Angiopoietin-2 during experimental human endotoxaemia and sepsis

Angiopoietin-2 (Ang-2) may be a key regulator of endothelial permeability in severe sepsis and septic shock. Ang-2 binds to the endothelial Tie 2 receptor and prevents the binding of Ang-1 to the same receptor. Ang-1 binding usually maintains vascular integrity. Kümpers et al studied the time course of Ang-2 release in relation to soluble adhesion molecules and circulating cytokines in the experimental human endotoxaemia model. In addition, the authors analyzed Ang-2 levels in patients with sepsis during the first 72 hours of admission to medical ICU. The predominant diagnosis in this patient group was pneumonia (57.1%)

Healthy volunteers (N = 21) were recruited from a trial investigating the effect of MAP kinase inhibition after a single infusion of 4 ng/kg body weight E. Coli endotoxin. Infusion of endotoxin increased Ang-2 levels from baseline (0.57 ± 0.20 ng/mL) starting at two hours and reaching peak levels after 4.5 hours (2.42 ± 0.54 ng/mL). Ang-1 and sTie2 levels did not change. The time course of Ang-2 release ran in parallel with early pro-inflammatory cytokines and preceded the release of soluble endothelial-adhesion molecules (E-selectin, ICAM-1). MAP kinase inhibition resulted in a dose dependent inhibition of Ang-2 release. There was a significant correlation (r = 0.6) between Ang-2 levels and the heart rate/MAP index as a marker of haemodynamic compromise. Ang-2 levels in septic patients were significantly increased at admission (9.8 ± 3.2 ng/mL) and remained elevated during the first 72 hours. Ang-2 levels were higher in non-survivors than in survivors. Furthermore, in non-survivors Ang-2 levels significantly increased from admission to 72 hours but remained stable in the survivors. Ang-2 levels at baseline or at 72 hours had high positive and negative predictive values in identifying non-survivors.

This study underlines the potential importance of Ang-2 in the pathogenesis of endothelial dysfunction in sepsis but by no means does it imply a causal relationship. The study clearly shows that endotoxin triggers the release of Ang-2 and that elevated or increasing levels of Ang-2 in sepsis imply a worse prognosis. If future studies confirm these results, Ang-2 modulation may become an important target in future sepsis trials.


Performance of minimally invasive cardiac output monitoring systems

With the declining popularity of the pulmonary artery catheter, the interest in minimally invasive cardiac output monitoring is increasing. De Wilde et al. studied the accuracy, precision and monitoring ability of the FloTrac-Vigileo (auto-calibrated pulse contour method), Modelflow (pulse contour method) and the HemoSonic transesophageal Doppler in 13 postoperative patients after CABG or mitral valve reconstruction. All patients included had normal ventricular function and had no persistent postoperative arrhythmias. Pulmonary artery thermodilution cardiac output (CO_D) was used as the gold standard.

Measurements were carried out within 2 hours of arrival in the ICU. Cardiac output was manipulated by four different interventions: 1) increase in tidal volume with 50% for 5 minutes, 2) increase in PEEP of 10 cm H2O for 5 minutes, 3) after passive leg raising, and 4) after a head up tilt test. A total of 104 paired CO measurements were evaluated. Mean CO_D was 5.28 l/min (range 2.57 – 8.61 l/min). Bias between CO_D and FloTrac, Modelflow and Hemosonic were 0.33, 0.30 and -0.41 l/min respectively. Modelflow had the best precision with limits of agreement of 26%. Limits of agreement for FloTrac and HemoSonic were 34% and 44% respectively. Changes in cardiac output were overestimated by FloTrac and adequately tracked by Modelflow and HemoSonic.

The results of this study clearly show the potential of Modelflow cardiac output measurement with acceptable limits of agreement below 30%. Unfortunately, Modelflow is not yet commercially available. All devices perform well if the absolute values and not changes in cardiac output, are considered. The results should be confirmed in unstable ICU patients with compromised ventricular function.

de Wilde RBP, Geerts BF, Cui J, van den Berg PCM, Jansen JRC. Performance of three minimally invasive cardiac output monitoring systems. Anaesthesia, 2009;64:762–769