Effects of levosimendan versus dobutamine on left atrial function in decompensated heart failure

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BACKGROUND: Although the effects of levosimendan on the left ventricle (LV) have been studied, its effect on left atrial (LA) function is poorly understood, despite its key role in optimizing LV function.

OBJECTIVE: To compare the effects of levosimendan and dobutamine on LA and LV function in patients with decompensated heart failure (DHF).

METHODS: Seventy-four patients (mean $\pm$ SD) age 64 ± 10 years) with DHF and an LV ejection fraction of 35% or lower were randomly assigned to receive levosimendan (n=37) or dobutamine (n=37). LA active emptying fraction, LA passive emptying fraction (PEF) and the ratio of mitral inflow early diastolic velocity to annulus velocity (E/e) were evaluated with pulsed wave and tissue Doppler imaging along with plasma B-type natriuretic peptide (BNP) level measurements before and after drug infusion.

RESULTS: The ejection fraction was significantly increased in both groups. The levosimendan group had a greater decrease in BNP and a greater increase in active emptying fraction at 24 h compared with the dobutamine group. The PEF, E/e and deceleration time of the E wave were significantly improved in the levosimendan group, but not in the dobutamine group. Levosimendan-induced percentage change of BNP was significantly correlated with the percentage change of E/e and PEF ($r=0.48$ [$P<0.005$] and $r=-0.38$ [$P<0.05$], respectively).

CONCLUSIONS: In patients with DHF, levosimendan and dobutamine both improve LV systolic function. However, levosimendan also improves LV diastolic function and LA performance in parallel with a greater improvement in neurohormonal activation compared with dobutamine.

Key Words: *Decompensated heart failure; Dobutamine; Left atrial function; Levosimendan*

Levosimendan is a novel drug that improves myocardial contractility by sensitizing troponin C to calcium without increasing myocardial oxygen demand (1,2). As an inotropic drug, it has proven effective in the treatment of patients with moderate and advanced heart failure (3-5). Levosimendan improves vasodilatory properties, facilitating the opening of ATP-dependent potassium channels, and also has anti-ischemic effects (6,7). Unlike other positive inotropic agents, the primary actions of levosimendan are independent of interactions with adrenergic receptors (8). Compared with dobutamine-treated patients, levosimendan-treated patients have marked decreases in B-type natriuretic peptide (BNP) level and also show more favourable hemodynamic improvement in decompensated heart failure (DHF) (9,10).

The left atrium (LA) serves multiple functions. It acts as a conduit (for blood from the pulmonary veins to the left ventricle [LV]) during early diastole, as an active contractile chamber that augments LV filling in late diastole, as a suction source that refills itself in early systole and as a reservoir during ventricular systole (11). Overall, atrial contraction contributes to approximately 30% of cardiac

Effets comparatifs du levosimendan et de la dobutamine sur la fonction auriculaire gauche dans l'insuffisance cardiaque décompensée

HISTORIQUE : Les effets du levosimendan sur le ventricule gauche (VG) ont été étudiés, mais notre compréhension de ses effets sur la fonction de l'oreillette gauche (OG) laisse encore à désirer, malgré son rôle clé dans l'optimisation de la fonction VG.

OBJECTIF : Comparer les effets du levosimendan et de la dobutamine sur la fonction OG et VG de patients souffrant d'insuffisance cardiaque décompensée (ICD).

MÉTHODES : Les auteurs ont randomisé soixante-quatorze patients (âge moyen [É.-T.] 64 ± 10 ans) souffrant d'ICD et présentant une fraction d'éjection VG égale ou inférieure à 35 % soit au levosimendan (n = 37), soit à la dobutamine (n = 37). Ils ont mesuré les fractions de vidange OG active (FVA) et passive (FVP), le rapport vélocité du flux mitral entrant en début de diastole:vélocité au niveau de l'anneau mitral (E/e) par ondes pulsées et Doppler tissulaire, de même que les taux de peptides natriurétiques de type B (PNB) plasmatiques, avant et après la perfusion des médicaments.

RÉSULTATS : La fraction d'éjection a augmenté significativement dans les deux groupes. Le groupe sous levosimendan a présenté une baisse plus marquée des taux de PNB et une augmentation plus nette de la FVA à 24 heures, comparativement au groupe sous dobutamine. La FVP, le rapport E/e et le temps de décélération de l'onde E se sont significativement améliorés dans le groupe sous levosimendan, mais non dans le groupe sous dobutamine. Le pourcentage de changement des taux de PNB induit par le levosimendan a été en corrélation significative avec le pourcentage de changement du rapport E/e et de la FVP ($r = 0,48$, $p < 0,005$ et $r = -0,38$, $p < 0,05$, respectivement).

CONCLUSIONS : Chez les patients souffrant d'ICD, le levosimendan et la dobutamine améliorent la fonction systolique VG. Toutefois, comparativement à la dobutamine, le levosimendan améliore également la fonction VG diastolique et le rendement OG, en parallèle avec une amélioration plus marquée de l'activation neurohormonale.

output (12,13). Although the effects of levosimendan on the LV have been studied (3-5,9,10), its effect on LA function is poorly understood despite its key role in optimizing LV function.

The aim of the present study was to evaluate the effects of levosimendan and dobutamine on LA and LV function among patients with DHF. The effects of both drugs on plasma BNP were also examined.

METHODS

Seventy-four consecutive patients with a documented LV ejection fraction of 35% or lower, and New York Heart Association class III or IV symptoms of heart failure were enrolled. Exclusion criteria were age younger than 21 years or older than 80 years, heart failure due to restrictive or hypertrophic cardiomyopathy, moderate or severe valvular disease, the presence of acute or chronic inflammatory or infectious diseases, recent myocardial infarction (within eight weeks) or chest pain at the time of random assignment, hepatic or renal impairment (creatinine greater than $221 \mu\text{mol/L}$), the use of immunosuppressive drugs, serious arrhythmias, cardiac tamponade, adult respiratory

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TABLE 1
Baseline clinical characteristics of the study patients

Characteristic	Levosimendan (n=37)	Dobutamine (n=37)
Age, years	64±10	66±8
Men, %	75	64
New York Heart Association class, %		
III	73	64
IV	27	36
Cause, %		
Ischemic	81	76
Nonischemic	19	24
Body mass index, kg/m ²	1.69±0.18	1.59±0.21
Diabetes mellitus, %	30	25
Systolic BP, mmHg	105±12	109±14
Diastolic BP, mmHg	64±7	67±8
Hypertension, %	28	34
Smoking (past or present), %	62	72
Creatinine, µmol/L	106±18	97±26
Hemoglobin, g/L	116±06	112±05
BNP, pg/mL	1979±1692	1934±1565
Medications, %		
Beta-blockers	84	89
ACE-I or ARB	100	100
Furosemide	100	100
Spironolactone	57	50
Digitalis	49	53

Data presented as mean ± SD unless otherwise indicated. ACE-I Angiotensin-converting enzyme inhibitor; ARB Angiotensin receptor blocker; BNP B-type natriuretic peptide; BP Blood pressure

distress syndrome, supine systolic blood pressure lower than 85 mmHg and septic shock.

A prospective randomized, open-label, blinded end point design was chosen because the primary objective of the study was to assess treatment effects on LA and LV function (14). After the optimization of diuretic treatment using intravenous furosemide, patients were randomly assigned, in a 1:1 ratio, to receive a 24 h infusion of either levosimendan (n=37) or dobutamine (n=37). All patients were evaluated echocardiographically and biochemically at baseline and 24 h after the completion of treatment (day 1). Informed consent was obtained from each patient and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in the a priori approval of the institution's human research committee.

Levosimendan (Simdax; Abbott Laboratories, USA) was given as a continuous infusion of 0.2 µg/kg/min without a loading dose for 24 h. A dobutamine infusion of 10 µg/kg/min was administered without a loading dose for 24 h.

Plasma BNP was measured using the rapid Triage BNP assay (Biosite Inc, USA). Blood samples were collected in 5 mL EDTA (K₃ salt) glass tubes. The measurable range of BNP was 20 pg/mL to 5000 pg/mL.

Echocardiographic imaging and analysis

Transthoracic echocardiographic examinations were performed with a Vivid 3 echocardiograph (General Electric, USA) using standard views and techniques according to the guidelines of the American Society of Echocardiography (15), with patients in the left lateral decubitus position.

LA volumes were calculated according to the Dodge method (16) using a biplane area-length formula:

$$V = 8A_1 \times A_2/3\pi L$$

where A₁ and A₂ represent the enclosed area of the atrial chamber from two orthogonal views, respectively, and L is the common axis shared and

directed from apex to base. The following measurements were made at baseline, and following the levosimendan and dobutamine infusions:

- LA maximal volume (V_{max}) at the point of mitral valve opening and LA minimal volume (V_{min}) at the point of mitral valve closure. LA volume at the onset of atrial systole (V_p) was considered to be the volume corresponding to the onset of the P wave on the simultaneously recorded electrocardiogram. All LA volume values were calculated as the mean of three consecutive beats and were corrected for body surface area.
- LA function was evaluated using the LA passive emptying fraction (PEF):

$$PEF = V_{max} - V_p/V_{max}$$

and the LA active emptying fraction (AEF):

$$AEF = V_p - V_{min}/V_p$$

The atrial reservoir function was determined by measuring the LA reservoir volume (RV):

$$RV = V_{max} - V_{min}$$

- From the parasternal long-axis view, the LV end-diastolic and end-systolic diameters were calculated. The LV ejection fraction was measured by using the modified Simpson's rule.

Peak velocities of early (E) and late (A) mitral diastolic filling, isovolumetric relaxation time (IVRT) and deceleration time (DT) were derived from transmitral Doppler recordings. Tissue Doppler imaging-derived systolic, and early (e) and late (a) diastolic velocities were derived from the septal and lateral mitral annulus, and averaged for each patient (17). The E/e ratio was also estimated as a marker of LV filling pressures. For standard echocardiography and pulsed wave Doppler measurements, including LA volumes and tissue Doppler imaging-derived variables, the inter- and intraobserver coefficients of variation ranged from 4% to 9%.

Blood samples for analyses of natriuretic peptide levels were drawn from patients in the supine position before the echocardiographic examinations (baseline and after 24 h) using ELISA (BNP; Biosite Diagnostics, USA) by an observer who was blinded to patient identity and treatments.

Statistical analysis

Results are presented as mean ± SD for continuous variables and as a percentage of total for categorical variables. Mean values of continuous variables were compared between groups using the Student's *t* test or the Mann-Whitney U test, according to whether variables were normally or non-normally distributed. Similarly, the paired *t* test or signed-rank analysis was used, respectively, to compare mean values before and after treatments. Correlations were obtained by estimating Spearman's coefficient. *P*<0.05 was considered to be statistically significant.

RESULTS

The demographic variables of the two groups are presented in Table 1. The two study groups were well balanced with respect to baseline characteristics and concomitant medications. No significant differences in systolic or diastolic blood pressure, or heart rate responses were encountered between the two treatment arms. All patients completed the study.

The LA V_p was significantly decreased in the levosimendan group, but not in the dobutamine group, after treatment (Table 2). The mean BNP and V_{min} decreased, and AEF and ejection fraction increased in both the levosimendan and dobutamine groups, although the reduction of BNP and the increase of AEF were significantly greater in the levosimendan group (−624±666 pg/mL versus −281±276 pg/mL [*P*<0.005] and −0.11±0.10% versus −0.034±0.037% [*P*<0.01], respectively). The PEF, DT and IVRT were significantly increased in levosimendan-treated patients but remained unaffected in dobutamine-treated patients.

TABLE 2
Clinical features of the study population before and after treatment

	Levosimendan (n=37)		Dobutamine (n=37)	
	Before	After	Before	After
V_{max} , mL/m ²	36.3±16.4	34.8±17.7	35.2±13.2	33.8±14.1*
V_{min} , mL/m ²	25.4±10.6	18.3±11.2†	25.7±11.8	23.5±10.3*
V_p , mL/m ²	30.2±13.8	24.5±12.1††	29.8±12.1	29.1±11.9
PEF, %	16.4±9.5	29.4±12††	13.8±7.4	14.7±9.9
AEF, %	15.8±8.9	25.9±11.3††	16.2±10.0	19.5±10.4*
RV, mL/m ²	10.9±7.4	16.5±6.8††	9.5±5.2	10.3±4.8***
Systolic BP, mmHg	105±3	108±3	107±4	112±4
Diastolic BP, mmHg	68±2	70±1	71±2	72±2
Heart rate, beats/min	83±15	91±14	84±15	92±17
LVEDD, mm	65.2±6.9	66.2±6.6	62.6±7.5	63.5±7.2
LVESD, mm	56.3±8.2	53.6±9.2	54.1±9.8	49.7±12.0*
LVEF, %	22.0±8.4	25.1±8.8†	23.6±8.5	26.5±9.2†
E, m/s	1.01±0.35	1.07±0.32	0.98±0.34	0.95±0.33
A, m/s	0.61±0.21	0.69±0.19**	0.62±0.16	0.59±0.18
E/A	2.11±1.50	1.69±1.03**	1.79±1.14	1.82±0.98
E/e	13.8±3.5	11.2±3.0††	12.9±3.0	12.4±3.1
DT, ms	123±31	158±57*	137±49	141±45
IVRT, ms	86±22	129±19†	98±22	106±25
BNP, pg/mL	1979±1692	1355±1343††	1934±1565	1653±1428†

Data presented as mean ± SD. * $P<0.05$; ** $P<0.01$; *** $P<0.005$; † $P<0.001$; †† $P<0.0001$. A Mitral inflow late diastolic velocity; AEF Left atrial active emptying fraction; BNP B-type natriuretic peptide; BP Blood pressure; DT Deceleration time; E Mitral inflow early diastolic velocity; E/A The ratio of mitral inflow early to late diastolic velocity; E/e The ratio of mitral inflow early diastolic velocity to annulus velocity; IVRT Isovolumetric relaxation time; LVEDD Left ventricular end-diastolic diameter; LVEF Left ventricular ejection fraction; LVESD Left ventricular end-systolic diameter; PEF Left atrial passive emptying fraction; RV Left atrial reservoir volume; V_{max} Left atrial maximal volume; V_{min} Left atrial minimal volume; V_p Left atrial volume at the onset of atrial systole

Likewise, E/e and E/A ratios were significantly reduced in the levosimendan group but remained unchanged in the dobutamine group.

LV end-systolic diameter significantly decreased after dobutamine treatment, although LV end-diastolic diameter did not change significantly in either group. In the levosimendan group, there was a significant correlation between the percentage change of BNP, and the percentage change of PEF and E/e ($r=-0.38$ [$P<0.05$] and $r=0.48$ [$P<0.005$], respectively), but not IVRT, ejection fraction, E/A or DT (Figure 1).

DISCUSSION

In the present study, we showed for the first time that the novel inodilator agent, levosimendan, improves LA performance and LV diastolic function in patients with severe heart failure receiving optimal conventional treatment. Levosimendan-treated patients had a greater decrease of BNP than the dobutamine-treated patients. Furthermore, a significant correlation was observed between the percentage decrease of BNP and the percentage decrease of the E/e ratio (a tissue Doppler imaging indicator of LV filling pressures), as well as the percentage increase of PEF (an indicator of LA and LV diastolic function) in patients with DHF.

In patients with chronic heart failure due to ischemic or idiopathic cardiomyopathy, systolic dysfunction is accompanied by an abnormal elevation of ventricular filling pressures associated with enlargement of the LA and LV chambers, and an increase of their stiffness (18,19). Many randomized studies have shown that plasma natriuretic peptide levels rise due to increased volume and myocardial tension during heart failure, and BNP levels are more closely related to indexes of LV filling (20,21). In a recent study (22) that evaluated patients with symptomatic heart failure, BNP levels were correlated with several indexes of diastolic function,

Figure 1 Correlations between the levosimendan-induced percentage decrease in plasma B-type natriuretic peptide (BNP) levels and the percentage decrease in the ratio of mitral inflow early diastolic velocity to annulus velocity (E/e) (A), as well as the percentage increase in the left atrial passive emptying fraction (PEF) (B)

including DT, E/e and LA area. Barclay et al (23) showed that LA volume index correlated significantly with BNP level. Levosimendan- and dobutamine-induced reductions in BNP or N-terminal pro-BNP levels have been reported in several placebo-controlled or nonrandomized clinical studies. In a randomized, placebo-controlled trial of patients with acute DHF, Adamopoulos et al (24) compared the effects of levosimendan with those of dobutamine. The authors reported that N-terminal pro-BNP levels were significantly reduced by levosimendan treatment at both 24 h and 48 h, but remained unchanged with dobutamine treatment (24). In The Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE) study (9), levosimendan caused a greater decrease in BNP level than dobutamine at 24 h; this decrease persisted for five days. In agreement with these studies, we demonstrated that BNP was significantly decreased by both levosimendan and dobutamine treatment at the end of the 24 h infusion period; however, levosimendan treatment produced a greater reduction of BNP levels.

Although LV systolic and diastolic function was compared after levosimendan or dobutamine infusion in patients with advanced heart failure, the effects of levosimendan on atrial function have not been reported previously. We showed that both levosimendan and dobutamine increased AEF, which expresses LA systolic function and is analogous to LV ejection fraction (25,26). However, levosimendan, but not dobutamine, improves PEF, which reflects the passive emptying of the LA into the LV during

early diastole. This depends on the LA and LV diastolic properties and pressures, which in turn, rely on LV systole (27,28). Barraud et al (29) reported that treatment with the calcium sensitizer, levosimendan, improved both systolic and diastolic cardiac function in septic animals, but dobutamine only improved systolic function. Capomolla et al (30) compared the acute adaptations of the LV performance, LA function and mitral regurgitation that accompanied hemodynamic improvement during intravenous dobutamine and nitroprusside infusions in patients with severe chronic heart failure. After nitroprusside infusion, maximal and minimal LA volumes decreased, whereas atrial pump volume increased. Although the administration of dobutamine produced a significant reduction in minimal atrial volume, LA pump volume did not change. The Doppler mitral flow patterns improved from restrictive or pseudonormal to normal pattern after nitroprusside but not after dobutamine infusion (30). In a recent study (31), it was reported that levosimendan causes a greater reduction of the E/e ratio than dobutamine in acute systolic left heart failure. Consistent with these studies, the present study demonstrated that levosimendan, but not dobutamine, decreased E/e and E/a, and also increased PEF and DT significantly, although the LV systolic function was significantly improved in both groups. Furthermore, in the levosimendan group, we found a significant correlation between the percentage decrease of BNP and the percentage decrease of the E/e as well as the percentage increase of PEF.

Our results indicate that levosimendan improves LV and LA diastolic function in addition to LV systolic function in patients with DHF. Furthermore, the improvement of LV diastolic function and the increased LA performance were significantly correlated with the neurohormonal improvement. Although previous studies demonstrated that levosimendan decreased BNP more favourably than dobutamine in patients with DHF, our findings suggest a significant association between the improvement in neurohormonal activation, and the improvement of LA performance and LV diastolic function after treatment with levosimendan in patients with DHF.

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