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EDITORIAL

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Levosimendan: from coronary care to intensive care?

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Numerous multi-centre clinical trials have demonstrated that levosimendan is an effective agent in the management of decompensated heart failure [1]. It has a novel pharmacological profile which makes it particularly suited to improving the performance of the decompensated heart [2]. In the myofilament, levosimendan enhances the sensitivity of troponin C to calcium and stabilizes the Ca^{2+}-troponin C complex [3]. The rate of formation of myosin actin cross bridges is increased, although the rate of dissociation of cross bridges is unaltered, so that there is a greater rate of force development during systole, while diastole is not impaired [4, 5]. Increased contractility is not accompanied by increased cellular metabolism, so that myocardial oxygen consumption is not elevated [1, 3]. There is no effect on heart rate. The inotropic properties of levosimendan are not compromised in the acidotic or hypoxic heart [3].

Levosimendan is also a potent stimulator of vascular ATP-dependant potassium channels (K^+-ATP channels), inducing systemic vasodilation and reducing afterload [5, 6]. Coronary arterial vasodilation is induced, improving coronary perfusion [5]. Levosimendan also stimulates mitochondrial K^+-ATP channels, increasing potassium influx and preserving mitochondrial activity during stress, via a complex and poorly understood mechanism [7, 8]. For this reason, levosimendan pretreatment has been suggested for the prevention of ischaemia-reperfusion injury in coronary bypass surgery and may be beneficial in other forms of myocardial stress [9].

Given these exciting and almost magical properties of levosimendan, it is understandable that intensivists would wish to consider using this potent inotropic agent to support the myocardium in sepsis [10]. Circulating cytokines have a potent depressant effect on myocardial contractility. The mechanism is poorly understood but probably multifactorial [11]. Several animal studies have suggested that levosimendan is of value in septic shock [12]. It has not yet been studied in any detail in human sepsis, although some preliminary work suggests it may be an effective inotrope where dobutamine has failed [13].

However, there is a fundamental problem with the use of levosimendan in sepsis which relates directly to its mechanism of action. It is a potent vasodilator, and this action may compound the effects of sepsis-induced reductions in systemic vascular resistance (SVR), worsening tissue perfusion [12]. Two recent linked animal studies suggest that levosimendan does not improve tissue perfusion in sepsis unless combined with adequate fluid resuscitation and additional inotropes [14, 15]. This impression has been confirmed in other models of septic shock [16].

In this issue of *Intensive Care Medicine*, Schwarte et al. [17] examine the effect of levosimendan on cardiac output and tissue perfusion in the presence of hypoxia in a canine model. The aim was to determine whether levosimendan could prevent the fall in cardiac output in response to hypoxia without inducing tissue hypoperfusion, as determined via changes in systemic oxygen

consumption, arterial pH, base excess, blood lactate levels, and gastric mucosal oxygenation. In additional studies, the vasodilating action of levosimendan, which is mediated via vascular K^+-ATP channels, was antagonised by the simultaneous infusion of glibenclamide, a K^+-ATP channel inhibitor. In this study, Schwarte et al. found that when levosimendan was infused before hypoxia was induced, myocardial contractility, stroke volume and cardiac output were preserved in spite of the hypoxic insult. Systemic vascular resistance fell, but gastric mucosal oxygenation was maintained and systemic oxygen consumption was unaltered, suggesting as in previous cardiac studies that the hypoxic heart is supported by levosimendan, but that a potent vasodilator action is present. This much is an expected result. The novel aspect of this study is the examination of the antagonising effect of glibenclamide on the action of levosimendan. When given alone, glibenclamide caused a rise in SVR and a significant fall in blood glucose-predictable effects of this agent, offering indirect proof that the infused glibenclamide was acting to block K^+-ATP channels. When levosimendan was administered in the presence of glibenclamide, levosimendan caused a significant rise in cardiac output, as a direct result of improving myocardial contractility (expressed as dV/dT_{max}), indicating that this action of levosimendan is due to its calcium-sensitising effect on myocardial muscle rather than an action on K^+-ATP channels. It might also have been anticipated that glibenclamide would prevent the systemic vasodilating action of levosimendan, but in fact the observed fall in SVR was preserved. This is likely to be due to additional vasodilating mechanisms of levosimendan. This agent stimulates vascular endothelial release of nitric oxide, and it might be speculated that this would exacerbate the fall in SVR commonly observed in sepsis [8]. Levosimendan also induces vasodilation via large-conductance Ca^{2+}-activated potassium channels (BK_{Ca} channels), which are present in both vascular endothelium and smooth muscle and are not blocked by glibenclamide [18]. Several other potent vasodilating mechanisms are also proposed [18]. In this context, therefore, it is not surprising that glibenclamide was unable to reverse the fall in SVR in response to levosimendan as observed in this study.

Overall, there are glimmers of real promise for levosimendan as an agent to support the myocardium in sepsis. However, there remains a vast amount of experimental work to be undertaken first. In contrast to the literature in heart failure, it is startling how little experimental work has been undertaken with this drug in the setting of septic shock. Further in vitro and animal studies are urgently required to give us a thorough understanding of the vasodilating action of levosimendan, and the consequent effects, positive or negative, on end-organ perfusion. These studies would help us to understand how best to antagonise the fall in SVR induced by levosimendan, or indeed, whether such action is even necessary. Only then will it be possible to design rational and focussed clinical trials that would allow levosimendan to take its rightful place in intensive care.

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