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*Review article*

# Is ventilator-induced lung injury a promoter of multiple organ failure in adult respiratory distress syndrome? The effect of permissive hypercapnia on oxygenation and outcome

KEITH G. HICKLING

B6 Intensive Care Unit, Queen Elizabeth Hospital, 30 Gascoigne Road, Kowloon, Hong Kong

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## Ventilator-induced lung injury

Evidence from many animal studies has shown that mechanical ventilation (MV) can cause a form of acute lung injury which is histologically similar to adult respiratory distress syndrome (ARDS) (reviewed in [1–4]). This injury can result in progressive respiratory failure and sometimes death, and in some animal models it is associated with an inflammatory response. In saline-lavaged rabbits, conventional MV resulted in hypoxemia, an increase in microvascular permeability to albumin in systemic and pulmonary vessels, and hyaline membrane formation and granulocyte infiltration of the alveolar septa [5]. These changes were all dependent on granulocytes, and did not occur in granulocytopenic animals [5]. Pulmonary hypertension also occurs in this model, and can be prevented by indomethacin or by thromboxane A2 receptor blockade [6]. Borelli et al. [7] studied lung injury induced in anesthetised sheep by ventilation with a peak inspiratory pressure (PIP) of 50 $cmH_2O$, and compared subsequent management using extracorporeal $CO_2$ removal ($ECCO_2R$) and apneic oxygenation with that using conventional MV with a tidal volume (Vt) of 10–15 $ml \cdot kg^{-1}$. In sheep with mild lung injury (produced by 18 h of high PIP ventilation) 3 of 11 managed with conventional MV survived, compared to 9 of 11 managed with $ECCO_2R$. Sheep with severe lung injury (produced by 27 h of high PIP ventilation) all died in both groups. Deaths were not due to respiratory failure but to progressive severe hypotension unresponsive to intravenous fluid therapy, associated with renal failure, the mechanism of which was not clear. MV with a high Vt in isolated rat lungs resulted in a much higher concentration of interleukin 1-beta in lung lavage fluid than ventilation with a low Vt; the use of positive end-expiratory pressure (PEEP) with a high Vt reduced the interleukin 1-beta to intermediate concentrations [8]. When rats were challenged with endotoxin, and their lungs then excised and ventilated, high Vt ventilation resulted in higher concentrations of tumor-necrosis factor alpha in the lung lavage fluid than low Vt ventilation [9]. Conventional MV in saline-lavaged rabbits resulted in increased concentrations of platelet-activating factor, thromboxane B2, and 6-keto-prostaglandin F1-alpha in lung lavage fluid [10]; an increased number of neutrophils in the lung [11]; and decreased chemotaxis of circulating neutrophils [11]. Tumor-necrosis factor alpha and interleukin-6 have also been demonstrated in the perfusing fluid in isolated perfused mouse lungs following high-volume ventilation [12], demonstrating that these substances could enter the systemic circulation and so could result in systemic effects. Thus, in animal models, MV can result in an inflammatory response in the lung, which could potentially cause important systemic effects, perhaps inducing or amplifying a systemic inflammatory response syndrome.

High volume MV or MV with a low end-expiratory volume may also promote translocation of bacteria from the lung into the systemic circulation. Ventilation of rabbits with a high Vt following tracheal innoculation of *Escherichia coli* led to reduced bacterial clearance from the lung, and positive blood cultures occurred only in animals ventilated with a high Vt [13]. More recently [14], dogs were ventilated after instillation of *E. coli* into the trachea. In animals ventilated with low Vt, no positive blood cultures occurred and they developed little pulmonary edema. Animals ventilated with high Vt and low PEEP developed pulmonary edema, and five of six developed positive blood cultures. However, animals ventilated with high Vt and high PEEP showed little

*Address correspondence to*: K.G. Hickling

pulmonary edema, and positive blood cultures were seen in only one of six ($P < 0.05$ versus high Vt/low PEEP group). Reduced bacterial clearance and translocation of bacteria to the systemic circulation could potentially further amplify an inflammatory response.

If such consequences of MV occur in patients with ARDS, this could conceivably contribute to the development of multiple organ dysfunction syndrome, and could result in increased mortality from this cause, as well as from respiratory failure. Evidence is emerging to suggest that it may be possible to substantially reduce mortality in patients with ARDS, both that from multiple organ dysfunction syndrome and that from respiratory failure, by using modified ventilatory strategies.

Ventilator-induced lung injury occurs in animal models when lung overdistension is produced by a high peak lung volume. The detailed mechanisms are not well understood, but "stress failure" of rabbit lung capillaries which were perfused at increased microvascular pressure was more frequent at high lung volume than at normal lung volume [15], as shown in Fig. 1. The capillary wall stress resulting in stress failure apparently results from a combination of transmicrovascular pressure and alveolar wall stretch [15]. Thus, it may be important to limit transmicrovascular pressure as well as lung volume to prevent ventilator-induced injury. Ventilator-induced lung injury occurs in surfactant-depleted lungs without overdistension, if ventilation occurs with a low end-expiratory lung volume, allowing collapse and re-expansion with each respiratory cycle [16,17]. This is thought to cause high shear stresses at the junctions between collapsed and aerated lung, and in the airway epithelium during repetitive ripping open of closed distal airways with each inspiration. Sufficient PEEP to prevent end-expiratory collapse largely prevents injury in this model, provided that overdistension is avoided [16,17]. Thus, two distinct processes appear to contribute to ventilator-induced injury.

## The lung in ARDS

Gattinoni et al. [18] have demonstrated that the reduced compliance in early ARDS is not a result of a uniform increase in elastic recoil of lung tissue, but rather a reduced amount of aerated lung; the remaining

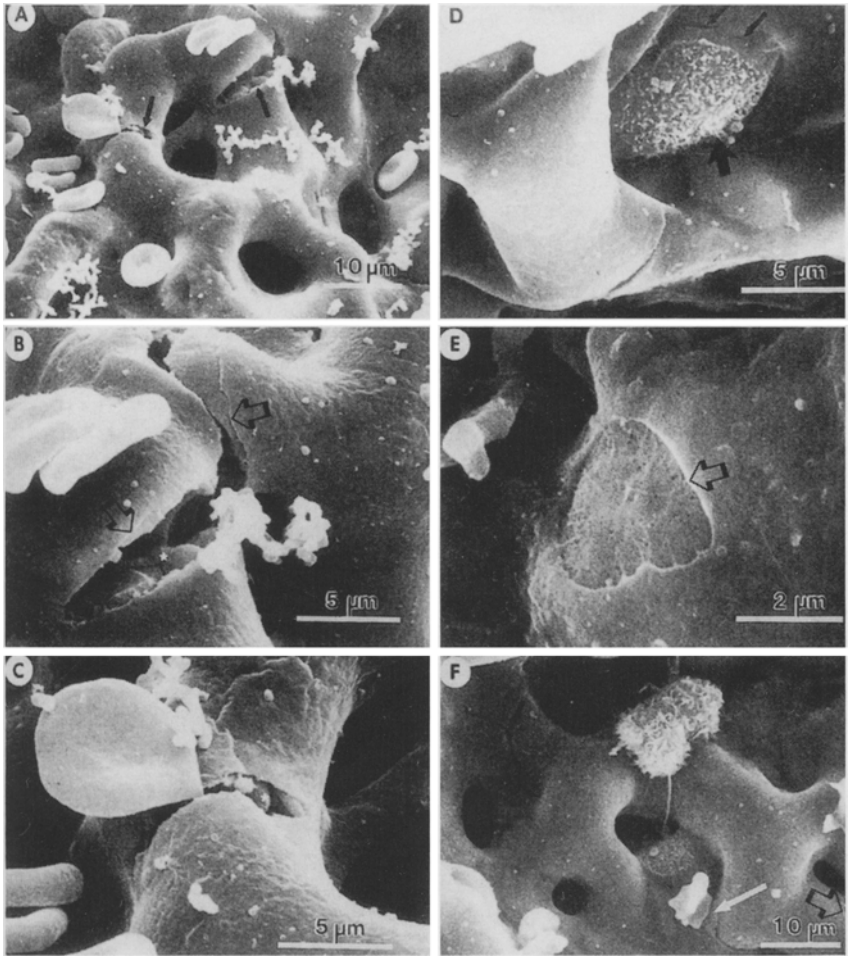


**Fig. 1A–F.** Scanning electron micrographs showing examples of disruptions of blood-gas barrier in rabbit lungs inflated to a transpulmonary pressure of 20 $cmH_2O$ and perfused with a transmural pressure of 52.5 $cmH_2O$. **A** Adjacent capillaries with complete rupture of blood gas barrier (*solid arrows*) at various angles to the capillary axis. **B** and **C** Higher magnifications. Red blood cells and proteinaceous material are seen on the alveolar surface. **D–F** Show lesions involving only the epithelium. (Reproduced from Reference [7] with permission)

lung is non-aerated and does not contribute to ventilation. The amount of aerated lung may be only half to one-third of normal, but its specific compliance (defined as compliance per unit volume of aerated lung tissue) usually appears to be relatively normal [18]. The use of a Vt of 10–15 $ml \cdot kg^{-1}$ will result in overdistension of the aerated lung, associated with increased PIP and end-inspiratory plateau pressure (PPL), and may result in progressive lung injury. The non-aerated lung occurs predominantly in the dependent regions (i.e., posteriorly in supine patients) and redistributes rapidly when patients are placed in the prone position [19]. The non-aeration of the dependent lung regions appears to be mainly a result of gravitational compression by the overlying lung; the amount of PEEP required to prevent end-expiratory collapse at any lung level is similar to the superimposed pressure from the weight of the lung above this level [20]. The lung thus behaves like a wet sponge; the distribution of water is relatively uniform throughout, but the lower regions are compressed by those above. The amount of PEEP required to recruit lung which is non-aerated as a result of this mechanism should be equal to the hydrostatic pressure resulting from the overlying lung. This may be as much as 20 $cmH_2O$ in a large patient with severe ARDS; in an average patient it would not normally be more than 15 $cmH_2O$ [20]. A small amount of additional recruitment may sometimes be achieved with higher levels of PEEP, but this will be of lung which is non-aerated as a result of different processes. An important implication of these findings is that if sufficient PEEP is applied to maximally recruit dependent lung regions, the non-dependent regions will be overdistended; the use of conventional Vt may then result in overdistension injury. In the later stages of ARDS the pathophysiology changes, and PEEP is often less effective in achieving lung recruitment.

## Strategies designed to avoid ventilator-induced lung injury

Strategies designed to avoid ventilator-induced injury therefore aim to prevent end-expiratory collapse and tidal recruitment by using sufficient PEEP, and to avoid end-inspiratory overdistension of the aerated lung by limiting Vt. A Vt of 3–6 $ml \cdot kg^{-1}$ will usually be required [21,22,4], and in many patients this will result in hypercapnia.

The best method of selecting PEEP to minimize ventilator-induced injury is unknown [23]. However, in early ARDS the thoracopulmonary pressure-volume curve usually shows a lower as well as an upper "inflection point" (Pinf), and marked hysteresis. In animal models of surfactant deficiency induced by saline lung lavage, the use of PEEP greater than the lower inflection point [16,17] largely prevents lung injury (probably by preventing repeated collapse and re-expansion with each respiratory cycle), and this approach has been advocated in ARDS [24]. It has been suggested that the lower Pinf represents the region over which most recruitment of previously collapsed lung occurs during inflation, and that if tidal ventilation occurs over the linear portion of the pressure–volume (PV) curve between the lower and upper Pinf, end expiratory collapse and lung, overdistension should both be avoided [24]. However, the main effect of PEEP in early ARDS is to overcome the superimposed pressure from the overlying lung, as discussed above [20], whereas the lower Pinf is probably determined more by alveolar and airway opening pressures. The opening pressures of collapsed alveoli may greatly exceed the pressure required to maintain inflation; as each new lung unit is recruited during inflation, it would snap open and contribute an incremental volume in addition to the pressure-induced volume increase of previously aerated lung. Thus the slope of the static PV curve above the lower inflection point could sometimes be greater than the true thoracopulmonary compliance, because of such continuing recruitment. When recruitment is complete or diminishes greatly, the slope of the PV curve would reduce to that representing the true thoracopulmonary compliance, perhaps creating an upper inflection point. A mathematical model (K. Hickling, unpublished observations) suggests that the upper and lower inflection points may have little relationship to optimum ventilator settings, and that recruitment may continue on the linear portion of the PV plot. Much of the hysteresis of the PV curve is thought to be due to lung recruitment [25], and the deflation curve may give a better indication of the pressure required to prevent end-expiratory collapse, as opposed to the opening pressures shown by the inflation curve [25]. Maximum recruitment is probably indicated by the elimination of the lower inflection point and a marked reduction of hysteresis with sufficient PEEP [24]. A simpler bedside approach is to determine the level of PEEP giving the least difference between PEEP and plateau pressure during ventilation [26], using a low Vt to ensure that the upper inflection point is not reached before end-inspiration; if this point is reached before end-inspiration, the measured "best compliance" will be lower, and a lower PEEP level will be selected. The relationship between PEEP selected using approaches designed to maximise recruitment and those using oxygenation criteria (e.g., minimum PEEP for inspired fraction of oxygen; $[FiO_2] < 0.6$ or PEEP giving maximum oxygen delivery) has not been adequately determined.

When sufficient PEEP has been used to prevent end-expiratory collapse of the dependent lung regions, the

non-dependent regions will already be well above their normal end-expiratory volume [20]. A Vt of 10–15 ml·kg$^{-1}$, delivered to a greatly reduced amount of aerated lung which is already well above its normal end-expiratory volume, will result in considerable overdistension of the aerated lung. There is evidence from autopsy studies [27] and computed tomography (CT) scan studies [28] to suggest overdistension of non-dependent regions. Such overdistension will be indicated by a high PIP and PPL; because the specific compliance of aerated lung in early ARDS is usually relatively normal [18], the degree of distension of aerated lung will be similar to that of normal lung at the same PPL. PIP is affected by the resistance of the endotracheal tube and the airways; PPL gives a better indication of peak alveolar pressure and end-inspiratory lung distension. In sheep, ventilation with a PIP of only 30 cm$H_2O$ (and therefore PPL less than this) for 48 h resulted in lung injury [29]. However, the levels of PIP or $P_{PL}$ required to induce lung injury cannot easily be extrapolated between species because of variations in lung and chest wall compliance (which affect the degree of lung distension at any airway pressure), and because of possible inter-species variation in susceptibility to lung injury at a given distension [3]. It has been suggested that $P_{PL}$ should be limited to <35 cm$H_2O$ when possible [23], but the safe upper limit for $P_{PL}$ in ARDS is not known, and it may be less than 35 cm$H_2O$. When it is possible to do so without compromising oxygenation or causing severe respiratory acidosis, it may be preferable to limit $P_{PL}$ to 30 cm$H_2O$. However, many patients with ARDS have a reduced chest wall compliance, and in such patients a higher PPL may be acceptable. A recent study showed that many patients with ARDS had an upper inflection point on the static thoracopulmonary PV curve at pressures as low as 21–27 cm$H_2O$ [30]. The investigators interpreted this as an indication that regional lung overdistension would occur at higher pressures, and suggested that the $P_{PL}$ should be limited to the pressure at the upper inflection point. Alternative explanations could be an alteration of the elastic characteristics of lung tissue, or that recruitment is completed or becomes much less above the upper inflection point, as discussed above. Further studies are required to investigate the significance of upper inflection points occurring at such low pressures. A Vt of 6–7 ml·kg$^{-1}$ can be used initially in ARDS, and this should be reduced further if a high PIP or $P_{PL}$ results. A Vt of 4–6 ml·kg$^{-1}$ will often be required [2,21,22]. A Vt of 6 ml·kg$^{-1}$ has been shown to be safe and well tolerated in ARDS [21,22,31,32].

Practical aspects of the implementation of MV in ARDS, including the interpretation of airway pressures and estimation of lung distension during spontaneous breathing and with abnormal chest wall compliance, have been reviewed recently [2,4,33,34] and will not be discussed here.

## Permissive hypercapnia

The implementation of the ventilatory approach described above in patients with ARDS usually results in hypercapnia. However, following a reduction in Vt, the degree of hypercapnia is moderated because physiological dead space falls as Vt is reduced [32], probably because blood flow increases to ventilated lung units which were previously overdistended. Thus, in 11 patients with ARDS, mean $PaCO_2$ increased only from 38 to 65 mm Hg when Vt was halved, and minute ventilation fell from 12 to 5.4 l·min$^{-1}$ [35]. Most of the effects of acute hypercapnia appear to be due to the consequent intracellular acidosis, and during sustained hypercapnia the intracellular pH (pHi) is quite rapidly restored towards normal [2,4,34,36–41] (over several hours in most tissues). During moderate hypercapnia most of the functional disturbances are therefore relatively short-lived, and in hypercapnia of gradual onset the physiological consequences tend to be minor. During very severe hypercapnia, compensation of pHi may be incomplete, and the physiological consequences will be greater. The effects of hypercapnia have recently been reviewed [2,4,34, 36–41], and only the effects on tissue oxygenation and pulmonary gas exchange, and some possible immunological effects, will be considered in this review.

## Possible effects of hypercapnia on immune function and metabolism

Acidosis can have various potentially important effects on neutrophils and macrophages. Acidosis has been shown to suppress macrophage superoxide formation, phagocytosis, and tumor necrosis factor formation [42–44], although these changes are reduced by compensation of the pHi [43]. Protein synthesis is also reduced at low pHi [38], and thus potential reductions of antibodies and other proteins involved in host defences could occur during prolonged intracellular acidosis. The effect of these changes in critically ill patients is unknown, but they could potentially modify a systemic inflammatory response syndrome and host defences. If modified ventilation with permissive hypercapnia is shown to reduce mortality in ARDS, it is conceivable that such effects of respiratory acidosis could contribute to this reduced mortality. These effects of respiratory acidosis are unlikely to be of much importance during moderate hypercapnia because of the compensation of pHi. During prolonged severe hypercapnia, however, compensa-

tion of pHi may be incomplete and these effects could be important. Intracellular acidosis also decreases the activity of phosphofructokinase [38,45] and the rate of glycolysis and lactate formation. Intracellular pH is thus a major determinant of the lactate-to-pyruvate ratio [45,46].

### Effects on cardiac output and coronary blood flow

The cardiovascular effects of acute hypercapnia represent a balance between direct depressant effects and stimulatory effects resulting from increased sympathetic activity. In humans, acute hypercapnia caused an increase in oxygen delivery, cardiac output, and myocardial contractility [47]. There have been concerns that, in critically ill patients who may already have high endogenous catecholamine levels, and may be receiving infused catecholamines, the direct depressant effects of hypercapnia could predominate and cardiac output could fall. However, this appears to be very uncommon, and a number of studies have now shown that cardiac output almost always increases even in such patients [35,48,49]. Hypercapnia normally causes coronary vasodilation and an increase in coronary blood flow and coronary sinus $PO_2$ [50]. However, it is possible that in patients with ischemic heart disease, hypercapnia could increase blood flow to normal myocardium at the expense of ischemic myocardium, thus producing a coronary steal syndrome and further increasing myocardial ischemia [40]. The tachycardia and increase in cardiac work which frequently result from permissive hypercapnia could further worsen the myocardial oxygen supply-demand ratio. Hypercapnia should therefore be introduced gradually and with careful monitoring in patients with ischemic heart disease. A recent study in dogs [51] showed that clonidine could almost completely prevent the hemodynamic changes induced by hypercapnia, and it is possible that careful use of such drugs could be beneficial in patients with ischemic heart disease during hypercapnia. However, the use of such drugs would increase the risk of a reduction in cardiac output. Many arrhythmias can occur during acute hypercapnia, probably as a result of increased catacholamine concentrations [35,52–54], and tachyarrythmias may limit the tolerance of permissive hypercapnia or require a more gradual introduction.

### Effects on vascular resistance and regional blood flow

The effects of hypercapnia on vascular resistance vary in different organs, again reflecting a balance between direct vasodilatory effects and sympathetically mediated vasoconstriction [53,54]. The degree and rate of onset of hypercapnia are probably important in determining the effects. Oliguria progressing to anuria occurred in dogs during severe acute hypercapnia induced by neuromuscular blockade with apneic oxygenation for 30–45 min, during which arterial pH fell by 0.55 units [55]. After 30 min of apnea the urine output increased promptly following reinstitution of ventilation, but after 45 min of apnea urine output increased only slowly, suggesting that renal ischemia may have occurred. Renal blood flow was reduced but urine output maintained during more moderate hypercapnia ($PaCO_2$ 106 mm Hg) in rats [56]. Splanchnic blood flow may also be reduced during severe hypercapnia [53], but some studies have shown an increase [57]. In dogs, hemorrhagic erosions of the entire gastrointestinal tract occurred following 3 h of acute hypercapnia with $PaCO_2 >$ 100 mm Hg and arterial pH $< 6.9$ [58]. These erosions were prevented by alpha-adrenergic blockade instituted prior to the hypercapnia, suggesting that the erosions may have been caused by mucosal ischemia resulting from intense splanchnic vasoconstriction. In anesthetised ewes, both renal and splanchnic blood flow increased during hypercapnia that developed gradually over 12 h [59]. The effect of hypercapnia on splanchnic perfusion in critically ill patients is unknown, but such effects may also vary with the severity and rate of onset of the hypercapnia.

Little is known about the effect of hypercapnia on the regulation of microcirculatory blood flow, in either normal or diseased states. In a recent study of hemorrhagic shock in dogs [60], severe hypercapnia ($PaCO_2$ 118.2 mm Hg) increased the critical oxygen delivery from 7.8 to 14.1 $ml \cdot kg^{-1} \cdot min^{-1}$, and decreased the maximum $O_2$ extraction ratio from 0.76 to 0.54. Moderate hypercapnia ($PaCO_2$ 72.3) had no effect on these parameters. The mechanism of this effect was not determined, but it could be related to alteration of microcirculatory flow distribution or to altered cellular $O_2$ extraction.

The same investigators studied the effect of hypercapnia on the perfusion-pressure diameter relationship of rat diaphragm arterioles [61]. During normocapnia, the diameter remained constant as pressure increased. After endothelial removal, the diameter still remained constant as pressure increased, but was less than that before endothelial removal. During moderate hypercapnia ($PaCO_2$ 80 mm Hg), the diameter decreased with increasing pressure, but after endothelial removal this synergistic effect of hypercapnia and pressure on arteriolar tone did not occur. During severe hypercapnia ($PaCO_2 >$ 80 mm Hg), arteriolar tone was inhibited and the diameter increased with increasing pressure, and this effect persisted following endothelial removal. The authors concluded that the potentiation of pressure-induced increased arteriolar tone by moderate

hypercapnia was dependent on the release of endothelium-derived mediators, whereas the inhibitory effect of severe hypercapnia was a direct effect on vascular smooth muscle. Clearly, further studies are needed to investigate the effect of hypercapnia on microcirculatory flow regulation and $O_2$ extraction, both in animal models and in critically ill patients.

Hypercapnia increases pulmonary vascular resistance, but has less effect in this regard than hypoxia or lung hyperinflation [53]. This effect on pulmonary vascular resistance is mediated largely by the reduction in extracellular pH [62]. Pulmonary hypertension resulting from hypercapnia was reduced following bicarbonate therapy in children after cardiac surgery [63] and in adults with acute asthma requiring mechanical ventilation [64]. In ARDS, an increase of pulmonary hypertension associated with permissive hypercapnia can be largely reversed by low concentrations of inhaled nitric oxide [35], and this reversal of the increase of pulmonary hypertension may result in an increase in cardiac output in patients with right ventricular dysfunction.

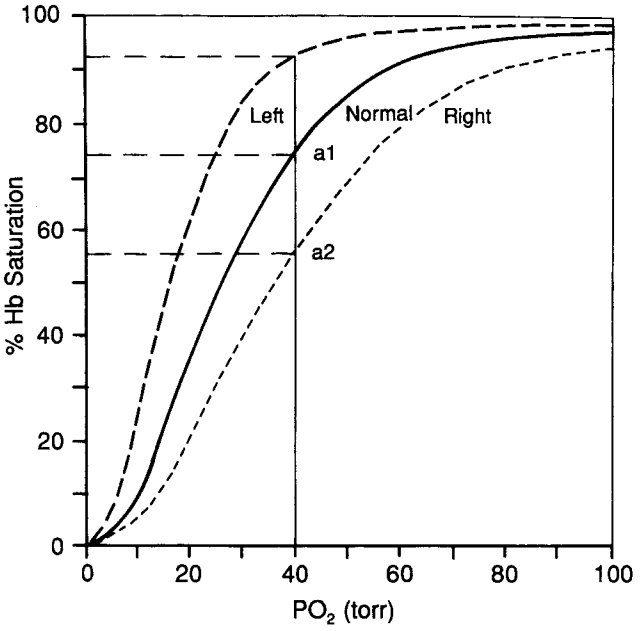


**Fig. 2.** Normal, left-shifted and right-shifted hemoglobin (Hb)-$O_2$ dissociation curves. The *vertical line* shows the arterial points (*a1* and *a2*) with a normal and right-shifted curve in a patient with hypoxemia due to a low alveolar oxygen tension ($PAO_2$), resulting in an arterial oxygen tension ($PaO_2$) of 40 mm Hg

## The effect of permissive hypercapnia on pulmonary gas exchange

Even moderate hypercapnia results in hypoxemia when the subject is breathing air, because the alveolar oxygen tension ($PAO_2$) falls according to the alveolar gas equation. The low $PAO_2$ limits oxygen uptake by the pulmonary blood flow so that arterial oxygen tension ($PaO_2$) is limited to this value. The rightward shift of the hemoglobin-oxygen dissociation curve caused by acute respiratory acidosis further reduces the arterial oxygen content ($CaO_2$) at the limited $PaO_2$ (Fig. 2). If $O_2$ extraction remains constant, venous $O_2$ content ($CVO_2$) is also lower with a right-shifted curve, and when $PaO_2$ is less than approximately 40 mm Hg, venous oxygen tension ($PVO_2$) is also slightly lower. In an experimental model of hypercapnic hypoxemia due to a low $FiO_2$ and high fractional inspired $CO_2$ concentration ($FICO_2$), buffering of the acidosis resulted in increased $CaO_2$ and reduced mortality [65]. Thus, when severe hypoxemia is due to a low $PAO_2$, hypercapnia is detrimental, both because of a further reduction of $PAO_2$ and because of the right ward shift of the hemoglobin-$O_2$ dissociation curve. However, the low $PAO_2$ can easily be corrected by a moderate increase of $FiO_2$.

In contrast, if hypoxemia is due to intrapulmonary shunt, the $PAO_2$ in ventilated lung can remain sufficiently high, even during hypercapnia, to ensure full saturation of hemoglobin leaving the ventilated lung compartment, provided that the $FiO_2$ is high enough. $CaO_2$ is then determined mainly by the percentage shunt (Qs/Qt) and $CVO_2$. A right-shifted dissociation curve then increases the $PaO_2$ at the predetermined $CaO_2$. If cardiac output and $O_2$ consumption ($VO_2$) remain constant, then $CVO_2$ will be unchanged and $PVO_2$ will also increase. Figure 3 shows the theoretical effect of a right-shifted dissociation curve on arterial and venous $O_2$ contents and tensions with intrapulmonary shunt and a high $FiO_2$. If the right shift is caused by acute respiratory acidosis, however, the reduction in $PAO_2$ associated with reduced alveolar ventilation and hypercapnia will modify these effects, and changes in cardiac output and Qs/Qt may also occur. In ARDS, hypoxemia is mainly a result of intrapulmonary shunt [66]. Theoretically, therefore, hypercapnia could improve $PVO_2$ and tissue oxygenation, provided that the $FiO_2$ is high enough to maintain $PAO_2$ at a level sufficient to allow full saturation of the pulmonary capillary blood in the ventilated lung compartment.

We constructed a mathematical model to investigate the effects of hypercapnia and the associated right-shift of the dissociation curve, with various values of Qs/Qt, $FiO_2$, and $PaCO_2$, on arterial and venous $O_2$ contents and tensions [67]. The model assumes a normal cardiac output, oxygen consumption ($VO_2$), hemoglobin concentration, and a uniform ventilation-perfusion ratio in the ventilated lung compartment. It predicts that with high Qs/Qt and $FiO_2$, $PaO_2$ and $PVO_2$ increase significantly at high levels of $PaCO_2$ as a result of the right-shift of the dissociation curve (Figs. 4, 5). In hypoxic tissues, the increased $PVO_2$ could theoretically result in

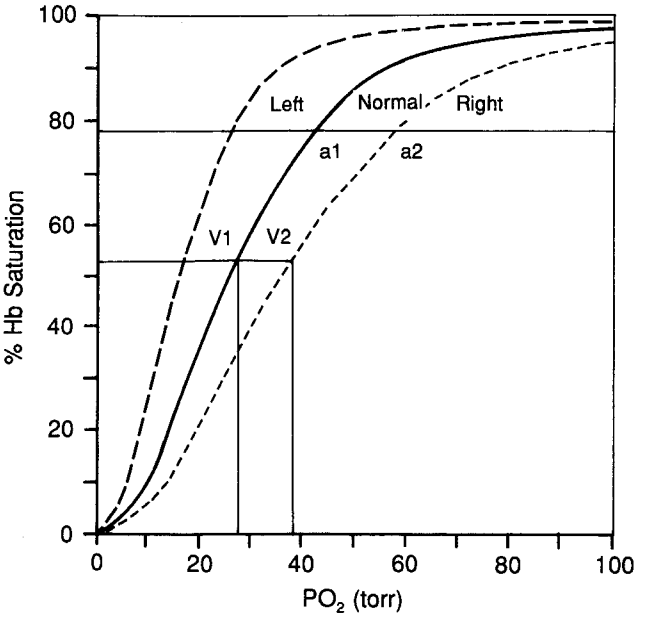


**Fig. 3.** Normal, left-shifted and right-shifted Hb-$O_2$ dissociation curves. The *upper horizontal line* shows the arterial points (*a1* and *a2*) with a normal and a right-shifted curve in a patient with hypoxemia due to intrapulmonary shunt while breathing a high inspired fraction of oxygen ($FiO_2$). It is assumed that venous oxygen content ($CVO_2$), percentage shunt (Qs/Qt), and end-capillary oxygen content (and hence arterial oxygen content [$CaO_2$]) do not change significantly between normal and right-shifted curves. The *lower horizontal line* shows the corresponding venous points, *V1* and *V2*. Both $PaO_2$ and mixed venous oxygen tension ($PVO_2$) are higher with a right-shifted curve

increased $VO_2$. We modified the model to investigate the potential magnitude of this effect by making $PVO_2$ constant and allowing $VO_2$ to increase with increasing $PaCO_2$. This resulted in substantial increases in $VO_2$ with increasing $PaCO_2$. A modest decrease in cardiac output with increasing $PaCO_2$ could negate these effects and reduce $PVO_2$ or $VO_2$, but in practice cardiac output usually increases during hypercapnia.

In tissues with a very high oxygen extraction ratio (and therefore a low regional venous $PO_2$), this beneficial effect of hypercapnia on venous $PO_2$ is less, and the optimum venous $PO_2$ occurs at a lower $PaCO_2$. This is because the rightward shift of the dissociation curve is small at very low $PO_2$ values. With an extremely high $O_2$ extraction ratio and very low venous $PO_2$, even moderate hypercapnia could reduce venous $PO_2$, because the reduced $O_2$ content of blood leaving the ventilated lung compartment (as a result of lower $PAO_2$) has a greater effect than the very small rightward shift of the dissociation curve at very low venous $PO_2$ [68].

However, the small reduction in $O_2$ content of blood leaving the ventilated lung compartment could usually be restored by a moderate increase in $FiO_2$, and whether this effect may be important in tissues with a high $O_2$ extraction ratio (such as the renal medulla) is not clear. In any case, changes in tissue blood flow are likely to be more important.

Several other physiological changes may affect tissue oxygenation during pressure-limited ventilation with permissive hypercapnia in ARDS. A reduction in cardiac output would decrease $PVO_2$, and this has been a major concern in critically ill patients with impaired cardiac function. In practice, however, cardiac output usually increases during hypercapnia, even in such patients [35,43,44]. As well as the direct effect of hypercapnia, cardiac output may also be affected by the reduction in intrathoracic pressure during pressure-limited ventilation.

Qs/Qt may also be affected by a number of factors during permissive hypercapnia. The reduction in mean airway pressure following the initiation of pressure-limited ventilation may increase Qs/Qt as a result of lung derecruitment [69]. This increase in Qs/Qt can often be prevented by increasing PEEP or by extending the inspiratory-to-expiratory ratio to prevent a reduction in mean airway pressure. An increase in cardiac output can result in increased Qs/Qt [70,71], probably because blood flow to non-ventilated lung is increased. This tends to offset the effect on $CaO_2$ of the increased $CVO_2$ resulting from an increased cardiac output with constant $VO_2$. Alterations of systemic vascular resis-

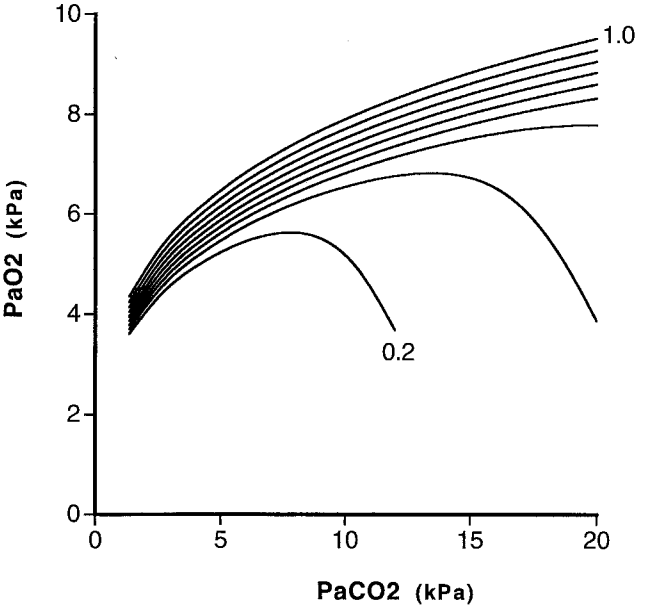


**Fig. 4.** The effect of varying arterial $CO_2$ tension ($PaCO_2$) on $PaO_2$ in a mathematical model of a lung with 50% intrapulmonary shunt. *Lines from top to bottom* are for inspired $O_2$ fractions of 1.0, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, and 0.2. The model assumes normal values of cardiac output, hemoglobin concentration, and 50% saturation tension $P_{50}$, and that cardiac output remains constant with changing $PaCO_2$. (Reproduced with permission from reference [67])

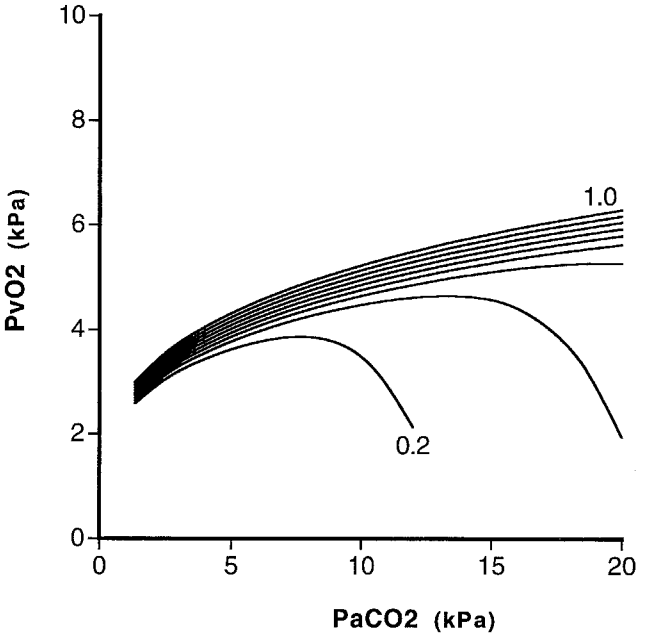


**Fig. 5.** The effect of varying $PaCO_2$ on mixed venous $O_2$ tension ($PVO_2$) in a mathematical model of a lung with 50% intrapulmonary shunt. *Lines from top to bottom* are for inspired $O_2$ fractions of 1.0, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, and 0.2. The model assumes normal values of cardiac output, hemoglobin concentration, and $P_{50}$, and that cardiac output remains constant with changing $PaCO_2$. (Reproduced with permission from reference [67])

tance, tone of the venous capacitance vessels, pulmonary artery pressure, and left ventricular function during hypercapnia could affect left ventricular end-diastolic and pulmonary capillary pressures. This could alter fluid fluxes in the lung and affect extravascular lung water and pulmonary blood volume, thus altering Qs/Qt. Acute respiratory acidosis per se can also affect Qs/Qt through direct or autonomically mediated effects on the pulmonary vasculature and, possibly, on the airways. Acidosis augments hypoxic pulmonary vasoconstriction, and therefore usually reduces Qs/Qt and increases $PaO_2$, while alkalosis has the opposite effect [72–74]. In dogs with oleic acid-induced pulmonary edema, and cardiac output maintained constant, metabolic alkalosis caused a marked increase in Qs/Qt from 44% to 62%; and a decrease in $SaO_2$ from 82% to 69%, in $PaO_2$ from 55 to 34 mm Hg, and in $PVO_2$ from 34 to 26 mm Hg [75]. Pulmonary vascular resistance decreased, suggesting that hypoxic pulmonary vasoconstriction was inhibited and so blood flow to unventilated lung increased. Metabolic acidosis had opposite effects on gas exchange; Qs/Qt fell from 44% to 33%, and $SaO_2$ increased from 82% to 87%, $PaO_2$ from 55 to 83 mm Hg, and $PVO_2$ from 34 to 43 mm Hg. However, pulmonary vascular resistance did not change significantly. Respiratory acidosis had no significant effect on Qs/Qt, $SaO_2$, or $SVO_2$. However, $PaO_2$ increased from 55 to 75 mm Hg, and $PVO_2$ from 34 to 47 mm Hg, perhaps partly because of an increase in $P_{50}$ [75]. However, when the respiratory acidosis was buffered with bicarbonate to maintain constant pH, gas exchange deteriorated, Qs/Qt increasing from 44% to 52% and $SaO_2$ falling from 82% to 77%. The authors suggest that the direct vasodilator effect of hypercapnia in hypoxic lung regions was opposed by acidosis, resulting in little overall effect on Qs/Qt from respiratory acidosis. However, when the acidosis was corrected by buffering, the direct vasodilator effect of hypercapnia was unopposed, resulting in inhibition of hypoxic pulmonary vasoconstriction and an increase in Qs/Qt. Hypercapnia increased $PaO_2$ in dogs with one lung ventilated with 100% $O_2$ and the other with 100% nitrogen [76], because of reduced blood flow to the $N_2$ ventilated lung, as shown by $^{133}Xe$ washout. $PaO_2$ also increased during hypercapnia in sheep with pneumonia [77]. Hypercapnia has been reported to have variable effects on the airways, with both an increase [78,79] and a decrease [80] of airway resistance being described, but inhalation of 10% $CO_2$ by humans caused no change in airways resistance [81]; this effect on the airways is probably less important than that on the pulmonary vasculature.

Thus, most studies suggest that acidosis reduces Qs/Qt, but that hypercapnia may increase Qs/Qt if the acidosis is buffered. The reduction of Qs/Qt by acidosis is beneficial to gas exchange, but it is possible that the diversion of blood flow away from consolidated lung could increase lung tissue ischemia; lung tissue oxygen consumption is increased in ARDS, and lung ischemia could possibly impede lung repair, and perhaps facilitate infection. Because of these complex and interacting mechanisms affecting oxygenation during hypercapnia, the final effect on $PaO_2$ is variable and unpredictable, but $PVO_2$ usually increases because of an increase in cardiac output, and because of the right-shift of the hemoglobin dissociation curve. Buffering of the respiratory acidosis could impair oxygenation, both by increasing Qs/Qt and by reversing the right-shift of the dissociation curve, thus reducing $PVO_2$; however, such buffering could possibly facilitate correction of any hypercapnia-induced hemodynamic changes [54] and reduce lung tissue ischemia.

Some patients with very severe ARDS may require a period of ventilation with a PPL of 40–50 $cmH_2O$, and perhaps inverse ratio ventilation, in order to achieve satisfactory oxygenation. Sustained inflations may also facilitate lung recruitment [82]. However, it is often possible to reduce Vt and PPL after 10–60 min without a substantial fall in arterial $O_2$ saturation, providing that sufficient PEEP is used. The opening pressures of collapsed alveoli may greatly exceed the pressure required to maintain inflation after recruitment. In saline-lavaged piglets, 10 min of ventilation with a PIP of

55 $cmH_2O$ was required to achieve satisfactory oxygenation and complete lung recruitment on CT scan; PPL could then be reduced to 30–35 $cmH_2O$ while lung recruitment and a low level of Qs/Qt were maintained [83]. Gattinoni et al. [84] have also shown that a high PPL may be required to achieve recruitment in dependent lung regions in ARDS. It may be necessary to repeat such recruitment maneuvers at intervals, but Vt and PPL should be reduced subsequently whenever possible. The maintenance of a relatively high end-expiratory alveolar volume in surfactant-depleted lungs may actually reduce the end-expiratory pressure needed to prevent end-expiratory collapse, according to Laplace's law; thus the recommendation to "open up the lung and keep the lung open" [85].

With high levels of $PaCO_2$, $PAO_2$ is substantially lower than with a normal $PaCO_2$ and the same $FiO_2$; for example, with a $PaCO_2$ of 150 mm Hg and a $FiO_2$ of 0.75, the $PAO_2$ is approximately the same as that with a $FiO_2$ of 0.6 and a normal $PaCO_2$ . The potential for oxygen toxicity is thus, presumably, reduced, and it may be reasonable to accept a higher $FiO_2$ in the presence of severe hypercapnia. However, alveoli in lung units with a high V/Q ratio will be exposed to a lower $PCO_2$ and a higher $PO_2$, and these regions could then be at risk of oxygen toxicity.

## Clinical studies

Several studies have examined the effects of permissive hypercapnia on oxygenation in ARDS. These generally confirm the expected findings during hypercapnia; an increase in cardiac output tends to increase $CVO_2$ and $PVO_2$, but because Qs/Qt usually increases as cardiac output increases, the effects on $PaO_2$ and $CaO_2$ are variable, but usually minor. $PVO_2$ and $PaO_2$ usually increase to a greater extent than $CVO_2$ and $CaO_2$ because of the right-shift of the dissociation curve.

Following a reduction of Vt in seven patients with ARDS until $P_{50}$ increased by 1 kilopascal (kPa) or pH decreased to 7.2 or less [48], the cardiac index (CI) increased in all patients (mean, from 4.5 to 5.5 $l \cdot min^{-1} \cdot m^2)^{-1}$; $CVO_2$ increased minimally, from 9.6 to 9.7 ml%; $CaO_2$ fell slightly, from 13.6 to 13.0 ml%; and oxygen extraction ($C(a\text{-}v)O_2$) decreased from 4.0% to 3.3 ml%. However, $PVO_2$ increased from 5.3 to 6.1 kPa (39.8 to 45.8 mm Hg) and blood lactate fell from 2.3 to 1.7 mmol/l. Five ARDS patients were studied before and after a period in which Vt was reduced from 10 $ml \cdot kg^{-1}$ to 7.5 $ml \cdot kg^{-1}$ [49]. $PaCO_2$ increased from 40 to 59 mm Hg and pH decreased from 7.49 to 7.34. CI increased from 5 to 6.1 $l \cdot min^{-1} \cdot m^{2-1}$, oxygen delivery index ($DO_2I$) increased in all patients (mean, from 600 to 688 $ml \cdot min^{-1} \cdot m^2)^{-1}$, and $PVO_2$ and $PaO_2/FiO_2$ did not change significantly (means increased from 34 to 40 mm Hg and from 146 to 152 mm Hg). Puybasset et al. [35] studied the effect of halving Vt, and of nitric oxide inhalation, in 11 patients with ARDS. $PaCO_2$ increased from 38 to 65 mm Hg during the reduced Vt period, and pH decreased from 7.41 to 7.22. CI increased, from 3.4 to 4.3 $l \cdot min^{-1} \cdot m^{2-1}$, and $DO_2I$ from 387 to 500 $ml \cdot min^{-1} \cdot m^{2-1}$; $PaO_2$ did not change significantly; intrapulmonary shunt increased; venous $O_2$ saturation increased; and $O_2$ extraction ($C(a\text{-}v)O_2$) decreased, from 3.7 to 2.9 ml/100 ml; suggesting improved oxygen availability. $PVO_2$ was not specified. Inhaled nitric oxide resulted in a further increase in CI and venous $O_2$ saturation during hypercapnia. In a randomized trial of permissive hypercapnia in ARDS, Amato et al. [86] found a higher $DO_2$ and lower blood lactate concentration in the study group during the first 48 h, but after this period the difference was not significant, suggesting that compensatory changes had occurred. Other studies [87,88] also demonstrated an increase in cardiac output during permissive hypercapnia. McIntyre et al. [89] found that mild permissive hypercapnia resulted in little hemodynamic disturbance in 15 patients with ARDS.

In most of these studies, it is not possible to differentiate an increase of $PVO_2$ resulting from a right shift of the dissociation curve from that due to an increase in $CVO_2$ because of increased cardiac output. However, in the study of Thorens et al. [48], mean $PVO_2$ increased from 5.3 to 6.1 kPa (39.8 to 45.8 mm Hg), whereas mean $CVO_2$ changed only minimally, from 9.6 to 9.7 ml/100 ml, suggesting that the increase in $P_{50}$ may have been the major cause of the increased $PVO_2$. Two studies showed a reduction of blood lactate concentration during hypercapnia [48,85], suggesting that tissue oxygenation may have improved. However, elevated blood lactate concentration can occur in the absence of tissue hypoxia in patients with sepsis [90]. In addition, intracellular acidosis decreases the activity of phosphofructokinase (and other enzymes) and reduces the rate of glycolysis and lactate formation [91]. Hypercapnia or hydrochloric acid infusion decreased blood lactate concentration during experimental lactic acidosis [92]; in ventilated patients receiving an infusion of lactic acid, respiratory alkalosis decreased lactate clearance and increased blood lactate concentration [93]. Thus, the reduced lactate concentrations during hypercapnia in these studies must be interpreted with caution and cannot necessarily be assumed to indicate improved tissue oxygenation.

## Effects of acute hypercapnia on cellular energy stores

Intracellular acidosis decreases the activity of many enzymes. Thus, during severe acute hypercapnia, deple-

tion of adenosine triphosphate (ATP) could occur (perhaps without an elevated blood lactate concentration) if energy production by glycolysis and other metabolic pathways was inhibited to a greater extent than energy consumption. This depletion of ATP could potentially threaten cellular integrity. However, ATP levels were maintained in rats' brains even during severe hypercapnia with $PaCO_2$ of 490 mm Hg and pH of 6.6 [94]; even when $PaCO_2$ was increased to 750 mm Hg with a pHi of 6.2 under hyperbaric conditions, brain ATP levels were preserved [95]. In a study of cerebral ischemia, severe hypercapnia ($PaCO_2 > 400$ mm Hg) did not increase the severity of ischemic injury [96]. The lack of adverse effects during and following severe hypercapnia, both in patients [21,22,97] and in animal models [56,98–100], also suggests that depletion of cellular energy stores does not occur. Tang et al. [101] showed that the reduction of myocardial contractility resulting from respiratory acidosis was associated with a reduced myocardial oxygen consumption, and suggested that this may represent a protective "cardioplegic" effect. Other studies [102,103] have shown that acidosis decreases intracellular $Ca^{2+}$, and this decrease may explain the reduced myocardial contractility and oxygen consumption.

Some ex-vivo studies have shown that intracellular acidosis is cytoprotective during anoxia. Cells survived for several hours of complete anoxia when the pH of the perfusing fluid was 7.0 or less [104,105]. Following reoxygenation and an increase in pH of the perfusing fluid to 7.4, cell death occurred as intracellular pH (pHi) increased to 7.0, but if pHi was maintained low by perfusion with a low pH fluid, or by the blocking of $Na^+/H^+$ exchange with dimethylamiloride, cell death was markedly reduced [106,107]. In contrast, monensin, a $Na^+/H^+$ ionophore, accelerated the rise in pHi when extracellular pH was increased without reoxygenation, and caused more rapid cell death [107]. If pHi was allowed to increase very gradually following reoxygenation, cell viability could be maintained. These studies were designed to simulate the cellular hypoxia of ischemia and subsequent reperfusion, and suggest that the extracellular acidosis that occurrs during shock may have a cytoprotective role by facilitating the maintenance of intracellular acidosis during ischemia and subsequent reperfusion [107]. Similar observations were made with a variety of cell types; with isolated perfused liver and papillary muscle [107,108]; and also with renal tubular cells [109]. The cytoprotection by intracellular acidosis in these studies did not appear to be a result of alteration of intracellular free $Ca^{2+}$ concentration [107]. Intracellular free $Ca^{2+}$ concentration increased progressively during anoxia and was not changed significantly during reoxygenation. Intracellular $Ca^{2+}$ was similar whether reoxygenation occurred at pH of 7.4 or of 6.2, although cell death was prevented at pH 6.2. Dimethylamiloride greatly reduced cell death following reoxygenation at pH 7.4 (by reducing the rise in pHi), but did not reduce intracellular free $Ca^{2+}$. In contrast, dichlorobenzamil, an inhibitor of $Na^+/Ca^{2+}$ exchange, caused a decline in intracellular $Ca^{2+}$, but did not prevent cell death.

The mechanism of this cytoprotective effect has not been determined; the investigators suggest that degradative enzymes, such as phospholipases and proteases, which are activated during ATP depletion and may result in cell injury, are rendered inactive at acidic pH. The clinical relevance of these studies is not yet clear, but they do tend to support the view that even severe intracellular acidosis resulting from permissive hypercapnia is unlikely to be intrinsically harmful, and should not result in tissue injury, provided that myocardial function and tissue oxygenation remain adequate.

## Outcome with modified ventilatory strategies in ARDS

Mortality rates substantially lower than those of 50%–60% previously described [110] in ARDS have recently been reported in several uncontrolled studies using modified ventilatory strategies with permissive hypercapnia. Table 1 shows the outcomes in some uncontrolled studies. However, the mortality rate in ARDS is known to be affected by many factors, including age, the underlying illness, co-morbidities, and the number of organ failures, and therefore these uncontrolled outcome studies must be interpreted carefully. Sheridan et al. [111] reported 54 children with burns (mean burn area 44%, range 0%–98%) and inhalational injury or ARDS requiring MV for 12.5 days (range 1–56 days). The PIP was maintained $<40$ cm$H_2O$, and maximum $PaCO_2$ was 39–111 mm Hg. There were no deaths, except for those of 2 patients who were brain dead soon after admission.

In a recent controlled non-randomized trial of permissive hypercapnia in 34 patients with ARDS following trauma [112], one clinical service used permissive hypercapnia while two used conventional management. Hypercapnia was allowed even in head-injured patients providing that intracranial pressure remained normal. The mortality rate was 9% (1 of 11 patients) in the permissive hypercapnia group versus 52% (12 of 23 patients) in the control group ($P = 0.016$). Even head-injured patients had a lower mortality rate in the permissive hypercapnia group (0 of 5 versus 8 of 18 patients, $P = 0.028$). However, the severity of head injury was slightly greater in the control group, and neurological outcomes were not reported. Thus, further studies of this approach are required in head-injured

**Table 1.** Studies of outcome in ARDS managed with pressure-limited ventilation and permissive hypercapnia

| *n* | Patients | Management | Mortality | Author |
|---|---|---|---|---|
| 50 | ARDS; LIS >2.5 | PH, PIP < 30–40 $cmH_2O$, always < 40 $cmH_2O$ | 16% | Hickling 1990 Reference 21 |
| 9 | ARDS | PH | 22% | Toth 1992 Reference 28 |
| 49 | Severe ARDS, referred for $ECCO_2R$ | PH, $ECCO_2R$ (24), NO (7), FPC | 24% | Lewandowski 1993 Reference 116 |
| 26 | Patients above not requiring $ECCO_2R$ | PH, NO, FPC | 8% | Lewandowski 1993 Reference 116 |
| 53 | ARDS, LIS >2.5 | PH, PIP < 30–40 $cmH_2O$ | 26% | Hickling 1994 Reference 22 |
| 20 | ARDS; 1979 ECMO crit, LIS 3.6 ± 0.2 | PH, NO, TGI, prone positioning | 30% | Levy 1995 Reference 117 |
| 53 | ARDS, LIS >2.5 | Mild PH, pH > 7.3, PPL 39 ± 15, PIP 44 ± 16 | 40% | Thompsen 1994 Reference 118 |
| 40 | Children with ARDS | PH, PCV, PIP < 35–40, $PaCO_2$ 71 ± 23 mm Hg | 30% | Nakagawa 1995 Reference 119 |
| 23 | Children with ARDS, LIS >2.5 | PH, PIP < 35 $cmH_2O$, $PaCO_2$ 39–94 mm Hg | 17.4% | Botero 1995 Reference 120 |
| 54 | Children, burns | PIP < 40 $cmH_2O$, $PaCO_2$ 39–111 mm Hg | 0% | Sheridan 1995 Reference 111 |

PH, Permissive hypercapnia; LIS, lung injury score; NO, nitric oxide inhalation; TGI, tracheal gas insufflation; FPC, frequent body position changes; PCV, pressure control ventilation; PIP, peak inspiratory pressure; 1979 ECMO crit, criteria used for selecting patients for entry to the 1979 randomized trial of extracorporeal membrane oxygenation in severe ARDS (adult respiratory distress syndrome) [121]; $ECCO_2R$, extracorporeal $CO_2$ removal; PPL, end-inspiratory plateau pressure; $PaCO_2$, arterial $CO_2$ tension; ECMO, extracorporeal membrane oxygenation.

patients. In the control group, death was due to multiple organ failure in 7 patients, cardiovascular instability in 2, sepsis in 1, head injury in 1, and respiratory failure in 1. The 1 death in the permissive hypercapnia group was due to multiple organ failure. Thus, the reduction in mortality was mainly due to fewer deaths from multiple organ failure, supporting the hypothesis that the conventional ventilatory approach may induce or amplify a systemic inflammatory response, and perhaps facilitate the development of multiple organ failure.

The first randomized trial of a ventilatory strategy using permissive hypercapnia in ARDS has now been terminated prematurely after 48 patients were enrolled, because of a significant survival advantage in the permissive hypercapnia group (64% versus 31%, $P$ = 0.00005) [113]. This study used an aggressive lung recruitment strategy in the permissive hypercapnia group, with PEEP titrated to the static thoraco-pulmonary pressure-volume curve, resulting in higher levels of PEEP than in the control group [114]. Pressure limitation and permissive hypercapnia were implemented from the commencement of ventilation, and Vt was limited to a maximum of 6 $ml \cdot kg^{-1}$, even during spontaneous breaths. There was a negative association between the amount of PEEP used in the first 36 h of ventilation and barotrauma, suggesting that PEEP was protective, provided that peak and plateau pressures were limited [115]. The duration of ventilation was substantially shorter in the permissive hypercapnia group ($P$ = 0.0002) [113]. The causes of death in this study have not yet been reported, but with such a large difference in mortality rate it is probable that deaths from multiple organ failure, as well as deaths from respiratory failure, must have been reduced in the study group, as occurred in the study by Gentilello et al. [112]. If this is the case, these data would further support the hypothesis that currently recommended ventilatory strategies may result in less systemic inflammatory response than older strategies. It would be valuable to study cytokine concentrations in broncho-alveolar lavage fluid and in plasma in future randomized trials of such strategies.

The evidence supporting pressure-limited strategies with maximum lung recruitment is now compelling, and it appears that it may be possible to achieve a substantial reduction in mortality rates, perhaps with fewer deaths from multiple organ failure, as well as from respiratory failure. If death from multiple organ failure is decreased with these strategies, this may be due to a reduction of a barotrauma-induced inflammatory response in the lung, but it is possible that respiratory acidosis may also down-regulate an inflammatory response, through effects on inflammatory cells. Several other randomized trials are now in progress, but even if these confirm an improved outcome with

modified strategies, it will probably be many years before the optimum ventilatory management can be determined.

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