CROSSTALK

Comments on the CrossTalk proposal and opposing view: There is/is there is not added benefit to providing permissive hypercapnia in the treatment of ARDS

Time to translate hypercapnia

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The ‘CrossTalk’ exchange on hypercapnic acidosis in acute lung injury (ALI) has been expounded in many venues over the last decade. While we have learned much about hypercapnic modulation of lung inflammatory responses, unfortunately data continue to be accumulated in cellular and healthy small animal models that may poorly mimic humans with ALI. Another limitation is failure to distinguish between ‘therapeutic hypercapnia’ (THC) and ‘permissive hypercapnia’ (PHC). THC (inspiration of low fractions of carbon dioxide) appears reproducible in the ability to attenuate varying ALI aetiologies via enhanced ventilation–perfusion (V/Q) matching, better haemodynamics, and more uniform whole lung tissue acidosis. PHC (hypoventilation) can result in significantly low tidal volumes causing alveolar derecruitment and atelectasis and yet still leave remaining functional gas exchange units relatively or absolutely alkalotic by virtue of their higher V/Q ratios. Both forms may result in profound systemic acidemia, which might be prevented while improving V/Q matching and creating immunomodulatory lung tissue acidosis by the administration of CO₂ during the later phase of inspiration (Brogan et al. 2004). This strategy of isolated lung hypercapnia comes without the deleterious systemic effects of increased respiratory drive, heightened sympathetic tone, and immunosuppression elsewhere in the body. Given these considerations, we believe the time has come for a careful prospective clinical evaluation of the safety and efficacy of PHC and THC in ARDS. Short of developing animal models with co-morbidities and age more relevant to patients, it is highly likely that we will continue to have these debates and move no closer to resolving the question.

Reference


Competing interests

None declared.

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Permissive hypercapnia and ARDS: balancing inflammation and infection

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This discussion as to whether there is, or is not, added benefit to providing permissive hypercapnia (PHA) in the treatment of ARDS highlights the juncture at which this field resides at present — at a cross-roads where further investigation is required to determine which view will prevail. Beitler et al. detail the benefits of low tidal volume intervention in the improvement in mortality associated with ARDS and challenge the evidence linking hypercapnia per se to a beneficial clinical outcome independent of the effects achieved from minimizing biomechanical injury. Curley et al. make the case for hypercapnia associated with low tidal volume intervention as being of potential added benefit (over and above the effects of reduced biomechanical injury) in ARDS (Kregenow et al. 2006). For me, there is compelling evidence emerging for CO₂ to act as a signalling molecule that can modulate inflammatory and immune signalling processes (Wang et al. 2010; Cummins et al. 2010; Taylor & Cummins, 2011; Oliver et al. 2012). The mechanisms underpinning this are not yet fully characterized but there is an intriguing conservation of CO₂-sensitive pathways between mammals and flies with respect to the NFkB pathway (Helenius et al. 2009). A better understanding of these pathways could lead to new therapeutic opportunities. Both authors express a word of caution with respect to PHA because there is potential for hypercapnia to create the double-edged sword of dampened inflammation but susceptibility to pathogen infection. The challenge going forward will be to harness the beneficial (anti-inflammatory) effects of hypercapnia whilst avoiding the detrimental (pro-infection) effects in ARDs and other conditions where modulation of inflammation/immunity is desirable.

References


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Hypercapnia and ARDS

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We read the CrossTalk on ‘permissive hypercapnia and ARDS’ with great interest, and appreciate the opportunity to comment on the experts’ assessments (Beitler et al.; Curley et al.). Hypercapnia increases cardiac output, and improves tissue oxygenation and perfusion (Akca et al. 2002, 2003). Effects on the heart appear to be rather inotropic than chronotropic, when tested up to $P_{aCO_2}$ of 60 mmHg in healthy humans (Akca et al. 2002). Improved oxygenation and perfusion is due to increasing cardiac output, peripheral vasodilatation, augmented ventilation/perfusion, and the rightward shifting of the oxyhaemoglobin dissociation curve leading to improvement of oxygen delivery at the tissue level (Bohr effect). In healthy humans and surgical patients, hours of duration of $P_{aCO_2}$ 45–60 mmHg under anaesthesia and controlled ventilation increased subcutaneous tissue, muscle and brain oxygenation while maintaining pH levels above 7.25 (Akca et al. 2002, 2003, 2006). Hypercapnia’s beneficial effects in diminishing inflammation and oxidant-induced injury, in addition to improving oxygenation and perfusion, present it as a potential therapeutic agent for proinflammation-based acute tissue injuries such as ARDS. However, hypercapnia’s anti-inflammatory effects may go too far resulting in impaired pulmonary epithelial healing and increased bacterial load in prolonged pneumonia (O’Croinin et al. 2008). In our opinion, further safety studies – including therapeutic dose and duration – need to be performed before recommending a protocol-based clinical utilization of hypercapnia. At the same time, there are benefits in considering its short-term use in the early phases of ARDS and acute lung injury.

References


Competing interests

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