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Editorial

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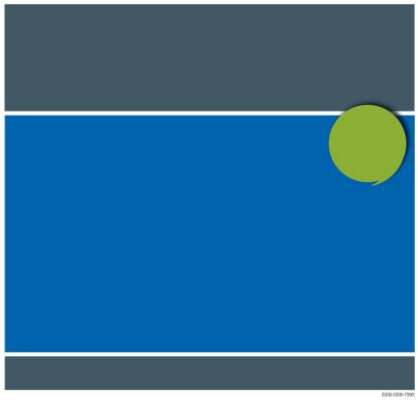

EDITORIAL

Sepsis and beta-blockade: a look into diastolic function.

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In the present issue of CMRO, Sanfilippo et al[1]discuss the results of a systematic review on the use of beta-blockade in patients with severe sepsis or septic shock. The authors found only two randomized controlled trials (RCTs) including a total of 195 patients, few small prospective and retrospective studies and several experimental studies. Therefore it seems reasonable to wait for more data before attempting a meta-analysis. Nonetheless, this promising new approach to the care of septic patients has generated enthusiasm in the intensive care community and more research is ongoing.

Sepsis is still burdened by high mortality[2,.3]. and one of its main hallmarks is the profound cardiovascular derangement characterized by a high cardiac output state, profound vasodilatation and tachycardia[4,.5]. In this context, reducing heart rate (HR) may optimize the

myocardial efficiency while reducing the myocardial oxygen consumption. Indeed, saving the heart almost 20 beats/min on average was safe in the RCT by Morelli et al.[6]. In this study a control of HR to a target range of 80-95 beats/min did not worsen any of systemic or pulmonary haemodynamic parameters investigated and, on the contrary, it showed a potential improvement in haemodynamics. Indeed, while maintaining the same mean arterial pressure target (> 65 mmHg), esmolol infusion improved the stroke volume index and the LV stroke work index. More importantly, in the esmolol group the dosages of norepinephrine decreased significantly (median reduction of 0.11 mcg/kg/min) despite a less positive fluid balance (median fluid administration lower by roughly 500 ml per 24 hour period); this was also associated with improvements in markers of perfusion such as arterial lactate levels and glomerular filtration rate.

These results point towards a beneficial cardiovascular effect of beta-blockade by blunting the septic hyper-adrenergic drive. Interestingly, in the VASST trial[7] a reduction in heart rate (HR) in the subgroup with less-severe septic shock was found in the treatment group (vasopressin) and was associated with a reduction in mortality, supporting the idea that avoidance of tachycardia and blunting catecholamine over-stimulation could be beneficial in septic patients.

Sepsis is associated with myocardial dysfunction both at systolic and diastolic leve[8] ENREF 5. Nonetheless, a recent meta-analysis did not find a correlation between left or right ventricle (LV or RV) systolic dysfunction and survival in patients with severe sepsis or septic shock[10]. On the other side, another recent meta-analysis found a strong correlation between LV diastolic dysfunction and mortality in septic patient[11,12]. With this background it is worth commenting about the potential beneficial action of beta-blockade on the LV diastolic function. For instance, carvedilol - a $alpha_1$/beta-blocker - has significantly improved LV diastolic function in patients with diastolic heart failure and normal LV systolic

function[13]. In patients with severe sepsis or septic shock, there are at least a couple of reasons why beta-blockade may improve LV diastolic function. First of all, a reduction of tachycardia should ameliorate the LV filling by increasing the diastolic time. Although reasonable, it remains speculative that this reduction in HR improved LV diastolic filling pattern in the trial by Morelli et al.[14] since this study did not include a structured echocardiographic assessment. In this regards, the ongoing ESMOSEPSIS trial may appropriately answer to this question because it includes a formal echocardiographic assessment of LV function. A second potentially beneficial action of beta-blockade on the LV diastolic function could come from their anti-arrhythmic effects. For instance, sepsis is a recognized independent risk factor for developing atrial fibrillation[15] which itself causes the loss of late (atrial) contribution to the LV filling during diastole. In patients with impaired LV diastolic function this loss is not always well-compensated and can severely affect cardiovascular dynamics. Also this hypothesis remains speculative to explain the benefits of beta-blockade since the incidence of atrial fibrillation and arrhythmias has not been reported by the studies on beta-blockade in sepsis.

On the other side, the study by Morelli et al.[6] has been criticized because almost half of the patients in the esmolol arm received infusion of the calcium-sensitizer levosimendan[16] in order improve systemic oxygen delivery. Levosimendan increases inothropism without alteration in myocardial oxygen demand and improves LV relaxation pattern by shortening the iso-volumetric relaxation time[17] Therefore it may have contributed to the possible improvement in LV filling pattern in a significant proportion of the population, and it is also worth noting that levosimendan is under investigation in septic patients as a strategy to prevent acute organ dysfunction (ongoing LeoPARDS trial)[18]

In summary, we are still at preliminary stage and more research is needed but there are reasonable chances that beta-blockade will become an option for the treatment of septic patients over the next few years.

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