Reciprocal Influence of Refractory Hypoxemia and High Intracranial Pressure on the Postoperative Management of an Urgent Neurosurgical Procedure

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A 20-year-old man was admitted in the neurology ICU after the drainage of a large frontal hematoma related to the spontaneous bleeding of a recently diagnosed cavernoma. On admission the Glasgow coma score was 4/15, with evidence of sub-falcorial herniation and elevated intracranial pressure. On the 4th postoperative day the patient developed acute lung injury, with an apparently normal bedside chest x-ray examination. Several episodes of critical oxygen desaturation (S_{pO_2} < 75%) occurred, which were not responsive to increasing PEEP and recruitment maneuvers. Hypoxemia was complicated by further increase in intracranial pressure. Ventilation in the prone position was not tolerated. The introduction of inhaled nitric oxide allowed a rapid and sustained improvement of both arterial oxygenation and cerebral hemodynamics. Interactions between acute brain and lung injury are complex. The correction of hypoxemia can usually be achieved by increasing PEEP or by alveolar recruitment maneuvers. Ventilation in the prone position can also be helpful in improving oxygenation, but is not always possible. The potential benefit of inhaled nitric oxide in similar cases has been described, but has still to be further explored. *Key words: intracranial hypertension; ventilator-associated pneumonia; hypoxemia; intrapulmonary shunts; recruitment maneuvers; inhaled nitric oxide.* [Respir Care 2012;57(7):1186–1190. © 2012 Daedalus Enterprises]

Introduction

Respiratory dysfunction represents a primary non-neurological system failure that is often associated with brain injury[1] and may compromise adequate oxygen delivery to the brain. Ideally, partial oxygen pressure should be maintained at a minimal level of 100 mm Hg,[2] with cerebral perfusion pressure (corresponding to the difference between mean arterial pressure and intracranial pressure [ICP]) ranging from 60 to 70 mm Hg,[3] and arterial carbon dioxide partial pressure from 32 to 35 mm Hg.[4] These guidelines are aimed at preventing any increase in ICP. The management of respiratory complications in patients with acute brain injuries may be difficult, as illustrated by the following report.

Case Report

A 20-year-old man (80 kg body weight) was admitted to the neurology ICU after the drainage of a large left frontal hematoma due to the acute bleeding of a previously diagnosed cavernoma. The preoperative computed tomography (CT) showed a large frontal paramedian hemorrhagic lesion of 66 × 40 × 38 mm, the presence of hydrocephalia, a left ventricular hemorrhagic contamination, and a probable mass effect on the mesencephalic structures. The patient had a Glasgow coma score of 4/15 (E1, V1, M2), with bilateral mydriasis. Effective decompression was noted at the end of the procedure.

In the immediate postoperative period the arterial blood gas analysis revealed pH 7.47, P_{aO_2} 80 mm Hg, P_{aCO_2} 34 mm Hg, base excess 2.2 mmol/L, and total CO_2 25 mmol/L. This was obtained with the following ventilator settings: pressure support ventilation, PEEP 5 cm H_2O, P_{max} 18 cm H_2O, tidal volume (V_T) 490 mL, respiratory rate 23 breaths/min, and F_{IO_2} 0.4. On the first postoperative day, as there was evidence for a right sub-falcorial herniation on the postoperative brain CT, controlled hy-

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perventilation was started (P_{aCO_2} 32–35 mm Hg) and the insertion of an intraventricular catheter was performed to allow cerebrospinal fluid drainage. On the same day, sedation was also started with propofol and remifentanil. Vasoactive support with norepinephrine became necessary to maintain cerebral perfusion pressure above 60 mm Hg.

On the second postoperative day, as ICP values remained high, the intensity of the treatment was further increased with addition of midazolam as a sedative agent, moderate hypothermia, and intermittent infusion of mannitol and hypertonic saline. A jugular catheter was inserted to allow continuous monitoring of venous jugular bulb oxygen saturation (S_{vjO_2}).

On the fourth postoperative day, hypoxemia worsened and led to the increase of F_{IO_2} up to 1.0 and of PEEP level up to 14 cm H_2O (determined as optimal PEEP). Other ventilator settings were: V_T 500 mL, respiratory rate 22–28 breaths/min, and P_{max} 30 cm H_2O. The chest x-ray showed a very limited pericardial infiltrate of the right lung (Fig. 1). Endotracheal aspirate revealed the presence of *Escherichia coli*, and C-reactive protein was 24.9 mg/dL (normal value $<$ 1.0 mg/dL). Fever was noted and, accordingly, empirical treatment with amoxicillin/clavulanic acid was started. Bedside ultrasonography of the chest did not reveal the presence of any pleural effusion, but was consistent with alveolar consolidation in the right basal lung.

On the fifth postoperative day a cardiac ultrasound ruled out an intracardiac shunt. The presence of a small pericardial effusion was documented. The right ventricle was normal, and so were the pulmonary and tricuspid flows. The inferior vena cava was not dilated (central venous pressure was measured at 7–9 mm Hg). Left ventricular shortening fraction was slightly decreased, at 27%. The calculated cardiac output was 11.8 L/min, based on the Fick equation:

$$\text{Cardiac output} = \dot{V}_{O_2}/(C_{aO_2} - C_{VO_2})$$

where $\dot{V}_{O_2}$ is oxygen uptake (in mL/min), C_{aO_2} (in mL/L) is arterial oxygen content, and C_{VO_2} (in mL/L) is venous oxygen content. $\dot{V}_{O_2}$ is equal to $10 \times \exp^{3/4}$ (-10% per degree below 37.6°C). This was confirmed by Swan-Ganz monitoring (cardiac output 12.3 L/min), which also concluded at the absence of pulmonary hypertension.

Measured intra-abdominal pressure was not increased. Still, on the fifth postoperative day, further oxygen desaturation episodes occurred, with peripheral oxygen saturation (S_{pO_2}) falling down to 75%. This was accompanied by sudden increase of ICP, to above 50 mm Hg. The patient could not be safely transported for brain and lung CT examination. Hyperventilation and recruitment maneuvers using a bag-valve device were followed by a further decrease of S_{pO_2}, S_{vjO_2}, and cerebral perfusion pressure, to

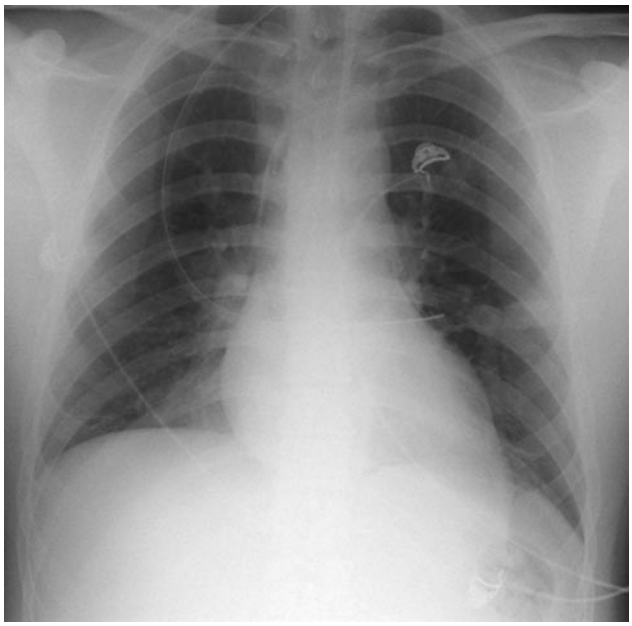

Fig. 1. Bedside chest x-ray examination (day 4).

critical values ($<$ 40 mm Hg), with a slight decrease of end-tidal CO_2 values (Fig. 2). At that time the calculated intrapulmonary shunt was 68%, based on the theoretical formula:

$$\dot{Q}s/\dot{Q}t = (C_{cCO_2} - C_{aO_2})/(C_{cCO_2} - C_{VO_2})$$

Ventilation in the prone position was not tolerated, and ventilation in lateral decubitus position was even worse, promptly leading to a deterioration of both respiratory and neurological parameters. With the introduction of inhaled nitric oxide (INO) at 10 ppm, based on a local protocol, a substantial improvement of the oxygenation parameters was obtained within one hour (Table). No further episodes of oxygen desaturation occurred, and ICP values came back to normal values. A first lung CT was performed on the same day (Fig. 3). It confirmed the presence of 2 limited consolidations in the lower dependent lobes. There was no evidence for pulmonary microembolisms.

The calculated intrapulmonary shunt had decreased to 51% on that day, and 34% on the sixth postoperative day. INO therapy was continued for 36 hours. ICP remained within normal over the following days. A progressive decrease of F_{IO_2} (to 0.8) was possible from the sixth day. A second lung CT, done on day 17, did not reveal a substantial regression of the consolidation of the lower lobes (see Fig. 3). The ventilator settings were at that time: airway pressure release ventilation with F_{IO_2} 0.35, P_{max} 22 cm H_2O, PEEP 6 cm H_2O, V_T 490–620 mL, and respiratory rate 22–25 breaths/min. The calculated intrapulmonary shunt on that day was 25%. Weaning from mechanical ventilation started, and extubation without further respiratory com-

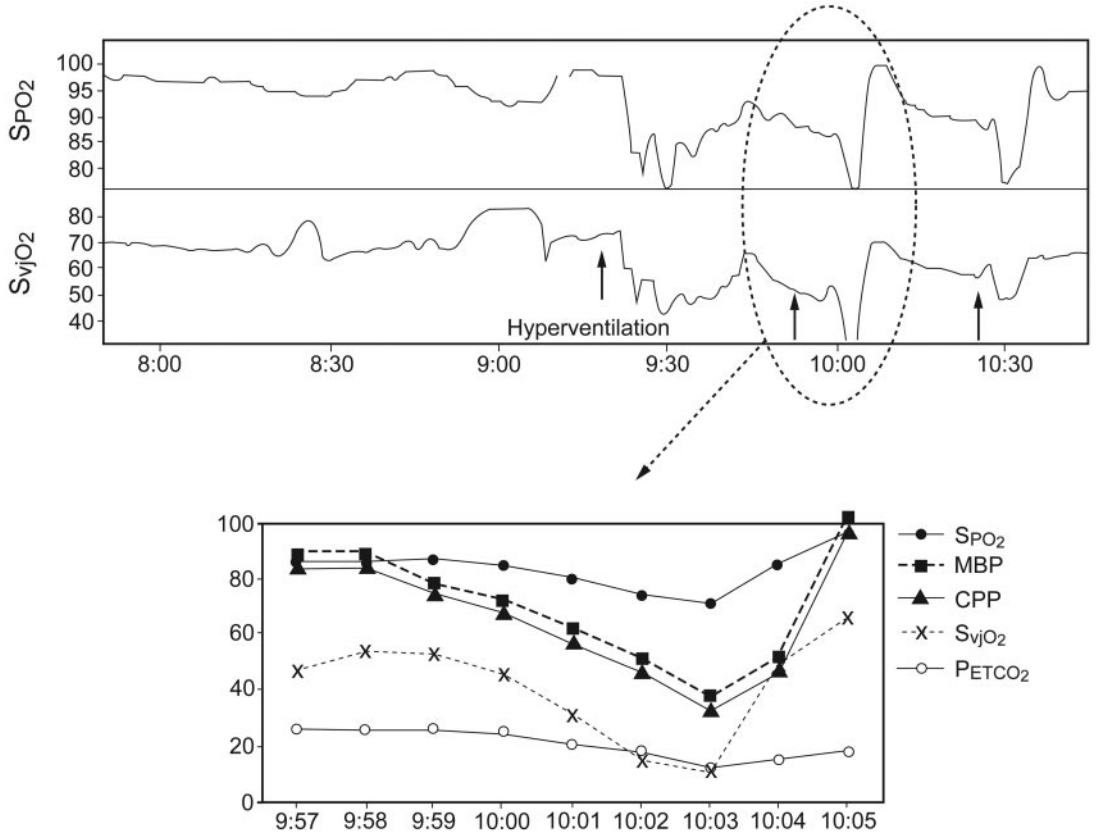

Fig. 2. Day 5 episodes of peripheral desaturation (S_{pO_2}), leading to increase of intracranial pressure with critical decrease of cerebral perfusion pressure (CPP) and venous jugular bulb oxygen saturation (S_{vjO_2}). Hyperventilation and recruitment with bag-valve resulted in further worsening of CPP and S_{vjO_2}, with a slow recovery of P_{O_2}) in arterial blood. MBP = mean blood pressure. P_{ETCO_2} = end-tidal partial pressure of CO_2.

Table. Oxygenation Parameters and Cerebral Hemodynamics Before and After INO

	Before INO	After 1 h INO 10 ppm	After 6 h INO 10 ppm
P_{aO_2}, mm Hg	49	67.5	62.8
F_{IO_2}	1.0	1.0	1.0
P_{aO_2}/F_{IO_2}	49	67.5	62.8
Intracranial pressure, mm Hg	41	5	14
Cerebral perfusion pressure, mm Hg	32	65	64
S_{vjO_2}, %	50	66	63.5

INO = inhaled nitric oxide
S_{vjO_2} = venous jugular bulb oxygen saturation

plications was possible on postoperative day 19. The Glasgow coma score was 13/15 when the patient was transferred to a rehabilitation unit. At 6-month follow-up he still presented substantial cognitive defects, due to the frontal injury.

Discussion

Among extracerebral organ failure, respiratory dysfunction, including pulmonary edema and pneumonia, is the most common complication in severely brain injured patients.[5] However, the pathophysiology of this respiratory failure is still not completely understood. The occurrence of neurogenic pulmonary edema is relatively rare and can, as in the present case, be excluded by the clinical and radiological changes. The 3 main potential causes of severe respiratory failure with refractory hypoxemia are ventilation-perfusion mismatch, structural parenchymal abnormalities, and changes in respiratory mechanics.[6]

Ventilation-perfusion mismatch is possibly caused by the brain injury itself, or by the ventilatory strategies. Indeed, ventilation-perfusion imbalance has been shown in trauma patients as a consequence of a redistribution of regional blood flow, partly under the influence of the hypothalamus.[6,7] Ventilation-perfusion mismatch may also occur after redistribution of regional perfusion to the non-ventilated areas, due to the dynamic pulmonary hyperinflation.[8] PEEP is applied to lower the intrapulmonary shunt by opening collapsed alveolar units, but in some patients it may cause a worsening of the shunt fraction by shifting the distribution of pulmonary flow toward non-ventilated regions of the lungs.[8] Hypocapnia is used to reduce cerebral blood flow, but it may also lead to an

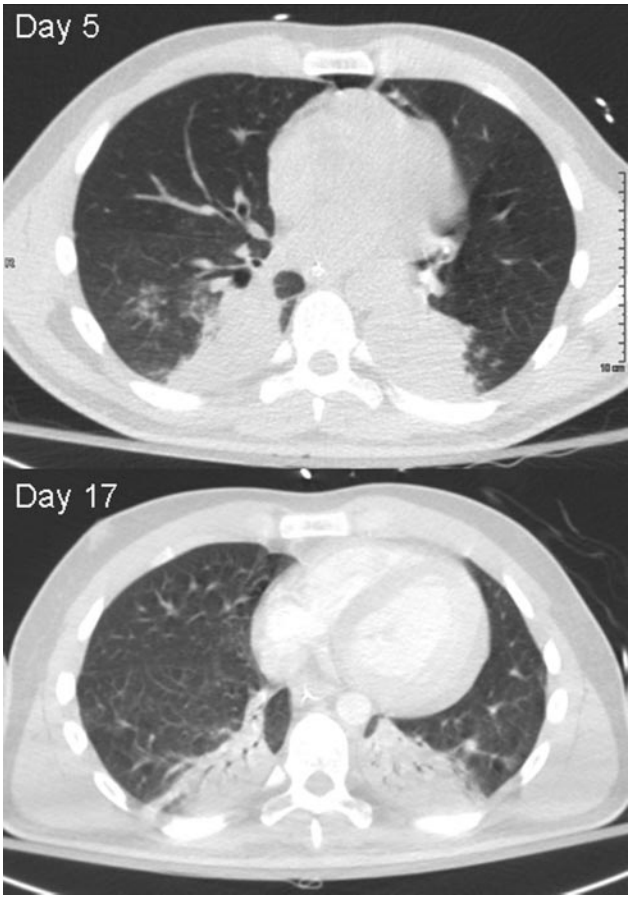

Fig. 3. Lung computed tomogram showing consolidations in the dependent regions (day 5 and day 17).

attenuation of the hypoxic pulmonary vasoconstriction and thus to an increased pulmonary shunting.[9] This effect is mediated by changes in arterial pH.[10] Alkalosis inhibits the increase in pulmonary arterial and venous resistances and thus limits the effects of hypoxic pulmonary vasoconstriction.[11] Changes in the vascular tone of cerebral arteries are also pH-mediated rather than CO_2-mediated, and alkalosis induces vasoconstriction.

Some medications, and in particular anesthetic agents, have been shown to influence hypoxic pulmonary vasoconstriction. In the present case, large doses of propofol were used, but there are no data indicating that this drug has an inhibitory effect on hypoxic pulmonary vasoconstriction.[12] Finally, lung surfactant depletion due to excessive sympathetic stimulation and hyperventilation could also be responsible for ventilation-perfusion mismatch.[6]

Structural parenchymal changes are mainly linked to passive atelectasis or infectious complications. In most of the patients there is clinical and microbiological evidence for ventilator-associated pneumonia. However, as in our case, the chest x-ray may appear relatively normal, although the gas exchanges are extremely compromised. In contrast, the lung CT scan may reveal lung consolidations in the dependent regions, while the nondependent lung regions appear relatively healthy and well aerated.[13] Brain injury may also cause the systemic release of inflammatory mediators and catecholamines, which can lead to further lung injury.[6]

Additionally, the respiratory mechanics in brain injured patients appear also to be modified through different mechanisms. Increased intra-abdominal pressure and chest wall elastance were found by some authors.[13] It seems also that airway resistances increase and the role of hypocapnia due to therapeutic hyperventilation may be discussed.[9,14] Tantucci et al found in a group of brain injured patients an increase in airway resistance while the patients were therapeutically hyperventilated ($P_{aCO_2} = 30.4 \pm 4.2$ mm Hg).[15] In contrast, other authors suggested that in patients with controlled P_{aCO_2}, the airway constriction may result from the sympathetic neurologic control of the airway caliber.[13] In this case report we had insufficient respiratory system data to allow deferred calculations of lung compliance and elastance. Those evaluations were, unfortunately, not immediately done in the setting of a dramatically deteriorating situation.

As illustrated by the present case, the management of refractory hypoxemia in brain injured patients may be particularly difficult. Worsening hypoxemia will result in a rise of ICP and impaired cerebral oxygenation, as assessed by the decrease of S_{vjO_2}.[16] These changes could in turn negatively influence respiratory function through the release of inflammatory mediators and catecholamines.[17]

While PEEP can improve gas-exchange and respiratory mechanics when prevalent atelectasis is present, in brain injured patients with ventilator-associated pneumonia or lung collapse and severe respiratory failure, raising the PEEP up to 15 cm H_2O does not systematically affect oxygenation, and this lack of response is paralleled to small alveolar recruitment.[13,16] Ventilation in the prone position should be tested, but is not always well tolerated, particularly in patients with unstable cerebral hemodynamics.[16,18]

In the present report the administration of INO at 10 ppm led to a rapid improvement of both oxygenation and cerebral hemodynamics. This beneficial effect of INO in severely head injured patients with acute lung injury has been suggested by at least 3 previous observations.[19-21] In each case the addition of INO to the aggressive neurointensive care modalities allowed a rapid (< 1 h) improvement of arterial oxygenation and a decrease of ICP. NO is a potent vasodilator, but it is generally admitted that INO is promptly inactivated in the bloodstream, leading to an almost exclusive effect on pulmonary vasculature, without major effect on systemic blood pressures.[19,20] In patients suffering from ARDS, INO has been shown to selectively dilate blood vessels only in those lung segments that are actively participating in gas exchange at the alveolar-capillary level, thus improving ventilation-perfusion

matching. This effect is described for INO concentrations as low as 2 ppm.[22] NO has important regulatory functions within the central nervous system. Low levels of NO (produced by local synthesis in the endothelial cells) might be associated with vasoconstriction of cerebral vessels, while increased production of NO (by neuronal cells) could result in cytotoxicity.[23] In anesthetized pigs, INO decreased cerebral blood volume and cerebral transit time, whereas cerebral blood flow remained unchanged, suggesting a vasodilator action of INO in the cerebral vasculature, which may occur preferentially in the venous compartment.[24] In a child with traumatic brain injury, INO was administered (up to 35 ppm) for pulmonary hypertension and did not result in important changes in ICP and S_{vjO_2}.[20]

Extra-pulmonary effects of INO are still debated. As in the previously published cases, pulmonary vasodilation and increased PEEP could have provided improved oxygenation to the brain, thus decreasing ICP.[21] Another hypothesis should be that INO-induced pulmonary vasodilation could allow more of the blood volume to remain in the thorax or to drain from the cerebral circulation to the thorax.[21] Finally, extra-pulmonary anti-inflammatory effects of INO may also be involved downstream, beyond the delivery of NO to the lung.[21]

In conclusion, the interactions between acute brain and lung injury appear to be complex. Refractory hypoxemia may appear despite limited structural parenchymal abnormalities, mainly in the dependent regions of the lungs. Inhibition of hypoxic pulmonary vasoconstriction in non-ventilated areas could be directly related to the ventilatory strategies (hyperventilation) used to treat high ICP. While there is a rationale for investigating the best PEEP level able to improve alveolar recruitment, high PEEP levels may have deleterious effects on cerebral hemodynamics.[25] The potential benefit of INO in patients combining acute brain and lung injuries has still to be further explored.

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