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Adjunctive Drug Treatment in Severe Hypoxic Respiratory Failure

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Contents

Abstract

This article reviews the pharmacological treatment of severely hypoxaemic critically ill patients, notably those with acute respiratory distress syndrome (ARDS), acute lung injury or the sepsis syndrome.

Haemodynamic support in hypotensive patients often initially requires aggressive fluid resuscitation with crystalloids or colloids, combined with vasopressors to maintain adequate end-organ perfusion. The catecholamine of choice in severe hypotension with low systemic resistance is norepinephrine (noradrenaline); dopamine is often used in mild hypotension. Once haemodynamic stabilisation is achieved, loop diuretics such as furosemide (frusemide) are used to obtain the lowest volaemia that guarantees adequate perfusion. If the fraction of inspired oxygen necessary to achieve the satisfactory haemoglobin oxygen saturation of 90% approaches 1, a trial of nitric oxide with or without almitrine is justified. Oxygen consumption can be lowered by treating fever with paracetamol (acetaminophen) and physical cooling. Occasionally, deep sedation using a combination of an opioid (most often morphine or fentanyl) and a benzodiazepine (lorazepam or midazolam) is necessary; in the presence of renal or hepatic insuf-

ficiency, propofol is a valid, although expensive, alternative. Paralysis with pancuronium or vecuronium has been associated with critical illness polyneuropathy and is used only as a last resort.

Corticosteroids may be indicated in the subacute (fibroproliferative) phase of ARDS. Other anti-inflammatory treatments (such as cytokine antagonists, cyclooxygenase inhibitors, antioxidants or monoclonal anti-endotoxin antibodies), as well as surfactant supplementation, have failed to improve prognosis in randomised trials.

The main supportive measure in severely hypoxaemic critically ill patients remains the institution of positive pressure ventilation, either non-invasively[1] or through intubation. This review article covers adjunctive drug treatment aimed at optimising oxygen supply and extraction in critically ill patients with acute hypoxaemic respiratory failure.

Sepsis is the most common risk factor for acute respiratory distress syndrome (ARDS), accounting for approximately 50% of cases;[2,3] nearly 85% of patients with severe sepsis require ventilatory support and almost 50% meet the criteria for ARDS.[4] Therefore, therapy must initially consider both entities. Sepsis and ARDS share many of the proposed pathophysiological mechanisms, but differ initially in supportive treatment. The definitions of ARDS, acute lung injury (ALI),[5] sepsis and septic shock[6] are summarised in table I.

Despite promising animal studies and numerous large-scale randomised controlled clinical trials, positive drug studies in ARDS and sepsis remain scarce. Several factors may explain the disappointing results. First, ARDS and ALI are descriptions of a set of symptoms with a wide variation of patient risks, rather than a well-defined disease. In an attempt to describe a more homogenous set of patients, additional diagnostic features were recently proposed.[7] Given the heterogeneous aetiology, pharmacological therapies are not likely to be equally effective in all forms of ARDS and ALI. Secondly, ARDS is a relatively uncommon disease[8] with multiple risk factors, making it difficult to design a study with adequate sample size to detect smaller effects of the tested drugs. Thirdly, the timing and dose of the tested drug may be inappropriate. In addition, physiological counter-regulations and potentially confounding variables, such as the recently described anti-inflammatory effect of adrenergic agonists,[9] may be uncontrolled for. Moreover, a fatal outcome in ARDS is more often caused by multiple organ failure rather than by respiratory failure,[10] and therefore therapies directed simply at improving oxygenation may be life-saving in rare instances, but are not expected to improve outcome in the majority of patients. The interpretation of clinical outcome studies in ARDS is further complicated by a possible reduction in mortality of ARDS in recent years.[11]

Our review is based on pathophysiological considerations, and, thus, we will discuss pharmacological modulation of the transport of oxygen to the alveoli, pulmonary haemodynamics, systemic haemodynamics and oxygen transport in the circulation, the uptake of oxygen into the cell, the modulation of inflammation and, finally, the reduction of oxygen consumption. To identify relevant literature, we performed a computerised Medline search using the keywords ARDS, acute lung injury, sepsis, septic shock, therapy, drug therapy and drug treatment. Additionally, we checked our personal files and the reference lists of the extracted studies and major textbooks.

1. Optimising Oxygen Delivery

1.1 Volume Management

After intubation of critically ill patients, hypotension often ensues.[12] The haemodynamic management of patients with hypotension after intubation, caused either by relative hypovolaemia in ARDS or by septic shock, is complicated by diffi-

Table I. Definitions of adult respiratory distress syndrome, acute lung injury, sepsis and septic shock

Disease	Definition
Adult respiratory distress syndrome	Bilateral infiltrates on chest x-ray, PCW ≤18mm Hg (or if PCW not available, no evidence of left atrial hypertension), PaO_2/FiO_2 <27 kPa
Acute lung injury	Bilateral infiltrates on chest x-ray, PCW ≤18mm Hg (or if PCW not available, no evidence of left atrial hypertension), PaO_2/FiO_2 <40 kPa
Sepsis	Systemic response to infection, with at least 2 of the following symptoms: temperature >38°C or <36°C heart rate >90/min respiratory rate >20/min white blood cell count >12 × 10^9/L or <4 × 10^9/L or >10% band forms
Severe sepsis	Sepsis with the presence of organ dysfunction, hypoperfusion or hypotension
Septic shock	Sepsis-induced hypotension despite adequate fluid resuscitation with the presence of perfusion abnormalities: systolic blood pressure <90mm Hg or ≥40mm Hg decline *and* one of the following elevated lactate level oliguria (<0.5 ml/kg/h) acute alteration in mental status

FiO_2 = fraction of inspired oxygen; **PaO_2** = arterial oxygen tension; **PCW** = pulmonary capillary wedge pressure.

culties in the clinical determination of volaemia and by uncertainty concerning the desired goals. Table II depicts a simplified approach to the volume management of patients with ARDS and sepsis.

1.1.1 Fluid Therapy

In hypotensive patients with possible hypovolaemia, aggressive fluid therapy should be initiated as early as possible. There is controversy whether crystalloid (normal saline or lactated Ringer's solution) or colloid (plasma, albumin, hydroxyethyl starch or dextran) solutions are the best choice. Consensus guidelines developed in 1993 recommended initial use of crystalloids, but accepted nonprotein colloids after the infusion of 2L of crystalloids without effect.[13] Recent reviews increasingly recommend crystalloid-based infusion regimens.[14-17] Formation of lung oedema does not depend on colloid oncotic pressure or serum albumin concentration,[18] and, therefore, we start fluid resuscitation with frequent boluses of normal saline and check the patient for signs of volume overload (tachypnoea, jugular distension). The rate of infusion depends greatly on the clinical circumstances. In severely septic intubated young patients, several litres of crystalloids per hour may be needed. On the other hand, in elderly patients with possible pre-existing heart failure, 1 L/hour may be a safer choice. Because of the capillary leak, large amounts of crystalloids may be necessary (up to 20 L/day) to reach the goals of volume therapy (warm skin, normal sensorium, urine output >1 ml/kg/hour, reversal of lactic acidosis).

If rapid volume expansion is desired, synthetic colloids such as polygelatine, dextran or hydroxyethyl starch may be used; the most important adverse effects with these substances are anaphylactic reactions, occasionally fatal, and the possibility of renal failure if the colloid oncotic pressure exceeds 27mm Hg. In diseases characterised by endothelial injury and capillary leak, colloids may leak into the interstitium and remain there, leading to prolonged water accumulation.[19] A recent trial compared albumin solutions with 10% hydroxyethyl starch in critically ill surgical patients with trauma or the sepsis syndrome. Up to 5L of hydroxyethyl starch within 5 days was well tolerated and led to improved cardiac output and oxygen transport, and lower lactate levels than with albumin.[20] Dextran administration is associated with dilutional coagulopathy as well as decreased fibrin clot formation and reduced factor VIII activity. Hydroxyethyl starch exhibits fewer allergic reactions (<0.1% incidence), but alters haemostasis with increases in prothrombin time and bleeding time, and decreased levels of factors VIII:C and

VIII:Ag.[14] In animal studies, hydroxyethyl starch inhibited the stimulated release of von Willebrand factor, and it may, therefore, prevent endothelial activation and neutrophil adhesion.[21,22] In patients with sepsis, volume therapy with hydroxyethyl starch had beneficial effects on endothelial-associated coagulation.[23] Additionally, it improved microvascular blood flow and gastric tissue oxygenation after major abdominal surgery.[24] *In summary*, synthetic colloids can be recommended in patients who require rapid volume expansion, but are unable to tolerate larger amounts of crystalloids or require prevention of thrombus formation and leukapheresis.[14,25]

What constitutes a safe lower threshold of plasma albumin has not yet been determined in clinical studies, but values above 25 g/L are clearly not needed.[26] In a meta-analysis, the administration of albumin actually increased the risk of death in critically ill patients.[27]

Monitoring the adequacy of volume therapy is controversial. Based on retrospective studies, use of the pulmonary artery catheter has been discouraged;[28] alternatives such as extravascular lung water determination[29] and echocardiography[30,31] are available. In skilled hands, a pulmonary artery catheter provides useful information without the technical expertise required for echocardiography.[32] Until the results of an ongoing randomised trial are published, our indications for pulmonary artery catheterisation include central venous pressures reaching 15mm Hg without clinical improvement, substantial vasopressor requirements [e.g. norepinephrine (noradrenaline) >10 %g/min] and the need for potentially lung-toxic oxygen concentrations for a long time period [fraction of inspired oxygen (FiO_2) > 0.6]. Practice parameters for haemodynamic support of sepsis were recently published.[33]

1.1.2 Elevation of Cardiac Output

Under normal conditions, oxygen consumption ($\dot{V}O_2$) does not depend on oxygen delivery (DO_2): reductions in DO_2 are counterbalanced by increased oxygen extraction by the tissues. Whereas $\dot{V}O_2$ normally decreases only with extreme reductions in DO_2 (<4.5 ml/kg/min[34]), several investigators have reported a pathological dependence of $\dot{V}O_2$ and DO_2 in ARDS and sepsis. In an attempt to improve tissue oxygenation, supranormal haemodynamic values (cardiac index >4.5 L/min/m^2, DO_2 >600 ml/min/m^2 and $\dot{V}O_2$ >170 ml/min/m^2) have been proposed. In medical patients with septic

Table II. Fluid management in septic acute respiratory distress syndrome. 'Filling pressure' is central venous pressure, or pulmonary capillary wedge pressure if available

State	Clinical signs	Intervention	Goals of therapy
Hypovolaemia	Cold skin Tachycardia, hypotension Decreased sensorium Inspiratory decrease in arterial blood pressure Low filling pressures Oliguria	Frequent boluses of NaCl 0.9% (e.g. 250 ml/15min) Nonprotein colloids acceptable if rapid volume expansion desired Albumin solutions acceptable in severely hypoproteinaemic patients	Warm skin Reversal of lactic acidosis Mean arterial pressure >60mm Hg Filling pressures approximately 15mm Hg Urine output >1 ml/kg/h
Euvolaemia	Warm skin Urine output >1 ml/kg/h Filling pressures approximately 15mm Hg Stable vasopressor requirement Reversal of lactic acidosis	Diuretics [furosemide (frusemide) 5-80mg IV] Dobutamine in persistent lactic acidosis	Define lowest filling pressure consistent with adequate organ perfusion
Hypervolaemia	Filling pressures >18-20mm Hg Jugular distension Chest x-ray shows distended central vessels Peripheral oedema (also seen in capillary leak)	Diuretics (furosemide 5-80mg IV)	Define lowest filling pressure consistent with adequate organ perfusion

IV = intravenous.

shock, however, attempts to reach these values may be detrimental.[35] In the largest study, 54% of the patients did not reach the desired supranormal values and mortality was not different between the control and intervention group;[36] the 1 trial studying only patients with septic shock also failed to find a benefit.[37] In mixed surgical patients with sepsis syndrome and/or ARDS, elevation of DO_2 >600 ml/min/m^2 was of benefit only in patients <75 years, and overtreatment with possible harmful effects, especially myocardial infarction, was a problem.[38] Interestingly, $DO_2/\dot{V}O_2$ dependency and independency can be found at different times in the same critically ill patients.[39] Whether attempts to increase oxygen delivery in patients with proven pathological $DO_2/\dot{V}O_2$ dependency can improve outcome remains to be studied. The positive studies reported used supranormal values prophylactically in high-risk surgical patients and not as a therapy in established tissue hypoxia.[40-42] For these reasons, most authors do not support the practice of increasing oxygen delivery to supranormal values.[43]

1.1.3 Transfusion Requirements

The appropriate haemoglobin level in ARDS and sepsis has not yet been determined. As discussed above, manipulating oxygen delivery with transfusions generally did not improve prognosis in ARDS with or without sepsis. In volunteers, acute hypovolaemia induced by withdrawal of 900ml of blood induced no changes in regional splanchnic and renal haemodynamics and could easily be compensated by crystalloids.[44] In patients with sepsis, elevation of haemoglobin levels did not improve oxygen delivery,[45] but induced signs of splanchnic ischaemia.[46] Clinical judgement considering the individual patient is clearly important. Circumstances that will increase the desired haemoglobin target are comorbid conditions such as coronary artery disease, bleeding activity, signs of tissue hypoxia and expected further blood loss. A recent multicentre study in stable critically ill patients found that a restrictive transfusion policy, aiming at haemoglobin levels between 7 and 9 g/dl, was superior to a liberal policy with target values of 10 to 12 g/dl.[47] Interestingly, patients with cardiac disease did not have more adverse outcomes with a transfusion threshold of 7 g/dl; this is in contrast with an earlier report showing a trend to higher mortality in patients with coronary artery disease and haemoglobin levels below 9.5 g/dl.[48]

In summary, recently published guidelines advocate a lower transfusion threshold, combined with clinical judgement,[49,50] than former recommendations.

1.1.4 Vasopressor Therapy

Most patients with septic shock will require vasopressor therapy. It is initiated in patients who are volume resuscitated with filling pressures (central venous pressure or pulmonary capillary wedge pressure) of approximately 12 to 15mm Hg and persisting hypotension. The mean arterial pressure should reach at least 60mm Hg.[33] Earlier intervention is needed in patients with severe hypotension (e.g. systolic blood pressure <75mm Hg), preexisting severe hypertension or arteriosclerotic disease with the possibility of critical stenoses of the coronary or cerebral arteries. Table III lists the principal actions of the most commonly used vasopressors in septic shock and table IV gives the differential indications of the most commonly used catecholamines.

Some practical points deserve to be mentioned. Dopamine was considered to be a first-line agent because of its ability to increase renal blood flow in low doses. In clinical trials, however, norepinephrine was at least as effective as dopamine in preserving renal function and superior in reaching predetermined haemodynamic values.[51] In combination with norepinephrine, low-dosage dopamine (typically 2 to 5 μg/kg/min) preserved renal plasma flow in volunteers[52] and increased diuresis in patients with septic shock.[53] In patients at risk for renal dysfunction, dopamine increased diuresis, but only dobutamine increased creatinine clearance.[54] In critically ill patients, however, dopamine clearance and plasma concentrations are unpredictable, limiting its practical usefulness.[55] At higher dosages (>10 g/kg/min), dopamine may increase splanchnic oxygen requirements, whereas

Table III. Vasopressors commonly used in septic shock

Drug	Dosage (g/kg/min)	Effect on				Comment
		BP	CO	SVR	PCW	
Dopamine	1-10	+	+	0 to +	+	Mainly dopaminergic and β-adrenergic
Dopamine	10-20	++	++	++	++	Mainly α-adrenergic action
Norepinephrine (noradrenaline)	0.05-2	++	++	+++	+	Particular useful in low SVR, in low doses β-effect
Dobutamine	2.5-10	0 to +	+	—	—	Useful in pulmonary congestion. BP may fall if hypovolaemic
Phenylephrine	2-10	++	–	+++	+	Purely vasoconstrictive, no cardiac stimulation, useful in arrhythmias
Epinephrine (adrenaline)	1-10 g/min	+	++	+	0 to +	May worsen lactic acidosis

BP = arterial blood pressure; **CO** = cardiac output; **PCW** = pulmonary capillary wedge pressure; **SVR** = systemic vascular resistance (mean arterial pressure – central venous pressure/cardiac output); +, ++, +++ indicate slightly, moderately or strongly increased, respectively; **–**, **––** indicate slightly or moderately decreased, respectively; **0** indicates no effect.

norepinephrine improved splanchnic oxygenation.[56] Both catecholamines may mask hypovolaemia by increasing central venous pressure. It is therefore mandatory to continue fluid resuscitation.

Dobutamine is contraindicated as primary agent in patients who are not fully fluid-resuscitated; otherwise, because of its potent reduction in preload and afterload, fatal declines in blood pressure can occur. Once adequate filling pressures have been achieved, the addition of dobutamine may improve oxygen consumption and preserve splanchnic microcirculation.[57-59] In a recent study, combining dobutamine with norepinephrine or epinephrine (adrenaline)[60] improved gastric mucosal acidosis (as a marker of tissue oxygenation) in septic shock, whereas epinephrine monotherapy was followed by an increase in lactate.[61]

In the case of severe ventricular arrhythmias not responding to supportive therapy, phenylephrine lacks any relevant cardiac action and may be useful. It may, however, limit cardiac output and, as most arrhythmias can be controlled with supportive therapies (e.g. lowering of elevated filling pressures, digoxin, calcium antagonists or β-blockers), is only rarely indicated. Experience with newer agents such as dopexamine and phosphodiesterase inhibitors (e.g. milrinone or amrinone) is too limited to formulate valid recommendations.

In summary, the effects of vasoactive agents are often unpredictable in the critically ill, and therefore consideration of the regional circulation, espe-

Table IV. Differential indications for catecholamine therapy

Clinical situation	Preferred agent	Dosage	Limiting factors
High cardiac output warm skin severe hypotension low SVR	Norepinephrine (noradrenaline)	Initial 1 μg/min; maximal 2 μg/kg/min	May maintain BP in insufficiently volume-resuscitated patients
Moderate hypotension	Dopamine	1-20 μg/kg/min	May maintain BP in insufficiently volume-resuscitated patients
Low cardiac output hypotension cold skin oliguria high SVR	Dopamine	1-20 μg/kg/min	Insufficient BP response
	Dobutamine (especially if CVP/PCW >20mm Hg)	2.5-10 μg/kg/min	Insufficient BP response
	Epinephrine (adrenaline)	1-10 μg/min	Tachycardia, myocardial ischaemia

BP = arterial blood pressure; **CO** = cardiac output; **CVP** = central venous pressure; **MAP** = mean arterial pressure; **PCW** = pulmonary capillary wedge pressure; **SVR** = systemic vascular resistance (MAP – CVP/CO).

cially renal and splanchnic microcirculation, is important. In this respect, dopamine is least likely and dobutamine most likely to improve regional tissue hypoxia.[62] Vasoactive agents should be reserved for those patients remaining haemodynamically unstable after volume replacement or those showing signs of persistent tissue hypoxia (e.g. increased lactate).[63]

1.1.5 Diuretics

Once fluid and vasopressor therapy leads to stabilisation of the patient's condition and reversal of tissue hypoxia, care must be taken not to overfill the patient. ARDS is characterised by increased extravascular lung water. Reducing lung water by fluid restriction and the use of diuretics improved outcome in some studies.[29] At the bedside it is often difficult to determine when to start diuretic therapy. Our indications include stable vasopressor requirements, reversal of lactic acidosis, signs of pulmonary congestion on chest x-ray and adequate or increased filling pressures. In the absence of severe renal failure, patients will respond promptly to low doses (5 to 10mg) of intravenous furosemide (frusemide); with repeated doses of furosemide the lowest possible filling pressure compatible with adequate organ perfusion should be titrated. If sufficient diuresis is not achievable, the volume status must be checked, if necessary with the use of a pulmonary artery catheter. If doubts about adequate preload persist, echocardiography may be performed to detect stiff ventricles responsible for elevated filling pressures in hypovolaemic patients.[30] If boluses of furosemide up to 80mg are ineffective, a continuous infusion of furosemide (up to 500 mg/day) might achieve negative fluid balances.[64] Other possibilities include metolazone (5mg) or low-dose dopamine (2 μg/kg/min). Patients not responding to these measures are either still hypovolaemic, have a postrenal obstruction or are in acute renal failure. In the latter, haemofiltration is instituted.[65] Figure 1 offers a practical approach to the oliguric patient in sepsis and ARDS.

1.2 Surfactant

In patients with ARDS both the chemical composition and the functional activity of surfactant are altered.[66] In contrast with the neonatal respiratory distress syndrome (NRDS), these alterations develop only secondarily in patients with ARDS. It has been hypothesised that they play a critical role in the development of ALI and ARDS, and therefore in analogy to NRDS surfactant replacement may be beneficial in patients with ARDS. Numerous case reports and small phase II studies in patients with ARDS show encouraging results, suggesting that surfactant can be administered safely and that oxygenation and ventilation requirements can be improved transiently. However, none of these studies was designed to demonstrate an effect on final outcome and all these studies were different with respect to the mode of delivery of surfactant to the lungs, the administered dose and the exact chemical constitution of the surfactant. Gregory and co-workers,[67] in a double-blind randomised study in patients with ARDS, instilled up to 800 mg of bovine surfactant/kg bodyweight intratracheally via a catheter inserted through the endotracheal tube, and observed in 1 group (4×100 mg/kg) a slight improvement in oxygenation and in 2 groups (4×100 and 8×100 mg/kg, respectively) a nonsignificant reduction in mortality. Another small randomised study[68] demonstrated a nonsignificant reduction in mortality with synthetic surfactant administered continuously via a nebuliser.

In the only large multicentre randomised controlled trial of surfactant with reduction of mortality as a primary end-point,[69] 725 patients with sepsis-induced ARDS received either continuously administered synthetic surfactant or 0.45% saline in aerosolised form for up to 5 days. Neither 30-day survival (60%), nor duration of mechanical ventilation, nor physiological function were different in the 2 groups. The lack of efficacy could be due to a number of factors: (i) failure to deliver enough aerosolised surfactant to the patients' lungs, since only approximately 5% of the aerosolised surfactant had reached the lungs; (ii) the inclusion of only

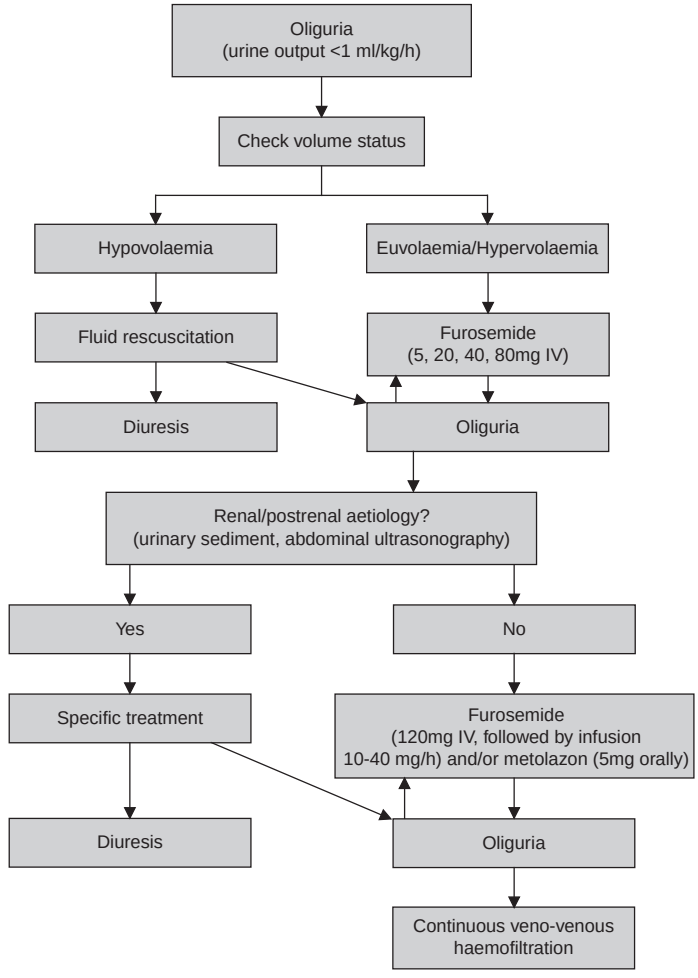

Fig. 1. Management of oliguria in acute respiratory distress syndrome and sepsis. **IV** = intravenous.

patients with sepsis-related ARDS; and (iii) the lack of surfactant-associated proteins in the preparation used.

In conclusion, despite some promising data in phase II studies, there is so far no proof for the efficacy of surfactant in sepsis-induced ARDS.

1.3 Pulmonary Vasodilators

Pulmonary haemodynamics may be manipulated with vasodilators, including nitric oxide (NO), and vasopressors such as almitrine or phenylephrine. Pulmonary artery hypertension worsens the prognosis in acute respiratory failure,[70] and, therefore, lowering pulmonary artery pressure might theoretically improve prognosis.

1.3.1 Nitric Oxide

In 1987 NO was identified to be the endothelium-derived relaxation factor.[71] Since then it has been studied extensively. NO is now known to be involved in many biological processes. It activates an intracellular soluble guanylate cyclase, which in turn stimulates conversion of guanosine triphosphate into cyclic guanosine monophosphate (GMP). cGMP causes relaxation of vascular smooth muscle

cells. Thereby, NO participates in the local control of pulmonary and systemic circulation.

In ARDS and ALI, low ventilated pulmonary areas may be highly perfused and highly ventilated areas may be low perfused. Ventilation/perfusion mismatching contributes to hypoxaemia. It is the rationale of NO inhalation to improve oxygenation by selective dilation of pulmonary vessels in ventilated lung areas. Thereby, the use of NO will decrease overall pulmonary vascular resistance and thus may be beneficial in pulmonary arterial hypertension. The first clinical data with inhaled NO were published on treatment of 7 patients with primary pulmonary hypertension.[72] It was found that NO induced a decrease in pulmonary resistance. Very promisingly, no change in systemic vascular resistance occurred. Later, Rossaint et al.[73] could replicate this finding in patients with ARDS with pulmonary hypertension. It is now well established that (as compared with other systemic vasodilator drugs) inhaled therapeutic NO selectively induces a relaxation of the pulmonary vasculature. The reason for its selectivity is the rapid binding of NO to haemoglobin in the blood stream. As the bound form has no vasodilator effects, inhaled NO is characterised by absence of systemic hypotension.

An almost linear dose-response relationship between pulmonary pressure changes and inhaled NO has been documented.[74] This is not the case for arterial oxygen tension (PaO_2). In most patients, oxygenation initially increases during inhalation of NO.[73,75] However, when dosages further increase, oxygenation is found to decrease after an individual optimum has been achieved. Thus, inhaled NO needs to be titrated for optimal effects on oxygenation. It is recommended to start with a low dose [0.1 and 0.5 parts per million (ppm) inhaled NO] and to continue to increase NO concentration (1, 3, 5, 10, 15, 30 and 50 ppm) until a optimal effect on PaO_2 has been recognised. In our experience, maximum effects on oxygenation are frequently seen between 3 and 5 ppm in patients with ARDS, but doses have to be increased to 15 ppm in some individuals. In clinical practice the continuation of NO should be discussed at least once every day. Invasive monitoring of pulmonary artery pressure is helpful when deciding about the clinical benefit. Since NO inhalation has potentially harmful effects, inhalation therapy with NO should be discontinued when no clear benefit is present. From animal studies, it is known that 20 000 ppm NO is lethal in dogs and that 10 ppm NO for 6 months or 2 ppm NO for life-long exposure is safe in mice.[76] Therefore, it is recommended to use NO concentrations of 5 ppm or lower for long term exposure in humans. This is below the allowed maximal workplace concentration for long term exposure in industrialised countries, and lower than the NO concentration found in tobacco smoke.

Some technical prerequisites need to be considered. For the purpose of therapeutic inhalation, NO gas should be scrubbed free of NO_2. This is of great importance since NO_2 is much more toxic than NO. It is known that pulmonary oedema occurs in dogs after a 1-hour exposure to 400 ppm NO_2, and that in humans with mild asthma 1 ppm NO_2 induces inflammation (as revealed by bronchoalveolar lavage).[77] Long term exposure to concentrations of >300 parts per billion of NO_2 is considered to be harmful to humans. Even in the absence of NO_2 in the NO gas reservoir, generation of NO_2 may result from contact between O_2 and NO during inhalation. NO_2 and haemoglobin quickly react to met-haemoglobin, which does not transport oxygen. A substantial increase in met-haemoglobin concentration was observed when therapeutic NO was above 15 ppm.[78] For safety reasons, NO and NO_2 concentrations in the inspiration gas should be measured continuously, and met-haemoglobin values should be assessed once daily if the NO concentration is 5 ppm or above. At the moment, the potential hazards of NO need to be further evaluated in long term studies. It should be tested whether doses higher than 5 ppm NO are safe for long term inhalation therapy.

It is remarkable that no tachyphylaxis occurs, even when NO is administered for up to 50 days,[79] but the individual response to repeated NO inhalation may be inconsistent over time in ARDS pa-

tients.[80] A sudden discontinuation of NO should be avoided because of a possible 'rebound' with rapid decreases of PaO_2 and dramatic increases in pulmonary vascular resistance.[81] Therefore, current guidelines recommend the presence of a back-up NO inhalation device in case of failure of the primary device.

Combination of almitrine (which enhances hypoxic pulmonary vasoconstriction at a dose of 4 g/kg/min)[82,83] or phenylephrine[84] with NO has been found to be more efficient than NO alone. Potential adverse effects of almitrine include neuropathy (seen in patients with chronic obstructive pulmonary disease treated long-term with high dosages), a decrease in distensibility of pulmonary arteries, and decreased right ventricular ejection fraction. Therefore, systemic administration of almitrine is only justified after individual documentation of improved oxygenation.

The most interesting clinical question is whether NO inhalation has a beneficial effect on the outcome of ARDS and ALI. Two randomised trials found no survival benefit in patients with ARDS.[85,86] This issue, however, remains highly controversial[87] and the interested reader should refer to the latest literature.

In conclusion, inhalation therapy of low-dose NO frequently improves oxygenation in ARDS and ALI. Modern NO delivery devices are safe and user friendly. At present, NO inhalation therapy, with or without a pulmonary vasoconstrictor, may be considered as rescue therapy in patients requiring oxygen concentrations of 100% and with PaO_2 <12 kPa.[88]

1.3.2 Prostaglandins

The vasodilatory prostaglandin alprostadil (prostaglandin E_1) is deactivated rapidly within the lung if administered as an aerosol. It causes selective pulmonary vasodilation and, like NO, improves gas exchange in patients with ARDS. The first studies of alprostadil in ARDS were done using intravenous infusion protocols: they revealed a decrease in pulmonary hypertension[89] and improved oxygen delivery and consumption.[90,91] Recently, aerosolised alprostadil was compared with NO inhalation in 10 patients with ARDS.[92] The investigators found that concentrations of 6 to 15 ng/kg/min aerosolised alprostadil or 2 to 10 ppm NO in the inspiratory gas were required to achieve a maximal increase in PaO_2. Both substances equally improved pulmonary vascular resistance and gas exchange by selective vasodilation in ventilated areas. If these results are confirmed, aerosolised alprostadil could be a more convenient alternative to NO inhalation in severe ARDS.

Epoprostenol (prostaglandin I_2, prostacyclin) is widely used in critical limb ischaemia as a vasodilator. In ARDS, short term infusion reduced pulmonary arterial pressure and pulmonary capillary wedge pressure without worsening oxygenation.[93] Inhaled epoprostenol induced selective pulmonary vasodilation and an increase in PaO_2 in patients with severe ARDS and was as effective as inhaled NO.[94] Additionally, it improved splanchnic oxygenation in patients with septic shock[95,96] and, in contrast with phentolamine, increased oxygen consumption in patients with sepsis and acute respiratory failure.[97] Further studies are needed to determine the role of epoprostenol in this setting.

1.3.3 Systemic Vasodilators

Other systemic vasodilators such as nitroglycerin,[89] nitroprusside[98] and diltiazem[99] were found to decrease pulmonary vascular resistance and pulmonary artery pressure, but their use resulted in increased right-left shunting with worsening oxygenation and systemic oxygen delivery.

1.4 Bronchodilators

In patients with ARDS and ALI, reduced lung compliance is usually considered the primary disorder of lung mechanics. The contribution of increased airflow resistance has been demonstrated in the sheep endotoxin model of diffuse lung injury and in few clinical studies,[100,101] and seems to be related to increased airway hyperreactivity observed in these patients. However, only 1 small placebo-controlled clinical study has directly dealt with the effects of bronchodilators (i.e. β_2-agonists) in the management of ARDS. Wright and co-workers[102] studied the effects of inhaled nebulised

orciprenaline (metaproterenol) in 8 patients with ARDS. They observed a significant decrease of airflow resistance across the lungs and a fall in peak and plateau ventilation pressure, together with a tendency to improved oxygenation.

These effects on lung and airway resistance are mainly responsible for a significant reduction in work of breathing during weaning from mechanical ventilation. This was shown with inhalation of salbutamol (albuterol) in a small group of patients with heterogeneous causes of respiratory failure.[103]

The optimal delivery system for bronchodilators in mechanically ventilated patients is still under debate: the American Association for Respiratory Care[104] suggests that metered-dose inhalers (MDIs) are effective in this population. However a small study with intubated patients has demonstrated the superiority of nebulised salbutamol over salbutamol administered by MDI through an endotracheal tube adapter.[105]

In conclusion, in spite of a lack of evidence from large clinical trials, aerosol bronchodilator therapy in patients with ALI and ARDS seems safe and justified, even if the optimal bronchodilator, dosage and delivery system (nebuliser or MDI) remain to be defined.

2. Anti-Inflammatory Therapies

In sepsis and ARDS a myriad of pro- and anti-inflammatory substances are released both locally and systemically.[106] Endotoxin is a lipopolysaccharide released by the cell wall of Gram-negative bacteria. It binds via the membrane receptor CD14 and binding proteins to macrophages, which in turn release tumour necrosis factor (TNF), interleukin (IL)-1, IL-6, IL-8 and platelet activating factor (PAF). These mediators activate arachidonic acid metabolism, the complement cascade, and the coagulation cascade. Release of these mediators in moderate amounts is beneficial and aids recovery from bacterial infection. However, in an overwhelming infection with impaired host defense, uncontrolled amplification of this inflammatory process may occur, leading to multiorgan failure and eventually death.[107] The possibility of inhibiting these mediators has lead to animal and human pilot studies which showed encouraging results. Unfortunately, virtually all the subsequent large randomised placebo-controlled studies have failed to demonstrate a benefit in terms of mortality, morbidity or length of stay in intensive care, although some improvement in physiological variables was occasionally observed.

In this section we will discuss the anti-inflammatory therapies used in established ARDS and subsequently mention the anti-inflammatory therapies used in sepsis that are aimed at preventing multiple organ failure, notably ARDS.

Corticosteroids inhibit a variety of inflammatory mediators, including TNF, the arachidonic acid cascade, and NO formation via inducible NO synthase. In animal studies and small human trials, high-dosage corticosteroids were effective in the early phase of ARDS. A subsequent large controlled trial using methylprednisolone 2 mg/kg in early ARDS failed to improve physiological parameters and mortality.[108] In the late phase of ARDS, fibroproliferative changes occur. Clinical differentiation between ventilator-associated pneumonia and ARDS can be difficult, as both entities are associated with pulmonary infiltrates and ongoing inflammatory signs. After careful exclusion of infection, prolonged administration of methylprednisolone 2 mg/kg/day resulted in significant physiological improvement and decreased mortality.[109]

Free radicals play a significant role in the pathogenesis of ARDS. Glutathione is essential as an antioxidant as well as for synthesis of proteins, transport of amino acids, enzyme and cell metabolism. Decreases in lung glutathione levels have been demonstrated in ARDS and sepsis.[110] The thiol donors acetylcysteine and procysteine can replenish glutathione levels, and have been tested in several studies. Although acetylcysteine may enhance recovery from ALI and improve oxygenation,[111] it did not improve mortality in most randomised placebo-controlled studies.[112-114] The antioxidants tocopherol and ascorbic acid

(vitamin C) have been studied in preliminary trials, but the data are insufficient to determine their usefulness in ARDS.

Cyclo-oxygenase inhibitors improve gas exchange and pulmonary hypertension in animal studies, and 1 small human trial reported improved arterial oxygenation and reduced venous admixture.[115]

Pentoxifylline is a phosphodiesterase inhibitor that has been shown in 2 small trials to induce slight improvement in arterial oxygen content, and to increase oxygen transport and uptake in patients with sepsis who are mechanically ventilated.[116,117] Double-blind placebo-controlled trials are needed to determine its role in the treatment of ARDS.

Ideally, anti-inflammatory treatment of sepsis would reduce the incidence of multiorgan failure and ARDS and thereby improve prognosis. In earlier trials, high-dosage methylprednisolone increased mortality from infectious complications in septic shock.[118] In patients with sepsis, moderate dosages of hydrocortisone (3 × 100mg intravenously for 5 days) improved outcome in patients with septic shock requiring catecholamines for >48 hours.[119] Several recent reviews cover the anti-inflammatory strategies in detail.[120-122] The following principles have been tested but never came into routine clinical practice:

- antibodies to the lipid A fraction of endotoxin[123] (a review discussing this approach was published recently[124])
- anti-TNF receptor[125]
- IL-1 receptor antagonist[126]
- PAF antagonists[127]
- ibuprofen.[128]

Ketoconazole, a thromboxane synthetase inhibitor, was effective in preventing ARDS in patients with sepsis,[129] but needs gastric pH <3 to be effective, a condition often not met by ventilated patients. A recent multicentre trial with ketoconazole apparently failed to improve outcome in sepsis, although details have not yet been published.[8] Antithrombin III is the most active physiological inhibitor of the serine proteases generated during blood coagulation. Its concentration is greatly reduced during sepsis and septic shock and correlates with survival. Correction of decreased plasma levels led to better survival in a subgroup of patients with septic shock.[130] Further studies are necessary to determine the utility of this substance in septic shock.

Haemofiltration may remove cytokines from the serum of patients with sepsis. However, it removes all compounds (inflammatory and anti-inflammatory) below a certain molecular weight, and its use in the absence of conventional indications remains unproven.[131,132]

Augmenting the immune response with granulocyte colony–stimulating factor (filgrastim), interferon-γ and IL-10 may be an alternative approach. However, controlled trials are lacking and there is a potential to increase pulmonary injury.[133]

In summary, in clinical practice, modulation of the inflammatory response is most often done with corticosteroids, either when mandated by an underlying disease or, in selected cases, where ongoing infectious processes have been excluded. If an ARDS patient shows no signs of improvement after 7 days, we would consider corticosteroid therapy. If signs of infection are present (fever, leucocytosis, elevated C-reactive protein), then blood cultures, a bronchoscopy, a computed tomography (CT) of the sinuses, exchange of central lines via guidewire with semiquantitative cultures and an abdominal CT are performed before administering methylprednisolone 2 mg/kg/day until resolution occurs.

3. Lowering Oxygen Consumption

3.1 Analgesia, Sedation and Paralysis

Analgesic, sedative and paralytic agents are often necessary in the critical care environment; reviews[134] and practice parameters[135] have been recently published. In patients who are ventilated with potentially toxic oxygen concentrations (FiO_2 >0.6), lowering oxygen consumption with these drugs is a reasonable goal. Boyd et al.[136] examined the relationship between sedation score (Ramsey score, where 1 denotes an anxious and agitated patient and 6 denotes a patient without re-

sponse to noxious stimuli) and oxygen consumption.[136] There was a significant correlation between sedation scores and oxygen consumption, the latter increasing from 70 ml/min/m^2 for a sedation score of 6 to 156 ml/min/m^2 for agitated patients. The temperature, however showed no correlation with oxygen consumption, which may be explained by the fact that the authors studied postoperative patients with possible paradoxically high oxygen consumption during rewarming.

Muscle paralysis leads to an approximately 20% reduction in oxygen consumption.[137] In another trial, therapeutic muscle paralysis with doxacurium reduced oxygen consumption from 200 to 149 ml/min. Interestingly, the gastric intramucosal pH increased from 7.21 to 7.29, indicating improved splanchnic perfusion.[138] A similar effect can be obtained by deep sedation with benzodiazepines and opioids.[139] However, adding the muscle relaxant vecuronium bromide did not further reduce oxygen consumption in this study. In a study during cardiopulmonary bypass, muscle paralysis and opioids were supplemented with midazolam/halothane or propofol. Propofol was superior in preserving hepato-splanchnic blood flow and oxygen consumption.[140] Whether propofol offers similar advantages in critically ill patients is not known. Selection of the specific drug combination is therefore guided primarily by anticipated adverse effects and costs. Considerations are prolonged effects in renal and hepatic insufficiency (where propofol would be a good choice), and haemodynamic instability (where fentanyl and paralysing agents with relatively low-dosage benzodiazepines is the preferred combination).

3.2 Treating Fever

Treating fever is another possibility to lower oxygen consumption. Ibuprofen is effective in lowering fever and oxygen consumption in sepsis, although survival is not improved.[128] The most effective intervention to lower fever is physical cooling,[141] but care must be taken to avoid shivering with subsequent increase in oxygen consumption. Lowering fever from 39.4 to 37.0°C in critically ill patients with respiratory failure significantly decreased oxygen consumption (from 359 to 295 ml/min), decreased CO_2 production and decreased the calculated energy expenditure by 20%.[142] In patients with severe sepsis, ibuprofen (10 mg/kg, maximally 800mg, intravenously 4 times daily) significantly decreased temperature from 38 to 37°C, heart rate decreased significantly and minute ventilation tended to decrease by 2 L/min. Within 20 hours, oxygen consumption decreased by 8% and lactate levels fell by 15% in treated patients, whereas oxygen consumption and lactate increased in the placebo group.[128] Unfortunately, this beneficial physiological response did not translate into improved survival. Further data

Table V. Miscellaneous drugs indicated in special situations in adult respiratory distress syndrome and sepsis

Drug	Indications	Dosage
Antibacterials	Empirical treatment in sepsis In severe ARDS until infection excluded	Depending on drug and renal function
Heparin or low-molecular-weight heparin	Prophylaxis of venous thromboembolism Disseminated intravascular coagulation	Heparin 10 000 IU/day Depending on clinical circumstances
Ranitidine	Mechanical ventilation >48 hours Enteral nutrition not possible	50mg intravenously 3 times daily
Corticosteroids[a]	ARDS >7 days without improvement Infection excluded (see text)	Methylprednisolone 2 mg/kg/day; if improvement, gradual reduction after 1 week
Nitric oxide (± almitrine)[a]	FiO_2 1 despite PEEP ≥10 cm H_2O NO responders	Start with low doses (0.1 to 0.5ppm), titrate to maximal effect. If dose >25ppm (rarely necessary), check met-haemoglobin daily

a Not generally accepted.

ARDS = acute respiratory distress syndrome; **PEEP** = positive end-expiratory pressure; **ppm** = parts per million.

are needed before evidence-based recommendations can be given.

4. Conclusions

The management of severely hypoxaemic patients with ARDS remains a clinical challenge. Despite improved ventilator strategies and supportive care, mortality remains high. At present, judicious fluid management and vasopressor treatment based on pathophysiological considerations and a few outcome studies remain the cornerstones of supportive treatment. Table V lists the most commonly used drugs in the supportive care of these patients. Nonpharmacological treatments, such as lung-protecting ventilation strategies and prone positioning, show promise for further improvements in the prognosis.

In the future, NO, aerosolised prostaglandins, and surfactant therapies might help to prevent further death from hypoxaemia in intensive care. However, more experience is needed to determine which patients will profit most from these interventions. Several multicentre studies will further elucidate the benefits of various anti-inflammatory therapies. Combining all available therapies will hopefully lead to a better prognosis in these critically ill patients.

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