotrauma (or volutrauma) and unnecessarily high fractions of inspired oxygen should be avoided [17, 45, 48, 76, 119]. Numerous variations in ventilation techniques offer alternatives to conventional volume-controlled PEEP ventilation [4, 16, 17, 82, 90, 135]. These partially maintain the patient's spontaneous respiratory drive and his respiratory muscle function while supporting ventilation with flexible technology (e.g. SIMV, CPAP with IPS, BIPAP, APRV; see the legend of Fig. 7). If gas exchange worsens further, progression to phase IV is necessary, and the most advantageous compromise has to be seeked to

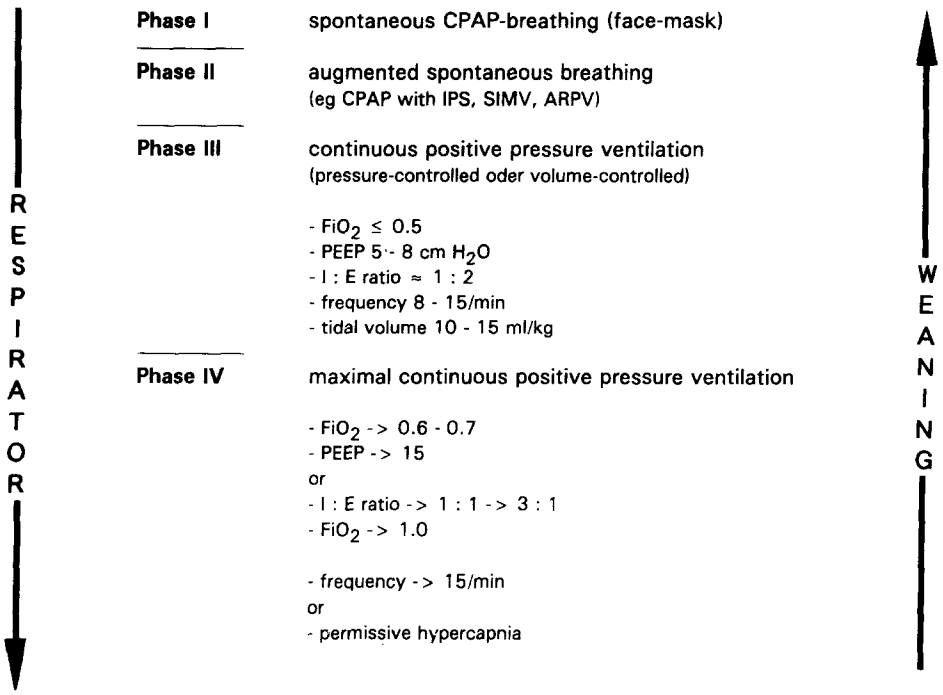


**Fig. 7.** Different phases of respirator therapy in ARDS. For details see text. *CPAP,* continuous positive airway pressure; *IPS,* inspiratory pressure support; *SIMV,* synchronized intermittent mandatory ventilation; *APRV,* airway pressure release ventilation; *PEEP,* positive endexpiratory pressure; *I:E ratio,* inspiration-expiration ratio.

maintain arterial oxygenation and $CO_2$ elimination on the one hand and to prevent barotrauma and prolonged $FiO_2$ values $> 0.6$ on the other. Under these conditions of severe respiratory failure, with increasing insufficiency of $CO_2$ removal, the concept of permissive hypercapnia represents an interesting new approach: physiologic $pCO_2$ levels are no longer attempted, but the arterial $CO_2$ content is allowed to increase considerably (to >80 mmHg) to avoid excessive increases in ventilated volumes (frequency times tidal volume) and thus barotrauma. A reduction of the mechanical work load of the lungs of more than 50% may thus be achieved. A concomitant decrease in pH (respiratory acidosis) is usually compensated for within hours by renal retention of bicarbonate; if necessary, bicarbonate is supplemented intravenously. Using this approach, an impressively low mortality rate among patients with severe ARDS was reported by Hickling et al. [45, 46] in a retrospective analysis.

Another recently developed technique is the intermittent prone or lateral positioning of ventilated patients; it attempts to recruit predominantly basally localized edematous/atelectatic areas, thereby improving gas exchange and lung mechanics [72]. CT investigations have demonstrated that periodic changes of body position (in a rhythm of 6–12 h) may achieve a reduction or redistribution of basally localized dense structures [33]. Kinetic beds have tried

to achieve this goal by a constant change between right and left lateral positioning. The overall benefit of these concepts has not been tested yet in controlled studies.

High-frequency jet ventilation and extracorporeal lung-assist techniques represent two alternative approaches for the management of severe ARDS. Concerning high frequency, however, presently available studies did not show clear benefits as compared with conventional ventilation [14, 50, 54]. Apart from specific indications (e.g. large airway leaks), there is no rationale for a widespread use of high-frequency jet ventilation in severe ARDS. The 1979 NHLBI study on extracorporeal membrane oxygenation, performed in patients with very high mortality, did not show a therapeutic benefit of this cost-extensive technique [81]. Further developments of the concept of extracorporeal gas exchange centered on $CO_2$ elimination ($ECCO_2$-R) or $CO_2$ elimination in combination with partial extracorporeal oxygenation (ECLA) [26, 63, 134, 138]. These techniques, available in a few specialized centers, have been optimized in the past few years, and impressively high survival rates of patients with seriously disturbed gas exchange were presented. It has to be kept in mind, however, that the improvements of conventional respirator therapy most probably also reduced mortality rates; a definite proof for the superiority of extracorporeal gas-exchange techniques from large controlled studies is still missing. A further recent approach is the use of an intravascular oxygenation/$CO_2$ removal device (IVOX). An elongated hollow fiber membrane oxygenator is temporarily implanted into the inferior vena cava and supplied with oxygen to support arterial oxygenation and $CO_2$ removal. However, the gas-exchange area of this device is still very small, and there is only limited experience with this new technology [47, 63, 130].

## Prevention of Nosocomial Pneumonia and Sepsis from Lung

Secondary nosocomial pneumonia represents a serious complication in ARDS, which perpetuates inflammatory events in the lung parenchyma and may result in a systemic distribution of microbial agents, their toxins, and secondary inflammatory mediators from the pulmonary focus. Thus, prevention and therapy of pneumonia deserve particular attention in ventilated patients. Important routes of microbial colonization of the airways include the retrograde migration of bacteria from the upper gastrointestinal tract via the patient's oropharynx. Impaired gastrointestinal motility and suppressed gastric acid production contribute significantly to gastric bacterial overgrowth and subsequent pulmonary colonization [21, 56]. As opposed to $H_2$ antagonists and antacids, stress-bleeding prophylaxis with drugs not influencing gastric pH (e.g. sucralfate) may thus represent a better choice to prevent nosocomial pneumonia in ventilated patients [25, 64, 122]. Definite proof for an increase in survival under this regimen is still missing. The general application of selective digestive decontamination (SDD; regular oral and/or gastric application of nonabsorbable antibiotics and antimycotics) remains controversial in ventilated patients. Several

studies have demonstrated that SDD reduces bacterial growth significantly in bronchial secretions. In most of these studies, this finding was correlated with a significantly reduced rate of secondary pneumonia (from approximately 40–50% in control groups to approximately 10% in SDD-treated patients) [30, 91, 117, 125]. Oropharyngeal decontamination alone may similarly reduce the incidence of nosocomial pneumonia [87, 99]. A significant reduction of mortality by the regular application of SDD has, however, not been demonstrated. The appearance of resistant strains caused by the continuous use of the antibiotics, in particular Gram-positive bacteria, and the high costs of the SDD regimen remain legitimate criticisms [53]. Overall, a conclusive evaluation of the benefits of SDD in the therapy of ARDS must await the results of further prospective clinical trials, including the registration of bacterial resistance profiles in institutes using this regimen. In any case, the basic concept justifiably draws attention to the fact that retrograde infections of the tracheobronchial space in ARDS patients via the oropharyngeal tract has to be prevented through strict oropharyngeal hygiene and disinfection, as preferred by the authors. The use of aerosol techniques for the improvement of local host-defense mechanisms of the lung, for example, through alveolar deposition of opsonins, antibiotics, or cytokines, poses interesting future perspectives.

## Lung Transplantation

In selected cases (single) lung transplantation may be considered when the ARDS has progressed to a proliferative-fibrotic stage, in the absence of overt lung infection and accompanying multiple organ failure [23, 27]. Alternatively, or as a preceding trial, a pulse therapy with steroids may be attempted in this very late stage of ARDS, and evidence has been presented for a beneficial effect of this drug under these specified circumstances, in contrast to the overall discouraging results with steroids in early ARDS as discussed above [77]. Up until now, transplantation was limited to a very few cases, not allowing valid conclusions at present.

## Conclusion

Despite major progress achieved in intensive-care medicine, mortality in ARDS is still high. The growing body of knowledge concerning the triggering pathogenetic events (inflammatory cells and humoral mediators) opens future perspectives for specific therapy. Until then, stage-appropriate application of therapies supporting lung function and avoiding accompanying failure of other vital organs are critically important. Secondary lung injury has to be avoided, including in particular the prevention of nosocomial infection and the triggering of proliferative-fibrosing events.

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