

## Chest 2009 Vasoactive therapy in septic shock: Levosimendan and novel vasoactive agents Daniel De Backer

### Levosimendan

- Levosimendan is an inotropic agent acting mostly as calcium sensitizer agent, with vasodilatory properties probably related to phosphodiesterase inhibition and activation of ATP-dependent potassium channels.
- Experimental studies in septic shock suggest that levosimendan improves cardiac more efficiently than dobutamine. This effect is associated with an improvement in splanchnic circulation.
- Levosimendan improved the microcirculation in an experimental model of septic shock
- In two small series of patients with septic shock, levosimendan increased cardiac output and cardiac function in patients with severe myocardial depression not responding to dobutamine administration <sup>1</sup>.
- In these trials, arterial pressure was relatively well preserved, mostly by infusing more fluids.
- The long term effect of this agent, and its impact on outcome still need to be evaluated.

### Nitric oxide inhibition

- Non selective inhibition of nitric oxide synthase increases blood pressure, but this is usually associated with a decrease in cardiac output. A large scale randomized trial in patients with shock showed that non selective nitric oxide inhibition is associated with an increased mortality rate. <sup>2</sup>
- Selective inhibition of nitric oxide synthase (iNOS) improves blood pressure and organ function in experimental models of sepsis. These agents are not yet available for human application.
- Modulation of nitric oxide through inhibition of guanylate cyclase with methylene blue has been shown to improve cardiac function and cardiac output in patients with septic shock <sup>3</sup>. Long term effects of this agent has not been tested.

### Vasodilatory agents

- Experimental and clinical studies show that microcirculatory perfusion is altered in sepsis and that vasodilatory agents may, paradoxically, have a place in the therapy of septic shock
- A recent small size randomized trial showed that nitroglycerin failed to affect the microcirculation <sup>4</sup>

### Selected lectures:

- (1) Morelli A, De Castro S, Teboul JL et al. Effects of levosimendan on systemic and regional hemodynamics in septic myocardial depression. Intensive Care Med 2005; 31(5):638-644.

- (2) Lopez A, Lorente JA, Steingrub J et al. Multiple-center, randomized, placebo-controlled, double-blind study of the nitric oxide synthase inhibitor 546C88: effect on survival in patients with septic shock. *Crit Care Med* 2004; 32:21-30.
- (3) Preiser JC, Lejeune P, Roman A et al. Methylene blue administration in septic shock: a clinical study. *Crit Care Med* 1995; 23:259-264.
- (4) Boerma EC, Koopmans M, Konijn A et al. Effects of nitroglycerin on sublingual microcirculatory blood flow in patients with severe sepsis/septic shock after a strict resuscitation protocol: A double-blind randomized placebo controlled trial. *Crit Care Med* 2009 (published ahead of print).