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Differential effects of inotropes and inodilators on renal function in acute cardiac care

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Pathological interplay between the heart and kidneys is widely encountered in heart failure (HF) and is linked to worse prognosis and quality of life. Inotropes, along with diuretics and vasodilators, are a core medical response to HF but decompensated patients who need inotropic support often present with an acute worsening of renal function. The impact of inotropes on renal function is thus potentially an important influence on the choice of therapy. There is currently relatively little objective data available to guide the selection of inotrope therapy but recent direct observations on the effects of levosimendan and milrinone on glomerular filtration favour levosimendan. Other lines of evidence indicate that in acute decompensated HF levosimendan has an immediate renoprotective effect by increasing renal blood flow through preferential vasodilation of the renal afferent arterioles and increases in glomerular filtration rate: potential for renal medullary ischaemia is avoided by an offsetting increase in renal oxygen delivery. These indications of a putative renoprotective action of levosimendan support the view that this calcium-sensitizing inodilator may be preferable to dobutamine or other adrenergic inotropes in some settings by virtue of its renal effects. Additional large studies will be required, however, to clarify the renal effects of levosimendan in this and other relevant clinical situations, such as cardiac surgery.

Introduction

Heart failure (HF), whether acute or chronic, is often accompanied by impairment of renal function of a greater or less degree of severity.[1] Whereas $\approx$5% of the general population have an estimated glomerular filtration rate (eGFR) $<$60 mL/min/1.73 m^2, a similar reduction in eGFR is seen in some 50% of patients with acute or chronic HF (with either preserved or reduced ejection fraction).[1]

This deterioration in renal performance is associated with increased mortality and readmission rates,[2] and with longer in-hospital and intensive care unit length of stay.[3,4]

Renal insufficiency evidenced by eGFR $<$60 mL/min/1.73 m^2, when encountered in HF patients, is associated with a significantly higher mortality rate than in otherwise similar patients without renal compromise.[5,6]

Risk factors for worsening of renal function include a history of chronic renal insufficiency, acute coronary syndrome, arterial hypertension, diabetes mellitus, old age, and severe atherosclerosis.[7] Acute decompensated heart failure (AHF) has immediate deteriorating effects on renal function due to decreased perfusion and oxygen supply to the kidneys, and diuretics given to relieve oedema increase indirectly the oxygen demands of the glomeruli. Low mean

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arterial pressure, low left and right ventricular ejection fractions and hyponatraemia are also implicated in worse prognosis.[8]

The interdependence of cardiac and renal dysfunction in HF management has led to the development of the concept of cardiorenal syndrome (CRS). This can be broadly described as a pathophysiologic interplay between the heart and kidneys whereby acute or chronic dysfunction of either organ may induce acute or chronic dysfunction of the other.[9,10]

It is therefore crucial to understand the renal effects of cardio- and vasoactive drugs used in HF. The effects of inotropes and inodilators on renal function in the specific setting of AHF merit particular attention, since those drugs directly affect cardiac output (CO), central venous pressure (CVP), and systemic arterial pressure. Inotropes constitute the third pharmacological pillar in the treatment of patients with decompensated HF, the other two being diuretics and vasodilators.[11]

Adrenergic/catecholaminergic inotropes

Exemplars of this group are dobutamine and dopamine. Dobutamine, a synthetic catecholamine, acts primarily on beta-1 adrenoceptors (and also, weakly, at beta-2 receptors). Dobutamine improves CO by reducing afterload as well as through its inotropic action.[12] Higher doses may also augment urinary sodium excretion, either via altered renal (or systemic) haemodynamics or via a direct effect on the kidney.[13] Effects of dobutamine on renal sympathetic activity associated with increases in renal blood flow (RBF) (11%) and glomerular filtration rate (GFR) (12%) have been described.[14] Separately reported research from the same authors has described a strong relation between the effect of dobutamine (or nitroprusside) on right atrial mean pressure in patients with HF and improvement in GFR. These data may signify a mechanism by which increased atrial pressures in the setting of congestive HF can lead to increases in sympathetic activity, with subsequent adverse effects on renal function.[15] Dobutamine exerts vasodilator effects on both afferent and efferent arterioles and increases RBF. However, it impairs oxygenation of the medulla, increasing the oxygen demand of kidney tissue.

These conceptual and hypothesis-generating ideas about the possible renal effects of dobutamine have to be set against tangible indications from multiple sources that use of dobutamine may be associated with adverse clinical outcomes.

Madeira et al.[16] recently reported findings from a retrospective data analysis of 108 consecutive patients with AHF who required inotrope therapy with either dobutamine (29% of patients) or levosimendan (71% of patients). These groups were not fully matched for baseline inclusion criteria: the dobutamine group had lower mean blood pressure on admission, while the levosimendan group had lower average left ventricular ejection fraction (LVEF); there were, however, no significant differences in eGFR or cystatin C levels. The incidence of CRS was higher in the dobutamine group, and those patients more often had incomplete recovery of renal function at discharge. The dobutamine group also had higher in-hospital mortality; the presence or persistence of CRS and the choice of inotrope proved to be strong predictors of in-hospital death.

These data are supplementary to observations from the Levosimendan Infusion vs. DObutamine (LIDO) trial,[17] in which the effects of dobutamine on GFR compared unfavourably with those of levosimendan in patients with severe low-output HF. Also relevant in this context is experience in the ALARM-HF registry, in which use of adrenergic inotropics, including dobutamine, was associated with substantially higher mortality than other interventions, including levosimendan (*Figure 1*).[18] Adverse effects associated with dobutamine use can be an obstacle to its deployment: these include increased myocardial oxygen consumption, tachyarrhythmias, arrhythmogenesis, hypotension, and hypokalaemia. Dobutamine's adrenergic mechanism of action means that it may be of reduced effectiveness in patients pretreated with beta-blockers,[19] as is now widely the case in HF, in response to guidelines recommendations.

The receptor-level effects of dopamine vary with dose. When infused at rates of 3-5 µg/kg/min (i.e. those generally applied for inotropic effect), the drug's effects are principally determined by the activation of beta-1 and beta-2 adrenergic receptors and are characterized by increased myocardial contractility, heart rate and CO. Lower doses of dopamine (≤ 3 µg/kg/min) act primarily at dopaminergic D_1 and D_2 receptors. Activation of D_1 receptors causes vasodilation of both the large-conductance and small-resistance renal blood vessels;[20] activation of D_2 receptors indirectly has a similar effect through indirect pathways. These renal effects of dopamine may become impaired in the more advanced stages of HF due to selective loss of renal vasodilating capacity.[21]

A potential renoprotective effect of low-dose dopamine was identified in various small open-label studies in which the drug was combined with diuretic therapy in patients with AHF.[22] This was subsequently investigated in larger controlled trials, including DAD-HF I and DAD-HF II.[23,24] The DAD-I ($N = 60$) trial, which compared high-dose furosemide
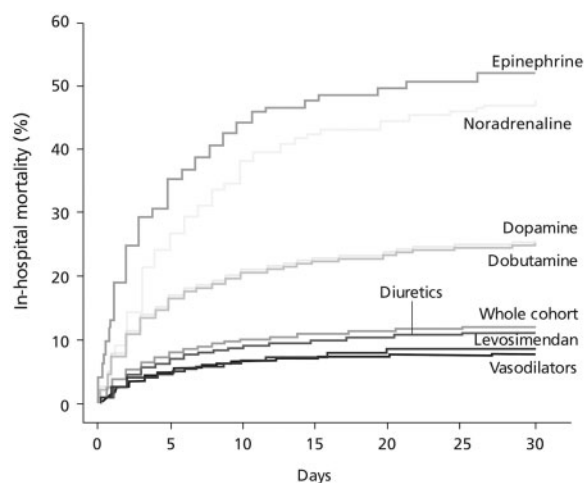

Figure 1 Impacts of principal i.v. vasoactive medications on in-hospital mortality (during the first 48 h) in acute heart failure patients in the ALARM-HF registry in patient subsets derived by propensity scoring methods. Based on Mebazaa et al.[18]

(20 mg/h) with dopamine (5 μg/kg/min) plus low-dose furosemide (5 mg/h), reported preservation of renal function but no significant differences in 60-day mortality and rehospitalization rates. In DAD-HF II ($N = 161$), the combination of low-dose dopamine (5 μg/kg/min/8 h) plus furosemide (5 mg/h) was well tolerated but not associated with beneficial effects beyond those attributable to low-dose furosemide alone. Moreover, the trial was terminated early due to an excess of tachycardia among patients assigned to the (dopamine + diuretic) group. Dopamine was not effective for improving renal function and was not associated with reduced mortality in this patient population.

The ROSE-AHF trial evaluated a more convincingly 'renal' dose of dopamine (2 μg/kg/min for 72 h) in 360 patients hospitalized for AHF and with evidence of renal dysfunction (GFR 15-60 mL/min/1.73 m^2) and systolic blood pressure (SBP) $\geq$90 mmHg. A comparison arm was randomized to nesiritide, the recombinant form of human B-type natriuretic peptide, at a dose of 0.005 μg/kg/min/72 h. High-dose intravenous (i.v.) furosemide (2.5 times the equivalent oral outpatient dose) was administered to all patients for the first 24 h of the study.[25]

The findings of the ROSE-AHF trial provided no firm support for the routine use of low-dose dopamine in AHF patients with reasonably well-sustained blood pressure. The incidence of tachycardia suggested that the relatively low dose used may not in fact be renal-specific in all patients.[26]

SOAP investigators also demonstrated a deleterious effect of dopamine on mortality and rate of new-onset arrhythmias in cardiogenic shock patients.[27]

Brief reference may be made here to fenoldopam, a D$_1$-receptor agonist, for which no strong case can be made.[28]

Phosphodiesterase inhibitors

These agents—exemplified by milrinone and enoximone—promote inotropy via the inhibition of phosphodiesterase (PDE) III in cardiomyocytes; they can also induce vasodilation by inhibition of PDE in vascular smooth muscle cells. As agents that act independently of beta-adrenoceptor-dependent pathways, their effects are not attenuated by beta-blockade. These effects offer theoretical advantages for renal function, with drug-induced vasodilation notionally enhancing transrenal perfusion pressure.

Lannemyr *et al.*[29] have recently reported on the renal effects of milrinone (0.04 mg/kg i.v. bolus then infusion of 0.30-0.50 μg/kg/min depending on the haemodynamic response) in seven patients undergoing cardiac surgery who developed AHF and low cardiac performance [cardiac index (CI) <2.1 L/min/m^2] shortly after weaning from cardiopulmonary bypass (CPB). A further 19 patients acted as controls (ClinicalTrials.gov identifier: NCT02405195). Observations were made before and up to 60 min after weaning from CPB.

In the control group, the filtration fraction was lower after weaning than at baseline (Δ13%; $P = 0.03$) and there was a trend towards decreased RBF and increased renal oxygen extraction (both P $\approx$ 0.06). In contrast, and also compared with baseline, milrinone administration increased RBF by 36% ($P < 0.05$) and renal oxygen delivery by 35% ($P < 0.05$), while renal vascular resistance was decreased by 29% ($P < 0.05$).

Relative to controls, milrinone treatment was associated with increased RBF ($P = 0.007$) and renal oxygen delivery ($P = 0.003$); renal vascular resistance ($P < 0.001$), filtration fraction ($P < 0.05$), and renal oxygen extraction ($P < 0.05$) all decreased. No significant changes in GFR or renal oxygen consumption were noted.

Overall, these data are consistent with the view that milrinone improved renal oxygenation. The investigators noted, however, that a prerequisite for any beneficial renal effect in this situation is the maintenance of mean arterial pressure (MAP) and renal perfusion pressure at the pre-milrinone level (by administration of noradrenaline). Without that intervention, MAP would probably have declined, counteracting any advantageous effects on renal perfusion.

The results of the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) trial of milrinone provided only limited indications of any advantageous renal effect and no demonstration that such changes could be related to wider clinical outcomes. A priori, this prospective, randomized, double-blind, placebo-controlled trial ($n = 951$) offered no support for the routine use of i.v. milrinone (0.5 μg/kg/min) in the treatment of patients hospitalized for an exacerbation of HF. No significant effects were seen on the outcomes of median number of days hospitalized for cardiovascular causes within 60 days after randomization, or in-hospital mortality, or the composite incidence of death or readmission. Furthermore, hypotension requiring intervention (10.7% vs. 3.2%; $P < 0.001$) and new atrial arrhythmias (4.6% vs. 1.5%; $P = 0.04$) occurred more frequently in patients who received milrinone.[30]

The authors of a separate retrospective analysis of OPTIME-CHF data concluded that 'Although milrinone treatment led to a minor improvement in renal function by discharge, the 60-day death and readmission rates were similar between the milrinone and placebo groups'.[31] A further retrospective interrogation of the OPTIME-CHF database concluded that clinical-event (endpoint) outcomes were worse among milrinone-treated patients who had HF of ischaemic origin than in those with non-ischaemic HF.[32]

Milrinone is subject to renal elimination and there is a widespread presumption towards careful dosing in situations of established renal dysfunction in order to minimize the risks of arrhythmias and hypotension. A recent review of this matter reiterated the value of milrinone in patients with advanced HF but acknowledged a lack of dedicated studies on dosage, patient selection and outcomes in situations of renal impairment.[33] A correlation has been demonstrated between plasma milrinone concentration and renal function in patients with cardiac disease.[34]

Enoximone is mainly eliminated by the liver and this may be prima facie an advantage over milrinone in situations of renal compromise. Few detailed investigations of this aspect of i.v. enoximone have been published.[35]

Levosimendan and renal function

Both the pre-clinical and clinical evidence for a renal-protective action of levosimendan is suggestive rather than conclusive. The findings are not always consistent and sometimes acquire statistical significance only when considered in meta-analyses. There are, nevertheless, suggestions of a renal-protective effect of levosimendan in a range of low-output states, including patients with acutely decompensated HF and renal impairment, and in critical illness situations, cardiac surgery and heart transplantation.[36-41]

Timely introduction of levosimendan may prevent the development or progression of renal dysfunction through several protective mechanisms involving both the macro- and microcirculation.[42] For example, levosimendan may augment renal perfusion via vasodilatation arising from its effects on adenosine triphosphate-dependent potassium (K_{ATP}) channels.

Levosimendan exerts a vasodilator effect mainly on the afferent arterioles of the kidney, increasing GFR without modifying renal oxygen consumption and extraction. Other potentially relevant mechanisms within the kidney relate to preconditioning, pleiotropic, anti-inflammatory and anti-apoptotic effects, and increased glomerular surface area.[43]

Pre-clinical insights on the effect(s) of levosimendan on renal function tend to be consistent within individual models but vary substantially between different models.[43] In septic models of renal compromise, any beneficial effects appear to be relatable primarily to improvements in haemodynamics, whereas the organ-protective effect of the drug dominates in situations of ischaemia/reperfusion injury. The opening of mitochondrial K_{ATP} channels may be involved in these situations.

Enhanced expression of nominally protective enzymes, along with significantly ($P < 0.001$) elevated levels of the antioxidant glutathione and lower levels of malondialdehyde, have been reported in renal tissue in a rat model, consistent with speculation that levosimendan reduces oxidative stress in renal tissue.[44]

Direct investigations of the renal effects of levosimendan in human patients include observations made in 2007 by Yilmaz et al.,[45] who randomized 88 patients hospitalized for the stabilization of acutely decompensated HF to levosimendan ($0.1\,\mu g/kg/min$, increased to $0.2\,\mu g/kg/min$ after 6 h of infusion if tolerated) or dobutamine ($5\,\mu g/kg/min$ for at least 6 h, with scope for later dose increases). Renal function indices, including serum creatinine, blood urea nitrogen (BUN), 24-h urinary output levels, and calculated GFR, were measured beforehand and for up to 72 h after inotrope infusion. Median baseline furosemide dosage was 60 mg/day in both groups and was kept constant in all patients during the trial.

LVEF increased by 4-5% in both treatment groups and 24-h urinary output was augmented (levosimendan: 1054 ± 441 mL at baseline to 1947 ± 870 mL at 24 h after infusion, 2535 ± 865 mL at 48 h and 1994 ± 609 mL at 72 h: all $P < 0.001$ vs. pre-treatment). Corresponding data for dobutamine were: 1066 ± 373 mL at baseline to
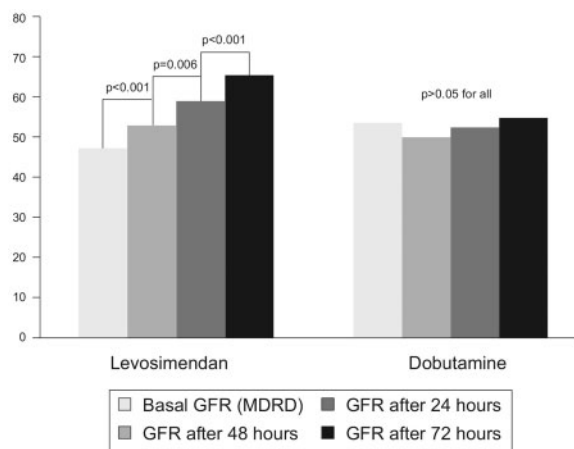
Figure 2 Comparison of the effects of i.v. levosimendan and i.v. dobutamine on glomerular filtration rate (GFR) in 41 patients with acute heart failure. GFR (shown on vertical axis) was calculated from the Modification of Diet in Renal Disease (MDRD) formula. Data from Yilmaz et al.[45]

1920 ± 599 mL after 24 h ($P < 0.001$), 1821 ± 523 mL at 48 h ($P < 0.001$), and 1523 ± 295 mL at 72 h ($P = 0.027$). However, progressive enhancement of eGFR 24 h after treatment infusions was observed only in patients randomized to levosimendan (Figure 2). (The increase in urine output with dobutamine was not regarded as proof of a beneficial effect on renal function from dobutamine; in these substantially fluid-overload patients, diuresis might have been achieved via inotropy and enhancement of cardiac function.)

In separate later observations, Fedele et al.[46] randomized 21 adult patients with acute decompensated HF, moderate renal impairment (GFR 30-60 mL/min/1.73 m^2), pulmonary capillary wedge pressure (PCWP) >20 mmHg and ejection fraction <40% to i.v. levosimendan ($6\,\mu g/kg/10\,min$ loading dose, then $0.1\,\mu g/kg/min$ for 24 h) or placebo, on top of standard therapy that was maintained during the study (ClinicalTrials.gov identifier NCT00527059). An intravascular renal artery Doppler examination was performed at baseline, after levosimendan bolus and 1 h thereafter. Renal blood flow, GFR, urinary output, serum levels of cystatin C, BUN, sodium excretion, and plasma sodium were measured.

Clear and progressive increases in GFR were seen during the observation period in the levosimendan group only. By 72 h, mean GFR had increased from 38.71 ± 7.94 to 53.34 ± 14.93 mL/min/1.73 m^2; various other specified indices of renal function also demonstrated significant improvements in response to levosimendan (Table 1).

These responses were accompanied by significant, nominally favourable changes in CI ($P = 0.029$) and PCWP ($P < 0.001$). A significant increase in CI was apparent from 24 h, while PCWP fell promptly after the commencement of levosimendan, reaching a new, lower level at 1 h that was thereafter maintained. Both mean pulmonary artery pressure and mean renal artery pressure also decreased significantly in the levosimendan group ($P < 0.05$ for both at 1 h).

Correlations were identified between changes in renal function indices and alterations in several dimensions of

Table 1 Changes in renal function variables at 72 h vs. baseline in response to i.v. levosimendan in 21 patients with acute decompensated HF and moderate renal impairment randomized to active treatment or placebo in addition to usual standard therapies

	Levosimendan baseline	Levosimendan 72 h	*P*-value	Control baseline	Control 72 h	*P*-value	P for interaction
GFR (mL/min)	38.71 ± 7.94	53.34 ± 14.93	0.002	43.33 ± 7.99	40.24 ± 6.58	>0.05	0.037
BUN (mg/dL)	45.08 ± 22.19	33.14 ± 16.63	0.019	44.4 ± 13.1	47 ± 12.8	0.6	0.014
Creatinine (mg/dL)	1.76 ± 0.37	1.51 ± 0.5	0.002	1.6 ± 0.2	1.7 ± 0.2	0.4	0.042
Cystatin C (ng/mL)	2577.5 ± 700.6	2083 ± 731.4	0.007	2498.5 ± 262	2470 ± 409.9	0.81	0.05
Urine output (mL)	1766.4 ± 514.2	2663.5 ± 721.2	0.004	1571.4 ± 125.3	1778.51 ± 798.1	>0.05	0.02

From Fedele *et al.*[46]

GFR, glomerular filtration rate; BUN, blood urea nitrogen.

renal haemodynamic parameters. The average RBF velocity in the levosimendan-treated patients increased from 18.71 ± 7.62 cm/s at baseline to 22.49 ± 0.27 cm/s after administration of the initial bolus ($P = 0.04$) and to 22.28 ± 9.76 cm/s at 1 h ($P = 0.03$). No significant alterations were noted in the placebo group. The inter-group test of statistical significance was not fulfilled for that outcome (P for interaction $= 0.055$) but a significant difference in favour of levosimendan was recorded for treatment effect on renal artery diameter (RAD) in comparison with placebo. In detail, mean RAD in the levosimendan group increased from 0.57 ± 0.18 cm at baseline to 0.60 ± 0.15 cm after 1 h ($P = 0.002$), whereas no meaningful change was observed in the placebo group [0.56 ± 0.12 cm at baseline, 0.56 ± 0.16 cm at 1 h ($P = 0.55$; P for interaction $= 0.033$)]. As a result of these changes, RBF increased in response to the initial bolus of levosimendan and during the first hour of infusion [from 301.3 ± 184.6 mL/min at baseline to 383.8 ± 198.9 mL/min at 1 h ($P < 0.01$; P for interaction vs. placebo $= 0.037$)].

These data are notable for the fact that levosimendan improved RBF before a significant effect on CI was recorded. This temporal discrepancy was interpreted as indicating that mechanisms other than enhancement of cardiac inotropy and output may contribute to the positive impact on renal function, with local vasodilation playing an important role. These findings are compatible with indications that assignment to levosimendan therapy predicted improved renal function independent of changes in left ventricular performance in patients with advanced chronic HF awaiting cardiac transplantation.[47]

Other relevant explorations in this area include research by Bragadottir *et al.*,[48] who performed a prospective, randomized, placebo-controlled trial in 30 cardiac surgery patients at risk of developing post-operative acute kidney injury due to low CO syndrome. Patients were randomized to levosimendan (12 μg/kg loading dose, then 0.1 μg/kg/min; $n = 15$) or placebo ($n = 15$) commencing 4–6 h after the completion of surgery. Of note, CVP was kept constant by colloid/crystalloid infusion.

Compared with placebo, levosimendan increased CI (22%), stroke volume index (15%), and heart rate (7%) and decreased systemic vascular resistance index (21%). It also significantly increased RBF, GFR, and renal vascular resistance relative to placebo, while causing no significant

changes in filtration fraction, renal oxygen consumption, or renal oxygen extraction.

These findings were regarded as compatible with the proposition that levosimendan induces preferential vasodilation of pre-glomerular resistance vessels, thereby increasing both RBF and GFR without jeopardizing renal oxygenation. This study did not include experimental measures to provide direct information on the oxygen supply/demand relationship of the renal medulla, so that the last of these conclusions should be regarded as a working hypothesis rather than a proven fact. Even so, it is in contrast to observations from the same researchers that vasopressin treatment in post-operative cardiac surgery patients increases renal oxygen extraction and may thereby compromise the renal oxygen supply/demand relationship in medullary tissue.[49]

Lannemyr *et al.*[50] compared the renal effects of levosimendan and dobutamine in patients with chronic HF (LVEF < 40%) and renal impairment (GFR < 80 mL/min/1.73 m^2) in a randomized, double-blind study (ClinicalTrials.gov identifier: NCT02133105). Patients ($n = 32$) were assigned to levosimendan (loading dose 12 μg/kg, then 0.1 μg/kg/min) or dobutamine (7.5 μg/kg/min) for 75 min. A pulmonary artery catheter was used to monitor systemic haemodynamics, and a renal vein catheter was used to measure renal plasma flow by means of para-aminohippurate clearance.

Both drugs had broadly comparable effects on systemic haemodynamics, with no statistically significant differences across a wide range of indices. Their effects on RBF were also similar and not significantly different (increase from 426 ± 197 to 518 ± 276 mL/min with levosimendan vs. increase from 397 ± 121 to 499 ± 154 mL/min with dobutamine; $P = 0.732$ for comparison of treatment effect in a linear mixed model). In contrast, the study drugs exerted differential effects on GFR, with an increase in the levosimendan group (from 36.5 ± 18.3 to 44.5 ± 19.0 mL/min; $P < 0.5$ vs. baseline) but no meaningful change in the dobutamine group (47.1 ± 14.5 mL/min at baseline vs. 47.3 ± 16.9 mL/min after treatment; $P =$ not significant vs. baseline; $P = 0.012$ for inter-group comparison). Filtration fraction was unaltered in the levosimendan group but declined by an average of 17% in the dobutamine group ($P = 0.045$). Small increases in renal oxygen consumption

were seen in both groups (levosimendan: 9.2 ± 6.3 mL/min at baseline, 10.1 ± 6.2 mL/min after treatment; dobutamine: 8.3 ± 2.6 mL/min at baseline, 8.9 ± 4.3 mL/min after treatment; $P \approx 0.8$ for inter-group comparison).

Other small studies have produced indications of renal benefits from levosimendan therapy, including in patients with biventricular HF.[47,51-53] However, robust indications of 'pro-renal' effects were not forthcoming from the SURVIVE or REVIVE trials, in both of which levosimendan was compared with dobutamine.

These various lines of investigation have recently been elegantly consolidated by Honore et al.[54]

- In acute decompensated HF, levosimendan has an immediate renoprotective effect by increasing RBF through preferential vasodilation of the renal afferent arterioles.
- In addition to increasing RBF, levosimendan increases GFR significantly. (No comparable effect is seen with dobutamine.)
- An isolated increase in GFR could jeopardize oxygenation of the medulla, which is sensitive to ischaemia, but this is unlikely to occur with levosimendan, because it causes balanced increases in GFR and renal oxygen delivery.
- CVP is an important predictor of renal dysfunction in HF patients. Elevated CVP will increase renal venous backward pressure and thus decrease renal perfusion pressure and impair renal function. An elevated CVP may adversely impact kidney haemodynamics and promote acute kidney injury even in the absence of volume overload.

These conclusions, which we endorse, highlight that in order to be beneficial an increase in RBF has to be accompanied by an increase in GFR but not at the cost of medullary hypoxaemia; levosimendan appears to deliver this suite of requirements. We would qualify those conclusions, however, with the observation that the evidence base for beneficial renal effects of levosimendan in HF settings is both heterogeneous and methodologically variable and that the largest of the well-powered regulatory studies has produced neutral or inconclusive results on these outcomes. These considerations do not restrict us from the conclusion that levosimendan may be preferable to dobutamine or other adrenergic inotropes by way of both its renal and wider therapeutic effects in AHF, including in those patients who are at risk of developing acute kidney injury due to hypoperfusion. However, additional large studies are required to clarify the renal effects of levosimendan in this and other relevant clinical situations, such as cardiac surgery and perhaps septic shock or acute HF/cardiogenic shock complicating acute coronary syndrome.[55] Pending such research, the ideas of Yilmaz et al.[43] regarding differential drug effects on RBF and perfusion also remain pertinent (Figure 3).

Conclusions

Congestion is a central clinical sign and therapeutic target in AHF patients, and a link is discernible between
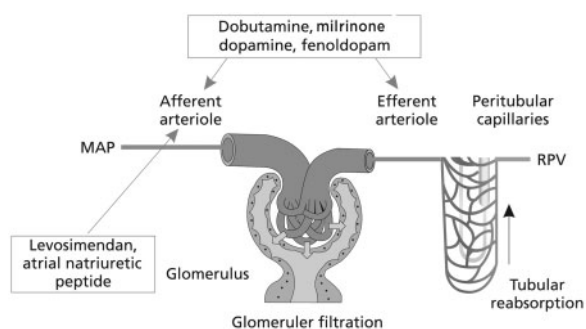
Figure 3 Differential effects of renal vasodilatation on preglomerular (afferent arteriole) and post-glomerular (efferent arteriole) renal vascular resistance. RBF, renal blood flow; MAP, mean arterial pressure; RPV, renal parenchymal volume; GFR, glomerular filtration rate. With a predominant afferent vasodilation: RBF↑ and GFR↑; with a predominant efferent vasodilation: RBF↑ and GFR↓; with both afferent and efferent vasodilation: RBF↑↑ and GFR↔. After Yilmaz et al.[43]

persistent congestion at discharge and subsequent prognosis and mortality. Eradication of clinical congestion by the time of hospital discharge may be considered a surrogate marker for the successful treatment of AHF. Inotropes can be used to augment cardiac function when there is a known low-output state in order to achieve better renal perfusion. It must be acknowledged, however, that there are little well-founded, objective data available to guide the selection or use of the various inotropes, even though this approach is quite widely used. These considerations apply to levosimendan as much as to the other agents discussed in this review, although the volume and quality of data available for levosimendan are arguably more encouraging than for some other drugs. The fact that the dataset includes direct observations of renal vascular responses and attendant functional changes provides some confidence that any views on renal-protective effects of levosimendan are grounded in testable criteria.

HF patients who might derive particular benefit from levosimendan administration include those with HF of ischaemic origins, those with well-sustained systemic blood pressure (SBP >100 mmHg) and those receiving concomitant treatment with beta-blockers. In contrast to levosimendan, dobutamine would be ineffective in patients receiving concomitant beta-blocker treatment.

Recent observations on the effects of levosimendan and milrinone on glomerular filtration differentiate these two inodilators as regards their renal effects, showing advantages of the former over the latter.[29,50] Moreover, the fact that milrinone undergoes renal excretion argues for its use with informed caution in patients with renal failure.[56] Other drugs currently under evaluation may be expected to expand the medical repertoire for the management or protection of renal function in AHF, although substantial additional work may be needed to provide a sufficient evidence base for their introduction as routine therapy.

Acknowledgements

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