The cholinergic anti-inflammatory pathway modulates the innate immune response via binding of the vagal neurotransmitter acetylcholine (ACh) to the α7 nicotinic ACh receptor (α7nAChR) expressed, among other things, on macrophages. Human data on this subject is scarce. Kox et al. investigated the effects of the “selective” α7nAChR agonist GTS-21 in the human endotoxaemia model.

This was a prospective, double blind, placebo controlled trial including 14 healthy volunteers. Three days prior to the endotoxaemia experiment the volunteers were given either GTS-21 150 mg three times per day (N = 7) or placebo (N = 7) with an extra 300 mg dose (or placebo) on the day of the experiment. The endotoxin solution was administered as an i.v. bolus injection at a dose of 2ng/kg body weight. GTS-21, 4-OH-GTS-21 and cytokine levels were measured at regular intervals. Plasma concentrations of GTS-21 and its metabolite 4-OH-GTS-21 were highly variable. LPS administration resulted in the haemodynamic, haematological and clinical changes without differences between the placebo and GTS-21 groups.

Plasma cytokine levels were not statistically different between the placebo and GTS-21 groups. However, higher GTS-21 levels were significantly correlated with lower TNF-α, IL-6 and IL-1RA levels.

Although the study outcome seems disappointing, insufficient median GTS-21 plasma levels could explain the results. Despite using the hitherto maximal oral dose in humans, plasma levels were highly variable. Interestingly, higher GTS-21 plasma levels correlated significantly with lower cytokine levels. It would appear reasonable to use a higher oral dose in future studies or administer GTS-21 intravenously. Also, other α7nAChR agonists could be tried. The cholinergic anti-inflammatory pathway appears to play an intriguing role in human homeostasis. As such, it deserves our full attention.


Adaptive support ventilation in patients with acute lung injury

Adaptive support ventilation (ASV) is a closed-loop mode of mechanical ventilation with continuous adaptation of respiratory rate and tidal volume aiming for a minimal breathing effort. However, the use of higher PEEP levels combined with recruitment manoeuvres could alter respiratory system compliance and change the respiratory rate – tidal volume relationship (RR-VT). Dongelmans et al. studied whether this could result in unacceptably high tidal volumes.

Consecutive patients with acute lung injury on controlled mechanical ventilation were included. The study endpoint was the change in RR-VT after the switch from PC ventilation (VT 6 ml/kg) to ASV, after a maximum of three additional recruitment manoeuvres and after pressure limitation if VT was > 8 ml/kg PBW in ASV mode. Ten patients with ALI were included (mean PEEP 10.9 ± 1.2 cm H2O). After switching from PC to ASV, the respiratory rate decreased significantly and tidal volume increased significantly from 6.5 ± 0.8 to 9.0 ± 1.6 ml/kg PBW (p = 0.02). Three patients showed no change in the RR-VT. These patients had a higher lung injury score and a lower compliance. Recruitment manoeuvres did not improve gas exchange and had no effects on RR-VT. Pressure limitation in ASV mode resulted in a decrease in minute ventilation > 20% in all seven patients with a VT > 8 ml/kg PBW.

The most important conclusion from this study is that a switch from PC ventilation to ASV in patients with ALI treated according to the open lung concept, results in an unacceptable increase in tidal volume in those with a better compliance. In more severely injured lungs, tidal volume does not increase. These results are consistent with the physiology of the open lung concept and should remind us that when using ASV an increase in compliance could result in dangerously high tidal volumes. Interestingly, as the authors discuss, this could also occur when there is improvement in the disease process. However, it is unclear if lower tidal volumes are still indicated in this later phase of the disease. This is definitely a subject for further research.