ORIGINAL RESEARCH

Differential Effects of Levosimendan and Dobutamine on Glomerular Filtration Rate in Patients With Heart Failure and Renal Impairment: A Randomized Double-Blind Controlled Trial

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***Background*—**The management of the cardiorenal syndrome in advanced heart failure is challenging, and the role of inotropic drugs has not been fully defined. Our aim was to compare the renal effects of levosimendan versus dobutamine in patients with heart failure and renal impairment.

***Methods and Results*—**In a randomized double-blind study, we assigned patients with chronic heart failure (left ventricular ejection fraction <40%) and impaired renal function (glomerular filtration rate <80 mL/min per 1.73 m^2) to receive either levosimendan (loading dose 12 μg/kg+0.1 μg/kg per minute) or dobutamine (7.5 μg/kg per minute) for 75 minutes. A pulmonary artery catheter was used for measurements of systemic hemodynamics, and a renal vein catheter was used to measure renal plasma flow by the infusion clearance technique for PAH (para-aminohippurate) corrected by renal extraction of PAH. Filtration fraction was measured by renal extraction of chromium ethylenediamine tetraacetic acid. A total of 32 patients completed the study. Following treatment, the levosimendan and dobutamine groups displayed similar increases in renal blood flow (22% and 26%, respectively) with no significant differences between groups. Glomerular filtration rate increased by 22% in the levosimendan group but remained unchanged in the dobutamine group (P=0.012). Filtration fraction was not affected by levosimendan but decreased by 17% with dobutamine (P=0.045).

***Conclusions*—**In patients with chronic heart failure and renal impairment, levosimendan increases glomerular filtration rate to a greater extent than dobutamine and thus may be the preferred inotropic agent for treating patients with the cardiorenal syndrome.

***Clinical Trial Registration*—**URL: https://www.clinicaltrials.gov. Unique identifier: NCT02133105. **(*J Am Heart Assoc*. 2018;7: e008455. DOI: 10.1161/JAHA.117.008455.)**

Key Words: dobutamine • heart failure • hemodynamics • levosimendan • renal function

Heart failure (HF) affects more than 26 million people worldwide and is a leading reason for hospitalization in Europe and the United States.[1] Cardiorenal syndrome, a condition in which renal impairment occurs as a result of cardiac dysfunction, is associated with an increased risk of hospitalization and death.[2,3] Indeed, renal dysfunction is a stronger predictor of mortality than New York Heart Association (NYHA) functional class or left ventricular ejection fraction.[4]

The use of inotropes in decompensated HF is considered an option for selected patients with severe reduction of cardiac output and compromised perfusion of vital organs, such as the kidneys.[5] The drugs most commonly used are dopamine, dobutamine, and milrinone and, outside the United States, levosimendan. All of these agents increase cardiac output; however, their effect on the cardiorenal syndrome is less well studied, and whether differences occur between agents is uncertain.

Levosimendan is a calcium sensitizer and an opener of ATP-dependent potassium channels that has inotropic and arterial and venous dilating properties.[6] Levosimendan has been suggested to have renoprotective properties in several settings, such as cardiac surgery,[7] heart transplantation,[8] sepsis,[9] and HF. The LIDO (Levosimendan Infusion versus

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Clinical Perspective

What Is New?

- In this randomized trial of short-term inotropic infusion in patients with heart failure and renal impairment, both levosimendan and dobutamine caused a similar increase in renal blood flow, but only levosimendan increased the glomerular filtration rate.

What Are the Clinical Implications?

- Levosimendan may be the preferred inotropic agent for treating patients with the cardiorenal syndrome and diuretic resistance.

Dobutamine) Study, which examined inotropic treatment among those with low-output HF, showed that levosimendan brought about a significant decrease in serum creatinine compared with dobutamine.[10] Subsequent studies have suggested that levosimendan has a beneficial effect on renal function among people with acute and chronic HF.[11–13] Bragadottir et al found that levosimendan, when compared with placebo, increased both renal blood flow (RBF) and glomerular filtration rate (GFR) in post–cardiac surgery patients with normal preoperative serum creatinine.[14] Still, there is a paucity of data on the effect of inotropic agents on RBF and GFR in individuals with HF and cardiorenal syndrome.

We examined the effects of levosimendan, compared with dobutamine, on RBF, GFR, and renal oxygenation in patients with chronic HF and impaired renal function in a randomized double-blind controlled study. Our hypothesis was that levosimendan would increase GFR to a greater extent than dobutamine would.

Methods

The analytic methods and the data set generated and/or analyzed during the current study are not publicly available, given patient-related confidentiality, but are available from the corresponding author on reasonable request.

Patients

The study protocol was approved by the Gothenburg (Sweden) Regional Ethics Committee. The study was registered at ClinicalTrials.gov (identifier NCT02133105). The study design follows the guidelines of the Declaration of Helsinki. Written informed consent was obtained from all participants before the study.

Patients with chronic HF who were scheduled for right-sided cardiac catheterization as part of an elective HF workup were screened for study participation. The inclusion criteria were (1) signed informed consent; (2) age ≥18 years, (3) chronic congestive HF, (4) left ventricular ejection fraction ≤40% measured within 2 days before the study, (5) serum NT-pro-BNP (N-terminal probrain natriuretic peptide) ≥500 ng/L measured within 2 days before the study, and (6) GFR estimated (Modification of Diet in Renal Disease)[15] or measured (^{51}Cr-EDTA [chromium ethylene diamine tetraacetic acid]) between 30 and 80 mL/min. The exclusion criteria were (1) untreated acute HF, (2) systolic blood pressure <100 mm Hg, (3) heart rate >100 beats/min, (4) Canadian Cardiovascular Society class III angina pectoris or higher, (5) aortic stenosis, (6) hypertrophic cardiomyopathy, (7) restrictive cardiomyopathy, (8) presence of kidney disease diagnosed before HF, (9) administration of radiographic contrast within the previous week, (10) radiographic contrast allergy, and (11) the opinion of the investigator that the prospective study participant had a clinically significant disease that could be adversely affected by study participation.

Study participants were evaluated at Sahlgrenska University Hospital's Clinical Cardiac Laboratory following a previously scheduled routine clinical examination. At the laboratory, the patients underwent a routine right-sided cardiac catheterization procedure with basic hemodynamic measurements (using a radial artery and a thermodilution pulmonary artery catheter) as part of a clinical examination. On completion of the clinical investigation, the protocol of the present study was followed with the 32 patients who agreed to participate.

Study Protocol and Randomization

The study was an investigator-driven, single-center, randomized double-blind controlled study. A permuted block scheme, with randomly varying block size (block size 2 or 4) and stratified by the level of the right ventricular end-diastolic pressure (>12 or <12 mm Hg at baseline), was used to randomize participants (1:1) to receive levosimendan or dobutamine. The randomization process was Web-based and provided by a data management company (dSharp, Gothenburg, Sweden). A study nurse, not otherwise involved in study procedures, performed the randomization and administration of the study drug. The infusion pump containing the study drug was concealed behind a curtain and equipped with an opaque infusion line to ensure blinding. Levosimendan administration was initiated with a loading dose of 12 μg/kg given over 10 minutes, followed by a continuous infusion of 0.1 μg/kg per minute for 65 minutes. Dobutamine was given as a continuous infusion started at 5.0 μg/kg per minute for 10 minutes and thereafter increased to 7.5 μg/kg minute for 65 minutes.

Duplicate baseline measurements (B_1 and B_2) of systemic hemodynamics and renal variables (arterial and renal vein

blood samples) were performed before initiation of the drug infusion. The study drug was then administered as described. Duplicate measurements were repeated after 60 and 75 minutes of treatment (T_1 and T_2).

To prevent drug-induced hypotension (ie, mean arterial pressure falling to <60 mm Hg for ≥3 minutes), a crystalloid fluid (Ringers-Acetate; Baxter Viaflo) was administered (50–100 mL/h) from the start of study drug administration in patients without clinical signs of hypervolemia (eg, jugular vein distension and/or central venous pressure [CVP] ≥12). Response to hypotension was standardized as administration of Ringers-Acetate, with the aim of keeping CVP 5 to 10 mm Hg, or secondary norepinephrine infusion, with the aim of keeping mean arterial pressure at 70±5 mm Hg.

Measurements of Systemic Hemodynamics

A radial artery and a pulmonary artery thermodilution catheter were inserted for measurements of arterial pressure, CVP, and pulmonary artery pressure (mean pulmonary artery pressure). Cardiac output was measured in triplicate with the thermodilution technique and was indexed to the body surface area for cardiac index. Pulmonary capillary wedge pressure was measured intermittently. Systemic and pulmonary vascular resistance index, stroke volume index, systemic oxygen delivery index, and systemic oxygen consumption index were calculated according to standard formulas, as described in Table 1.

Measurements of Renal Variables

An 8-Fr catheter was inserted in the left renal vein via the right internal jugular vein under fluoroscopic guidance. Its position was verified by venography using ultralow doses of iohexol (Omnipaque 300 mg I mL^{-1}; GE Healthcare). After the collection of a blood blank, an intravenous priming dose of ^{51}Cr-EDTA and PAH (para-aminohippurate) was given, followed by infusion at a constant rate individualized to body surface area and preoperative serum creatinine. Serum concentrations of PAH and ^{51}Cr-EDTA activity were measured by a spectrophotometer (Beckman DU 530; Life Science UV/Vis) and a well counter (Wizard 1480 automatic gamma counter; Perkin Elmer LAS). Renal plasma flow was calculated using the infusion clearance technique as the amount of infused PAH divided by the difference in arterial–renal vein PAH concentrations. Formulas for calculation of the various systemic and renal variables are described in Table 1. All renal data were normalized to a body surface area of 1.73 m^2.

Statistical Analysis

Based on previous studies, the standard deviation for the difference between 2 GFR measurements estimated by infusion clearance is ≈10 mL/min. Thus, to detect an estimated 20% difference in GFR between groups, with a power of 80% and α=0.05, a sample size of 26 (13 patients in each group) was required. In total, we planned to include 32 patients to allow for 20% dropout.

Normal distribution of continuous data was checked using histograms. Continuous normally distributed data are presented as mean±SD, and non–normally distributed continuous data are presented as median and interval from the first to the third quartile. Data on renal and systemic hemodynamic variables from the 2 baseline measurements (B_1 and B_2) and during study drug administration (T_1 and T_2) were pooled. The differential effects of levosimendan and dobutamine were studied using a linear mixed model with a compound symmetry matrix, with *time* (baseline and treatment) and *group* (levosimendan or dobutamine) as fixed factors. Changes within groups were studied with paired *t* tests.

Table 1. Formulas for Calculation of Systemic and Renal Variables

Variable	Formula
CaO_2	$1.39\times Hb\times SaO_2\times 0.01+0.0023\times PaO_2$
CvO_2	$1.39\times Hb\times SvO_2\times 0.01+0.0023\times PvO_2$
Systemic oxygen delivery index	$CO\times CaO_2/BSA$
Systemic oxygen consumption index	$CO\times (CaO_2-CvO_2)/BSA$
Stroke volume index	CO/HR/BSA
Systemic vascular resistance index	$80\times(MAP-CVP)/CO$
Pulmonary vascular resistance index	$80\times(MAP-PCWP)/CO$
RPF	(Amount of PAH infused)/([PAH arterial] −[PAH renal vein])
RBF	(Amount of PAH infused)/([PAH arterial] −[PAH renal vein])/(1-Hct)
FF	([^{51}Cr-EDTA arterial]−[^{51}Cr-EDTA renal vein])/(^{51}Cr-EDTA arterial)
Glomerular filtration rate	$FF\times RPF$
Renal vascular resistance	(MAP−CVP)/RBF
Renal oxygen consumption	$RBF\times(CaO_2-CrvO_2)$
Renal oxygen delivery	$RBF\times CaO_2$
Renal oxygen extraction	$(CaO_2-CrvO_2)/CaO_2$

BSA indicates body surface area (m^2); CaO_2, arterial oxygen content; CO, cardiac output (L/min); $CrvO_2$, renal vein oxygen content; CvO_2, venous oxygen content; CVP, central venous pressure (mm Hg); ^{51}Cr-EDTA, chromium ethylene diamine tetraacetic acid; FF, filtration fraction; Hct, hematocrit; HR, heart rate (beats/min); MAP, mean arterial pressure (mm Hg); PAH, para-aminohippurate; PaO_2, arterial oxygen tension (kPa); PCWP, pulmonary capillary wedge pressure (mm Hg); PvO_2, mixed venous oxygen tension (kPa); RBF, renal blood flow; RPF, renal plasma flow; SaO_2, arterial oxygen saturation (%); SvO_2, mixed venous oxygen saturation (%).

Differences between groups at baseline were studied with independent-samples *t* tests. $P<0.05$ (2-tailed) was considered significant. Predictive Analytics Software Statistics 18.0 (SPSS; IBM Corp) was used for all statistical analyses.

Results

Between April 2014 and May 2017, a total of 55 potential participants were assessed, of whom 33 were enrolled in the study. One patient, randomized to levosimendan, developed atrial fibrillation with circulatory instability before study drug administration and was consequently excluded. Thus, 32 people completed the study. In 3 patients (all in the levosimendan group), renal data were incomplete because of missing data (n=1) and/or displacement of the renal vein catheter during the experimental procedure (n=2). In the 2 latter patients, exceptionally high PAH concentrations confirmed that the blood samples were, to a great extent, sampled from the inferior caval vein and not exclusively from the renal vein. A study flowchart is shown in Figure 1.

Table 2 displays demographic and clinical characteristics of the 2 study groups. The majority were men, with a mean age of 58 years, an average body mass index of 29, and a median NYHA functional class of III. Dilated cardiomyopathy was the most common cause of HF, affecting 50% in the levosimendan group and 56% in the dobutamine group. Ischemic heart disease was prevalent in 50% of the patients in the levosimendan group and 38% in the dobutamine group. One participant in the dobutamine group had HF due to tachycardia-induced cardiomyopathy. The mean left

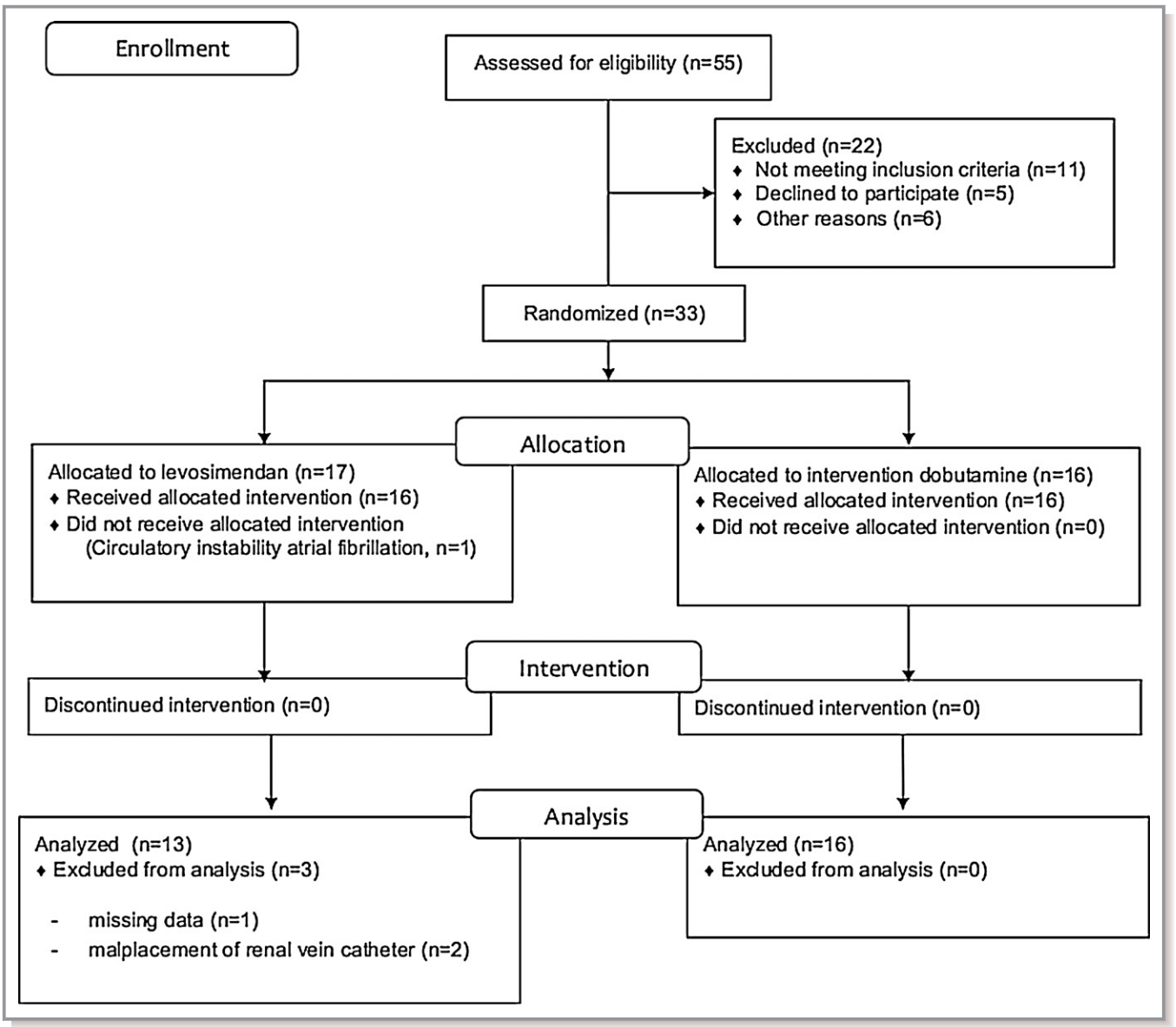

Figure 1. Study flowchart.

Table 2. Clinical Characteristics of the 2 Study Groups at Baseline

	Levosimendan (n=16)	Dobutamine (n=16)
Sex, male	14 (88)	14 (88)
Age, y	58.1±11.6	58.6±10.0
BMI, kg/m	29.1±4.2	28.6±5.5
Smoking		
Never	4 (25)	9 (56)
Previous	12 (75)	6 (38)
Current	0	1 (6)
NYHA class		
II	1 (6)	1 (6)
III	14 (88)	12 (75)
IV	1 (6)	3 (19)
DCM	8 (50)	9 (56)
Ischemic heart disease	8 (50)	6 (38)
Other cause	0	1 (6)
Myocardial infarction	7 (44)	6 (38)
PCI	8 (50)	6 (38)
CABG	4 (25)	2 (13)
Device		
None	0	3 (19)
ICD	9 (56)	8 (50)
CRTD	7 (44)	5 (31)
Hypertension	4 (25)	3 (19)
Diabetes mellitus	6 (38)	5 (31)
Atrial fibrillation	8 (50)	7 (44)
Pulmonary disease	1 (6)	3 (19)
Treatment		
β-blocker	14 (88)	16 (100)
ACEI	6 (38)	8 (50)
ARB	9 (56)	7 (44)
Aldosterone antagonists	9 (56)	12 (75)
Loop diuretics	15 (94)	15 (94)
Digoxin	1 (6)	4 (25)
Amiodarone	4 (25)	2 (13)
ASA	3 (19)	5 (31)
Anticoagulant	12 (75)	9 (56)
Statins	10 (63)	7 (44)
Oral antidiabetics	3 (19)	3 (19)
Insulin	3 (19)	4 (25)
LVEF, %	27.2±8.0	26.0±8.1
HR, beats/min	72±7	76±15
Hemoglobin, g/L	127±18	136±16
Serum creatinine, μg/L	143±37	122±31
NT-proBNP, ng/L	2290 (1500–4650)	1760 (1057–5995)
eGFR, mL/min	49.4±16.3	55.3±18.7
mGFR, mL/min	42.8±15.4	53.4±15.2

Values are shown as numbe (%), mean±SD, or median (interquartile range). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockade; ASA, acetyl salicylic acid; BMI, body mass index; CABG, coronary artery bypass grafting; CRTD, cardiac resynchronization therapy defibrillator; DCM, dilated cardiomyopathy; eGFR, estimated glomerular filtration rate according to the Modification of Diet in Renal Disease formula; HR, heart rate; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; mGFR, measured glomerular filtration rate; NT-proBNP, N-terminal probrain natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

ventricular ejection fraction was 27% in the levosimendan group and 26% in the dobutamine group.

Systemic Variables

Central hemodynamic and systemic oxygen transport variables at baseline and during inotropic treatment are shown in Table 3. These variables did not differ between study groups at baseline and did not show between-group differences with respect to treatment effects. After the study's drugs were administered, the levosimendan and dobutamine groups showed increased stroke volume index (14% and 13%, respectively), cardiac index (17% and 28%, respectively), systemic oxygen delivery (18% and 29%, respectively), and SvO_2 (4.7% and 7.8% units, respectively). CVP and pulmonary capillary wedge pressure decreased in both groups. Both drugs caused an increase in heart rate, which tended to be more pronounced in patients receiving dobutamine. There was a nominally larger fall in systemic vascular resistance index in the dobutamine group (−21%) compared with the levosimendan group (−8%). Neither group showed a significant decrease in pulmonary vascular resistance index.

Renal Variables

Renal circulatory and oxygen transport variables at baseline and during inotropic treatment are shown in Table 4. Baseline measurements (B_1 and B_2) of arterial PAH concentration were 0.29±0.12 and 0.29±0.11, respectively, in the levosimendan group (P=0.98) and 0.31±0.06 and 0.31±0.07, respectively, in the dobutamine group (P=0.51); this suggests that a steady state was reached in both groups. There were no significant differences between the groups at baseline. After treatment, RBF increased by 22% in the levosimendan group and 26% in the dobutamine group, with corresponding increases in renal oxygen delivery and no differences between groups. The renal

Table 3. Systemic Variables Before and After Study Drug Administration

Variable	Levosimendan, n=16		Dobutamine, n=16		LMM *P* Value
	Baseline	Treatment	Baseline	Treatment	
CO, L/min	4.78±0.87	5.64±1.34*	5.07±1.18	6.46±1.02†	0.143
CI, L/min/m^2	2.30±0.36	2.70±0.59*	2.41±0.58	3.08±0.53†	0.162
SVI, mL/beats/m^2	33.0±6.9	37.6±8.3‡	32.8±12.4	37.1±11.6	0.918
HR, beats/min	71±5	73±5‡	78±19	88±20‡	0.057
MAP, mm Hg	69±10	71±9	70±9	70±9	0.349
MPAP, mm Hg	31±9	29±9	25±10	24±11	0.864
CVP, mm Hg	9±5	7±4*	8±9	6±8*	0.728
PCWP, mm Hg	19±7	17±6	14±8	12±9*	0.795
DO_2I, mL/min/m^2	348±73	409±89*	391±110	504±102†	0.116
VO_2I, mL/min/m^2	129±18	136±24	130±29	129±16	0.367
SaO_2, %	93.4±3.6	93.8±2.5	95.1±2.2	96.1±1.9‡	0.298
SvO_2, %	57.4±10.3	62.1±6.3*	62.7±7.9	70.5±7.8†	0.369
SVRI (dyn s/cm^5/m^2)	2141±494	1961±491	2162±574	1704±338*	0.092
PVRI (dyn s/cm^5/m^2)	440±300	394±205	386±245	349±219	0.506

CI indicates cardiac index; CO, cardiac output; CVP, central venous pressure; DO_2I, indexed systemic oxygen delivery; HR, heart rate; LMM, linear mixed model; MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVRI, pulmonary vascular resistance index; SaO_2, arterial oxygen saturation; SVI, stroke volume index; SvO2, central venous oxygen saturation; SVRI, systemic vascular resistance index; VO_2I, indexed systemic oxygen consumption.
*P<0.01 vs baseline.
†P<0.001 vs baseline.
‡P<0.05 vs baseline.

vascular resistance decreased in both groups (−9% in the levosimendan group and −16% in the dobutamine group, P=0.25). GFR increased by 22% in the levosimendan group but remained unchanged in the dobutamine group (P=0.012). Filtration fraction was not affected by levosimendan and decreased by 17% with dobutamine (P=0.045). Renal oxygen extraction decreased in both groups with no differences between groups. The ratio between RBF and cardiac index

Table 4. Renal Variables Before and After Study Drug Administration

Variable	Levosimendan, n=13		Dobutamine, n=16		LMM *P* Value
	Baseline	Treatment	Baseline	Treatment	
RBF, mL/min	426±197	518±276*	397±121	499±154†	0.732
GFR, mL/min	36.5 ±18.3	44.5±19.0‡	47.1±14.5	47.3±16.9	0.012
FF	0.146 ±0.080	0.143±0.069	0.193±0.070	0.161±0.075*	0.045
PAH_{ext}	0.702±0.21	0.650±0.22‡	0.793±0.15	0.754±0.19‡	0.614
PAH_{art}	0.29±0.11	0.26±0.10†	0.31±0.06	0.27±0.07†	0.194
RVO_2, mL/min	9.2±6.3	10.1±6.2	8.3±2.6	8.9±4.3	0.801
RDO_2, mL/min	67.0±36.5	82.4±50.3*	65.0±23.8	82.2±29.3†	0.728
RO_2Ex, %	15.5±6.7	13.8±5.0	14.5±7.0	12.0±6.5*	0.487
$SrvO_2$, %	78.6±8.6	80.5±5.9	81.3±7.7	84.6±7.1*	0.117
RBF/CI, %	18.5±7.7	19.5±9.8	16.9±4.9	16.8±6.3	0.474
RVR, mm Hg/mL/min	0.161±0.05	0.147±0.05‡	0.171±0.07	0.144±0.06‡	0.249

CI indicates cardiac index; FF, filtration fraction; GFR, glomerular filtration rate; LMM, linear mixed model; PAH_{art}, arterial PAH concentration; PAH_{ext}, extraction of para-aminohippurate; RBF, renal blood flow; RDO_2, renal oxygen delivery; RO_2Ex, renal oxygen extraction; RVO_2, renal oxygen consumption; RVR, renal vascular resistance, $SrvO_2$, renal vein oxygen saturation.
*P<0.01 vs baseline.
†P<0.001 vs baseline.
‡P<0.05 vs baseline.

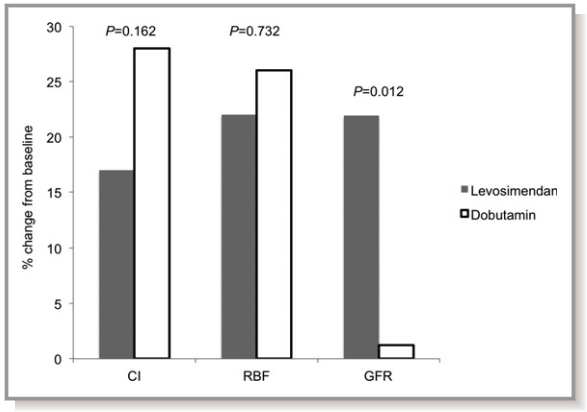

Figure 2. Relative (%) changes in cardiac index (CI), renal blood flow (RBF), and glomerular filtration rate (GFR) after administration of levosimendan vs dobutamine.

was not affected by either of the 2 agents. Both levosimendan and dopamine patients displayed a reduction in PAH extraction (−7% and −5%, respectively; P=0.61).

Changes in cardiac index, RBF, and GFR induced by the 2 agents are graphed in Figure 2.

In the dobutamine group, 3 patients received both norepinephrine and crystalloid, and 1 patient received only norepinephrine. One patient in the levosimendan group received norepinephrine for hypotension. Neither the mean infusion rate of the crystalloid nor the mean dose of norepinephrine differed between groups. No serious adverse events occurred during the trial.

Discussion

In this randomized double-blind controlled study we compared the acute renal and systemic effects of moderate doses of levosimendan (0.1 μg/kg per minute) and dobutamine (7.5 μg/kg per minute) among a group of patients with HF and renal impairment. Both agents induced a renal vasodilation and increased RBF to a similar extent. Only levosimendan increased the GFR (by 22%). In contrast, dobutamine had no effect on GFR.

To our knowledge, this study is the first evaluating the differential effects of levosimendan and a catecholamine on measured RBF, GFR, and renal oxygenation in patients with HF and renal dysfunction. Recently, Fedele et al measured RBF by the renal artery Doppler technique in patients with acute decompensated HF and found that levosimendan, in contrast to a placebo, increased RBF.[16] This is consistent with our findings; but in that study, neither GFR nor renal oxygenation was evaluated. The findings from the present study are also consistent with our earlier investigation on uncomplicated post–cardiac surgery patients with normal renal function, in whom levosimendan increased both RBF and GFR compared with placebo.[14]

In the present study, levosimendan and dobutamine exerted differential effects on GFR. Both inotropic agents induced a renal vasodilatory effect accompanied by an increase in RBF. The renal filtration fraction (GFR/renal plasma flow) remained unchanged in patients receiving levosimendan, and it decreased in those treated with dobutamine. These findings could mean that levosimendan preferentially causes vasodilation of the afferent arterioles—which, at a certain mean arterial pressure, induces a proportional increase in both RBF and GFR. The presence of ATP-dependent potassium channels on afferent arterioles and activation of these channels have previously been demonstrated in experimental studies.[17] Dobutamine, in contrast, seems to induce balanced vasodilation of both afferent and efferent arterioles, thereby increasing RBF, while maintaining a constant glomerular filtration pressure. This pattern is similar to that previously described for low-dose dopamine in post–cardiac surgery patients, in whom it induced a pronounced increase in RBF with no effect on GFR.[18]

Experimental studies indicate that levosimendan may exert a beneficial effect on the glomerular capillary ultrafiltration coefficient.[19] Smooth muscle–like cells in the mesangium of the glomerulus, the mesangial cells, regulate the glomerular capillary surface area. They respond to vasoconstrictors such as angiotensin II and react by decreasing the available surface area for filtration. This angiotensin II–mediated mesangial cell contraction is reversed by levosimendan.[19] One could speculate that the levosimendan-induced increase in GFR in HF patients, who are known to have high circulatory levels of angiotensin II,[20] could to some extent be explained by an inhibition of the angiotensin II–mediated mesangial cell contraction and an increase of the available glomerular capillary surface area.

A rise in CVP is an important predictor of renal dysfunction in HF patients.[21] Elevated CVP will increase renal venous backpressure and thus decrease renal perfusion pressure and impair renal function (GFR). Ylmaz et al suggested that levosimendan offered a more beneficial effect than dobutamine in patients with biventricular HF.[22] They found greater improvement of RV systolic function among patients treated with levosimendan, but data on CVP were not presented. One could thus argue that the favorable effect of levosimendan on GFR in the present study was due to an improvement in RV function and a more pronounced fall in CVP, compared with dobutamine; however, this is not supported by our findings because both inotropic agents reduced CVP to a similar extent.

Renal oxygen extraction (RO_2Ex) is a direct measure of the renal oxygen supply/demand relationship. In our HF patients, the RO_2Ex was 15%, which is considerably higher than in individuals with normal renal function, in whom RO_2Ex is ≈10%.[23,24] Consequently, renal oxygenation in HF patients

seems to be chronically impaired. This is caused by a considerable elevation of renal vascular resistance and reduction in RBF and renal oxygen delivery.[23,24] We repeatedly found a close positive correlation among GFR, tubular reabsorption, and renal oxygen consumption (RVO_2) in patients with normal renal function.[23,25–27] We had thus expected that our HF patients, because of low GFR levels, would display reduced RVO_2 but found instead that their RVO_2 levels were close to normal.[23,24] A higher than expected RVO_2 in HF could, in part, be explained by recent experimental studies showing that the oxidative stress caused by renal hypoxia increases mitochondrial activity and thereby enhances total RVO_2.[28]

A major goal in the treatment of the cardiorenal syndrome is to increase GFR. An increase in filtered sodium will increase tubular sodium load and uptake and thereby increase RVO_2.[29] An isolated increase in GFR could thus jeopardize the oxygenation of the renal medulla, which is sensitive to renal ischemia, given the highly oxygen-demanding sodium reabsorption process. For levosimendan, however, this is less likely to occur because treatment with this agent caused a balanced increase in GFR and renal oxygen delivery, as shown by the maintained RO_2Ex. Dobutamine, in contrast, caused a 26% increase in RBF with no effect on GFR, which improved the balance between oxygen delivery and consumption (reduced RO_2Ex), again, resembling the effects of low-dose dopamine.[18] Whether such "luxury" perfusion without increased organ function (glomerular filtration) could be favorable for renal outcome has yet to be established.

The 2013 American College of Cardiology Foundation/American Heart Association guidelines recommend temporary intravenous inotropic support in patients with low cardiac output and hypotension to preserve end organ function, such as the kidneys (class IIb; level of evidence C).[5] It has been assumed that any inotropic drug that displays a favorable effect on central and peripheral hemodynamics would, inevitably, also improve renal function.[30] The differential effects of levosimendan and dobutamine on GFR demonstrated by the present study are, therefore, of clinical interest and might imply that levosimendan could be the preferred inotropic agent for treatment of the cardiorenal syndrome. Our findings may also have implications for HF guidelines, which currently provide no information on whether inotropic agents may differ with respect to effect on renal function.

This study has some limitations. A major limitation is the relatively small sample size of the study population. Furthermore, our protocol was a pharmacological intervention of short duration, and only the acute effects of the administered inotropic agents were studied; therefore, the effect of a more prolonged (24–48 hours) period of levosimendan treatment on measured GFR is not known. Moreover, the participants of the study were not in need of inotropic support, in contrast to patients with acute HF, who are considered for such interventions. In addition, urine was not collected for analysis of, for example, sodium excretion. The strength of the study is that it was randomized and blinded, which give a more reliable and valid comparison of the 2 study drugs.

Conclusion

In patients with HF and renal impairment, the levosimendan-induced elevation of cardiac output not only increased RBF but also, and in contrast to dobutamine, enhanced GFR, suggesting a preferential dilation of preglomerular afferent arterioles. Based on these findings, levosimendan may be the preferred inotropic drug for treatment of patients with the cardiorenal syndrome.

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