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EDITORIAL

Levosimendan Improves Renal Function in Acute Decompensated Heart Failure: Cause and Clinical Application

Editorial to: "Levosimendan Improves Renal Function in Patients with Acute Decompensated Heart Failure: Comparison with Dobutamine by Yilmaz et al."

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Renal dysfunction and worsening renal function are common in patients with acute decompensated heart failure (ADHF), and both are strong and independent predictors of outcome [1, 2]. The most important cause of renal impairment in ADHF is reduced renal perfusion as a consequence of deteriorating cardiac output [3]. On the other hand, renal impairment itself may predispose to worsening heart failure, by continuous salt and water retention, diuretic resistance and neurohormonal activation, leading to increased cardiac workload [4].

In this issue of Cardiovascular Drugs and Therapy, Yilmaz and colleagues describe the renal effects of levosimendan infusion compared to dobutamine infusion in 88 patients with ADHF [5]. Both treatment regimens were associated with an increase in urine output, but only the group receiving levosimendan (on top of diuretic treatment), showed a significant improvement in estimated glomerular filtration rate (eGFR). This improvement in eGFR was consistent in those patients receiving levosimendan up to 72 h. Dobutamine had a neutral effect on eGFR. Unfortunately, no follow up data is available for these patients, and no adverse events were reported in the present study.

How can we explain the differences observed between these treatment groups? Both dobutamine and levosimendan are inotropic agents, specifically targeted at improvement of cardiac contractility [6]. Nevertheless, although both treatment regimens improved cardiac function and increased urine output, only levosimendan showed an improvement in eGFR. The explanation for this observation may be found in another, perhaps more important mechanism of action of levosimendan. Through activation of ATP-sensitive potassium channels, levosimendan causes both aterial, but preferently venous vasodilation [6]. This additive mechanism of action of levosimendan over dobutamine is crucial in ADHF, since central venous pressure is an important, and independent predictor of eGFR in patients with heart failure [3]. So, in patients with ADHF, renal function is dependent on renal blood flow and central venous pressure. Therefore, venodilation that occurs with levosimendan is probably the main mechanism distinguishing the effects of levosimendan and dobutamine on eGFR observed in the study by Yilmaz et al. [5].

This is not the first report to show that levosimendan improves eGFR in patients with heart failure. In a recent study, Zemljic et al. showed sustained improvement in renal function up to 3 months after infusion, in patients with advanced heart failure eligible for heart transplantation [7]. Also in the randomized controlled LIDO trial, levosimendan showed improvement of serum creatinine levels, compared to dobutamine [8]. The majority of randomised controlled trials with levosimendan showed an improvement in hemodynamic status, together with signs and symptoms of

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heart failure. However, these beneficial effects not always translated into improved prognosis in the outcome trials conducted with levosimendan. Both RUSSLAN and LIDO showed a survival benefit of levosimendan over respectively placebo and dobutamine in heart failure patients, but both trials were not designed and powered to test mortality [8, 9]. In SURVIVE, the primary endpoint of total mortality was not different between levosimendan and placebo [10]. In REVIVE-II, the combined clinical endpoint including mortality and symptoms did indicate a statistically significant benefit of levosimendan over placebo. However, even though plasma levels of BNP were significantly reduced by levosimendan, this was not accompanied by a survival benefit in REVIVE-II [11].

The central conundrum therefore remains, why levosimendan does improve renal function, hemodynamics, symptoms and signs, and short term outcome, while no survival benefit is achieved in long term follow up. The answer to this problem may lie in the selection of patients treated with levosimendan. By its potent vasodilation, levosimendan may reduce blood pressure and improve congestion, as also observed by Yilmaz and colleagues. Although levosimendan does possess some inotropic activity, the main effect is probably venodilation. Therefore, levosimendan may especially be suitable for patients who have severe venous congestion, but do not have low blood pressure and a low cardiac output. In these patients, the beneficial effects of levosimendan on reducing central venous pressure and improving pulmonary congestion may be offset by a drop in blood pressure, which jeopardizes renal blood flow. Patients with low blood pressure were also included in both SURVIVE and REVIVE-2, which might have partly explained their results [10, 11].

In conclusion, the study by Yilmaz et al. demonstrates beneficial effects of levosimendan compared to dobutamine on renal function in patients with ADHF. The inotropic effects of levosimendan will improve renal blood flow, but these effects on renal blood flow might be offset by the drop in blood pressure, in particular in patients with low baseline blood pressures. The main explanation of the findings by Yilmaz et al. is probably related to the venodilatory effects of levosimendan, reducing central venous pressure, which is an important determinant of renal function in heart failure patients.

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