Low tidal volume ventilation improves outcome in patients without acute lung injury

Low tidal volume ventilation improves morbidity and mortality in patients with Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS). Several cohort studies suggested that ventilation with low tidal volumes could also benefit patients without ALI. Determann et al. describe the results of a randomized controlled trial comparing conventional with low tidal volumes in patients without ALI.

Critically ill patients from an academic and a regional teaching hospital without ALI at the onset of mechanical ventilation were randomized to a control group (10 ml/kg predicted BW, volume controlled mode, N = 74) and a low tidal volume group (6 ml/kg predicted BW, volume controlled mode, N = 76). Patients were included within 36 hours following the start of mechanical ventilation. The anticipated duration of mechanical ventilation was > 3 days. Primary endpoints were cytokine levels in bronchoalveolar lavage fluid (BALF) and plasma which were measured every second day. Secondary endpoints were the development of ALI, duration of mechanical ventilation and mortality. Study groups were well balanced with respect to baseline demographics. Tidal volumes were significantly lower in the low tidal volume group during the first 4 days. BALF cytokines were not significantly different between groups. Plasma levels of IL-6 decreased significantly more in the low tidal volume group. There was no difference in the use of sedatives or inotropic agents between groups. Also, the need for higher PEEP levels or an FiO2 increase was not significantly different between groups. The trial was stopped prematurely because the incidence of ALI was significantly higher in the control group (13.5 versus 2.6%, p = 0.01). Multivariate analysis showed that tidal volume and PEEP level independently predicted the development of ALI. This is a landmark study showing that the use of low tidal volumes may also benefit patients without ALI. Furthermore, low tidal volume ventilation was not associated with an increased occurrence of side effects. The authors should be congratulated for the successful completion of this complicated trial. To date, this study provides the highest level of evidence supporting the use of low tidal volumes for almost all ventilated ICU patients. If confirmed, low tidal volume ventilation should be considered the standard of care.


The effect of endotoxin tolerance on ischemia-reperfusion injury in humans

Animal studies have shown that the development of endotoxin tolerance may also decrease the risk of other types of injury, such as ischemia-reperfusion. The underlying mechanism of the phenomenon is, however, unclear. Draisma et al. hypothesized that the attenuation of complement activation is responsible for this “cross-tolerance”.

The authors included 14 healthy volunteers in the study. Endotoxin tolerance was induced by the infusion of an incremental Lipopolisaccharide (LPS) dose on 5 consecutive days. Ischemia-reperfusion injury was monitored by 99mTc annexin A5 scintigraphy of forearm skeletal muscle after exercise during blockade of the circulation. Symptom scores and temperature were measured on Days 1 - 5 and blood samples for White Blood Cell count, circulating cytokine levels and complement activation before and after ischemia-reperfusion were measured on Days 1 and 5.

Endotoxin tolerance developed after 5 days of LPS administration as shown by decreased symptom scores, rise in temperature and cytokine levels. Ischemia-reperfusion did not result in increased complement activation. The development of LPS tolerance had no significant effect on annexin A5 targeting.

Although no definite conclusions can be drawn, the results of this study do not support a role for endotoxin tolerance in preventing ischemia-reperfusion injury. Unfortunately, the relatively mild ischemic stimulus did not result in complement activation and endotoxin tolerance could still be protective after a more severe degree of ischemia, for example, during vascular surgery or organ transplantation. Clinical application of endotoxin tolerance in order to protect against ischemia-reperfusion injury is an interesting idea, but should await further research to unravel the underlying mechanisms.

An elevated serum lactate level is an important marker of global tissue hypoxia. Prehospital lactate measurement could warn paramedics of pending organ failure despite normal global haemodynamic parameters. PA van Beest et al. studied the feasibility of implementing prehospital lactate measurements and the relation between lactate levels and clinical outcomes.

This was a retrospective ambulance chart review from prospectively obtained data. Ambulance personnel were given a 2-month training program before prehospital lactate measurement was started. Patients were divided into a clinical shock group and a clinical non-shock group. The clinical shock group was subdivided into those with a prehospital lactate < 4 mmol/l and ≥ 4 mmol/l. Capillary or venous lactate levels were measured using the Accutrend lactate meter, Roche Diagnostic GmbH. In 50% of potential cases, prehospital lactate was actually measured. The most important barriers were the fact that lactate measurement was considered time consuming, there was little experience in handling the apparatus and, there was non-compliance with the inclusion criteria. A total of 216 charts were considered fit for inclusion (non shock N = 81, shock N = 135). The median lactate level was significantly higher in the shock group (3.9 versus 2.8 mmol/l, p < 0.0001). Length-of-stay in the ICU and the hospital was also significantly longer in the shock group as was the mortality rate (26.7 versus 1.2%, p < 0.0001). In the shock group, 74 patients had a lactate level < 4 mmol/l and 61 had a lactate ≥ 4 mmol/l. patients with a lactate level ≥ 4 mmol/l more often needed endotracheal intubation, had a longer length-of-stay in the ICU and in the hospital and had a higher mortality (44.3 versus 12.2%, p = 0.002). The ROC curve for lactate predicting in-hospital mortality was high (0.827) with an optimal cut-off point of 3.2 mmol/l. Normotensive patients with a lactate level ≥ 4 mmol/l also had an increased mortality compared to normotensive patients with a lactate level < 4 mmol/l.

Despite the evident shortcomings in design, this study clearly shows the feasibility and potential importance of prehospital serum lactate measurements. The authors thoroughly discuss the barriers for implementation and give suggestions for further improvement. However, the most important issue still needs clarification: will aggressive prehospital treatment of elevated lactate levels improve outcome? As van Beest et al. already have experience with implementing prehospital lactate measurements, they would appear perfectly suited to perform such a study.


**Somatosensory evoked potentials may also predict a poor neurologic outcome during mild hypothermia after cardiopulmonary resuscitation**

The bilateral absence of the cortical N20 responses of median nerve somatosensory evoked potentials (SSEP) 24 hours after cardiopulmonary resuscitation (CPR), invariably predicts a poor neurologic outcome. It is unclear whether SSEP is also helpful in patients treated with mild hypothermia and subsequent prolonged use of sedatives. Bouwes et al. performed a pilot study to find the answer to this question.

This was a prospective cohort study conducted in two centres that included comatose patients admitted to the ICU after CPR and treated with mild hypothermia (32 - 34 °C). The authors tested the following hypotheses: absence of bilateral cortical N20 responses during hypothermia persisted during normothermia and is invariably associated with a poor neurologic outcome. The results of the hypothermic SSEP were not available for the treating physician.

After the exclusion of one patient with a subarachnoid haemorrhage, a total of 77 patients were included. After 30 days, 51 (66%) patients had a poor neurologic outcome. During hypothermia bilateral cortical N20 responses were absent in 13 patients (median time from resuscitation = 20 hours, range 14 - 24). Three patients died before a SSEP during normothermia could be performed. Of the 10 remaining patients, 9 also had absent bilateral cortical N20 responses during normothermia (median time from resuscitation 63 hours, range 49.5 - 90.5) and in one patient responses could not be determined (PPV 1.0, 95% CI 0.7 - 1.0). The neurologic outcome in patients with absence of bilateral cortical N20 responses during hypothermia was invariably poor (PPV 1.0, 95% CI 0.7 - 1.0). Only one patient with presence of bilateral cortical N20 responses during hypothermia had absent responses during normothermia.

This is an important pilot study suggesting that absence of bilateral cortical N20 responses during mild hypothermia after CPR is also associated with a dismal neurologic prognosis. These results should be confirmed in a larger study before we change clinical practice. Furthermore, only a small percentage of patients with a poor neurologic outcome after CPR actually have absence of bilateral cortical N20 responses. Therefore, other early indicators of a poor neurologic outcome after CPR are still needed.