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Acute effects of levosimendan on mitral regurgitation and diastolic function in patients with advanced chronic heart failure

Giovanna Branzi[a], Gabriella Malfatto[a], Alessandra Villani[a], Francesca Ciambellotti[a], Miriam Revera[a,b], Alessia Giglio[a], Francesco Della Rosa[a], Mario Facchini[a] and Gianfranco Parati[a,b]

Background **We analyzed the inodilator properties of levosimendan in patients with chronic heart failure and severe functional mitral regurgitation.**

Methods **We studied 20 patients under optimal treatment and in stable clinical condition (New York Heart Association 3.19 ± 0.66; 70 ± 7 years). Levosimendan was infused as a bolus (12 μg/kg in 10 min) followed by a 24-h infusion (0.1–0.2 μg/kg per min). Before and after infusion, Doppler echocardiography, brain natriuretic peptide determination and noninvasive hemodynamic monitoring with bioimpedance cardiography were performed.**

Results **Levosimendan improved left ventricular ejection fraction (ejection fraction 31 ± 4 from 27 ± 4, $P<0.05$), decreased brain natriuretic peptide (333 ± 139 from 629 ± 63 pg/ml, $P<0.01$), reduced mitral valve effective regurgitant orifice area to 27 ± 5 from 36 ± 7 mm^2 ($P<0.01$) and the velocity of displacement of mitral annulus [ratio between E and E′ waves on Doppler and tissue Doppler (E/E′) from 22.7 ± 1.6 to 13.1 ± 0.6, $P<0.01$]. Noninvasive hemodynamic monitoring showed increased acceleration index (a marker of inotropism), and reduced peripheral resistances and thoracic fluid content ($P<0.01$). After 4 weeks of washout, some of these effects were still evident.**

Conclusion **In patients with chronic heart failure and functional mitral regurgitation, levosimendan acutely improved systolic and diastolic function, reduced mitral regurgitation and modulated neurohormonal activation, with a tendency for these changes to persist over a short-term follow-up. *J Cardiovasc Med* 11:000–000 © 2010 Italian Federation of Cardiology.**

Journal of Cardiovascular Medicine 2010, **11**:000–000

Keywords: advanced chronic heart failure, diastole, functional mitral regurgitation, impedance cardiography, levosimendan

[a]Divisione di Cardiologia, Ospedale San Luca, Istituto Auxologico Italiano IRCCS and [b]Dipartimento di Medicina Clinica, Prevenzione e Biotecnologie Sanitarie, Università di Milano-Bicocca, Milan, Italy

Correspondence to Giovanna Branzi, MD, Divisione di Cardiologia, Istituto Scientifico Ospedale San Luca, via Spagnoletto 3, 20149 Milan, Italy
Tel: +39 02619112729; fax: +39 02619112625; e-mail: branzi@auxologico.it

Received 30 October 2009 **Revised** 28 December 2009
Accepted 27 January 2010

Introduction

Regardless of optimal pharmacologic and nonpharmacologic treatment, heart failure still evolves to a chronic advanced stage characterized by limiting symptoms, marked hemodynamic impairment, frequent hospitalizations and high mortality [1]. A feature of this stage is the presence of moderate to severe functional mitral regurgitation, originating from the interplay between local factors (ventricular remodeling, annulus enlargement and twisting, left atrial dilation, tethering and closing forces acting on valve leaflets) and hemodynamic status (mostly increased afterload) [2]. Mitral regurgitation contributes to the further progression of left ventricular dysfunction and predicts an adverse outcome [3]. Patients with advanced chronic heart failure and relevant functional mitral regurgitation may thus represent a population for whom new therapeutic options are needed, an issue as yet unresolved [1]. Surgical treatment does not significantly affect the prognosis in this subset of patients, whereas resynchronization and medical treatment seem to provide better results [4]. Regarding drug treatment, vasodilating drugs acutely improve regurgitation by affecting afterload [5] but in advanced disease they are effective only in subsets of patients [6] and no data are available on their long-term efficacy. On the contrary, the acute hemodynamic improvement afforded by inotropic drugs is obtained at the cost of intracellular calcium overload that may lead to myocardial cell death or lethal arrhythmias, or both [7]. Therefore, both vasodilators and inotropic drugs are used only for the short-term treatment of acute heart failure [8].

A new treatment for these patients may come from drugs combining inotropic and vasodilating activity, such as the calcium sensitizer levosimendan; large randomized trials have shown its safety and efficacy in the short-term support of impaired cardiac function in various clinical settings [9,10]. The action of levosimendan and of its long-acting active metabolites is multifaceted [11–13]. The drug can be defined as an inodilator, it binds to the

1558-2027 © 2010 Italian Federation of Cardiology DOI:10.2459/JCM.0b013e32833832f6

calcium-saturated cardiac troponin C in systole, stabilizing its conformational change and prolonging contraction [11] without negative effects on diastole, and activates IKAch channels, inducing vasodilation in peripheral and coronary vessels [12].

In this pilot study, we tested whether levosimendan could not only improve cardiac function but also reduce the degree and severity of functional mitral regurgitation by simultaneously affecting afterload through its vasodilating effect. We also evaluated the persistence of this drug's effect after acute administration [14].

Methods

Study population

Participants for this open-label internal control study were recruited from patients with systolic left ventricular dysfunction admitted to the Heart Failure Clinic of our institution for the management of a chronic advanced disease. Patients were screened for the study if they were currently taking the best optimized treatment for heart failure, had been in a stable clinical condition [New York Heart Association (NYHA) class III–IV] for at least 3 months, had a documented left ventricular ejection fraction of less than 35% and moderate to severe functional mitral regurgitation as specified below. Exclusion criteria were acute or chronic infectious or inflammatory diseases, recent myocardial infarction (8 weeks), acute myocardial ischemia, severe hepatic or renal impairment, use of immunosuppressive drugs, serious arrhythmias and supine systolic blood pressure less than 85 mmHg. This being a pilot investigation, it did not require a formal sample size calculation. Twenty patients were enrolled, their characteristics are summarized in Table 1. The investigation conformed with the principles outlined in the Declaration of Helsinki. Our institutional ethical committee also approved the study and all patients gave their written consent. To avoid, as much as possible, any placebo effect, patients received no information about the effects we expected, apart from a statement on 'a likely improvement in mitral regurgitation'.

Table 1 Clinical characteristics of the patients

N	20
Age (years)	70 ± 7
Sex (M/F)	14/6
Ischemic/nonischemic cause	13/7
NYHA class	3.19 ± 0.66
SAP (mmHg)	114 ± 8
EF (%)	27.2 ± 4.3
LVEDV (ml)	217 ± 55
EROA (mm^2)	36.3 ± 7.0
E/A	2.82 ± 0.89
Restrictive filling pattern (%)	80%
E/E′	22.7 ± 10.3
BNP (pg/ml)	629 ± 378
Stroke index (ml/m^2)	41.5 ± 17.1
Systemic vascular resistance ($dyne \times s \times cm^{-5}$)	1570 ± 423
Thoracic fluid content (/kΩ)	46.1 ± 8.4
Acceleration index ($/100/s^2$)	59.0 ± 17.5
ICD ± biventricular pacing (yes/no)	13/7
Pharmacological treatment (%)	
ACE-inhibitors/ARB	88%
β-blockers	81%
Diuretics	100%
Spironolactone	50%
Digitalis	0%
Nitrates	38%

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; BNP, brain natriuretic peptide; data are ± 1 SD; E/A, ratio between velocity of the E and A wave on Doppler transmitral flow; E/E′, ratio between E and E′ waves on Doppler and tissue Doppler; EF, ejection fraction; EROA, effective regurgitant orifice area; F, female; ICD, internal cardioverter defibrillator; LVEDV, left ventricular end-diastolic volume; M, male; NYHA, New York Heart Association; SAP, systolic arterial pressure.

Echocardiography

Patients were imaged in the left lateral decubitus position using a commercially available system (Vingmed Vivid Seven; General Electric-Vingmed, Milwaukee, Wisconsin, USA). Images were obtained using a 3.5 MHz transducer, at a depth of 16 cm in the parasternal and apical views (standard long-axis and four-chamber images). Standard two-dimensional (2D) and color Doppler data, triggered to the QRS complex, were saved in cine-loop format. Images were obtained according to the guidelines of the American Society of Echocardiography [15] by two independent observers. Interobserver and intraobserver coefficients of variation were less than 5% for conventional echo measurements, and less than 10% for tissue Doppler imaging (TDI) variables and quantification of effective regurgitant orifice area (EROA). Left ventricular volumes and ejection fraction were determined by manual tracing of end-systolic and end-diastolic endocardial borders using apical four-chamber and two-chamber views, employing the Simpson method for biplane assessment. Peak velocities of early (E) and late (A) diastolic filling and deceleration time were derived from transmitral Doppler recordings. TDI-derived peak systolic (S′), early (E′) and late (A′) diastolic velocities were derived from the septal and lateral mitral annulus and averaged for each patient, and the mitral ratio between E and E′ waves on Doppler and tissue Doppler (E/E′ ratio) was subsequently calculated [16]. Patients were evaluated for the presence of mitral regurgitation using inspection of the color Doppler jet area in the downstream chamber and the width of the vena contracta [17]. The extent of mitral regurgitation was calculated considering jet geometry, jet area, vena contracta width and the EROA with the proximal convergence method (proximal isovelocity surface area, PISA) [17]. To enter the study, individuals must have had moderate to severe mitral regurgitation, that is, an EROA more than 0.20 cm^2 [3,17].

Bioimpedance cardiography

Noninvasive hemodynamic evaluation was obtained by performing impedance cardiography (ICG; BioZ ICG Monitor; CardioDynamics, San Diego, California, USA), all parameters were stored in the monitor's electronic

memory for subsequent analysis. Also known as bioimpedance monitoring, ICG applies a high-frequency, low-amplitude current to measure the resistance to the flow of the alternating electric current [18] and changes in thoracic electrical impedance. These data are used as a noninvasive estimate of cardiac output, cardiac filling pressures, cardiac inotropism and peripheral resistances [18,19] and the results are quite reliable when focusing on changes over time [19]. Table 2 details the variables derived from ICG. For this study, we took into account only systemic vascular resistances ($SVR = dyne \times s \times cm^{-5}$), acceleration index ($ACI = /100/s^2$) as an index of inotropism [18,19], stroke index ($SI = ml/m^2$) and thoracic fluid content ($TFC = /k\Omega$).

Protocol

After a 3-month run-in period of clinical stability, levosimendan (Simdax; Abbott Laboratories, Abbott Park, Illinois, USA) was administered intravenously with an initial loading dose of 12 μg/kg over 10 min, followed by continuous infusion of 0.1–0.2 μg/kg per min for 24 h. Echocardiography was obtained at baseline, within 12 h before the first infusion, within 12 h after the end of infusion and after 1 month of washout. The usual medical treatment was maintained during the infusion, and meals were allowed. Simultaneously, blood samples were collected to measure plasma B-type natriuretic peptide concentrations [brain natriuretic peptide (BNP), Triage meter; Biosite Diagnostics, San Diego, California, USA], serum creatinine and electrolytes. Noninvasive hemodynamic evaluation by ICG was performed before and immediately after drug infusion. To test for persistence of the drug effects, patients underwent a further collection of clinical and instrumental data after 4 weeks. This interval was chosen because after this time frame neither the drug nor its active metabolites are detectable [13,14].

Statistics

Data were analyzed using commercial software (Origin 7.0 MicroCal; MicroCal, Inc., Northampton, Massachusetts, USA). Continuous variables are expressed as mean ± 1 standard deviation (SD). Categorical variables were compared using the χ^2 test. Mean values were compared between groups by Student's *t*-test or the Mann–Whitney U test (whether variables were normally distributed or not as tested by the Kolmogorov–Smirnov test). The paired T test was used to compare mean values before and after infusion of the drug, whereas analysis of variance (ANOVA) for repeated measures (with Tukey's test when allowed) was used to test for effects of the drug at baseline, after infusion and after washout. Bivariate correlation was used to investigate potential relationships between variables. A P less than 0.05 was considered as the minimum level of statistical significance throughout the study.

Results

Baseline conditions

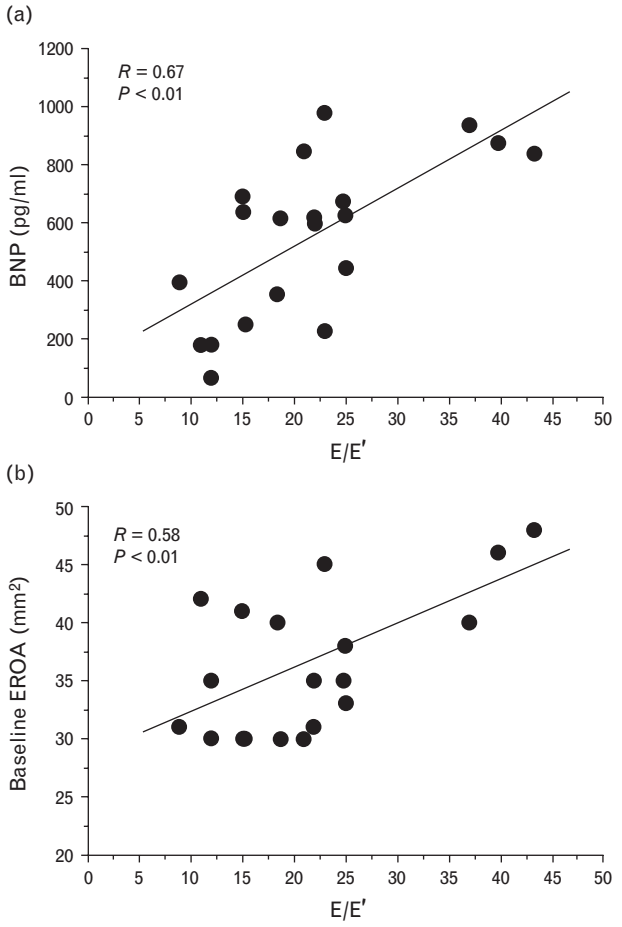
Table 1 shows the clinical characteristics of the patients. At baseline, a restrictive pattern of left ventricular filling was present in the majority of patients (16 out of 20, i.e. 80%). The severity of diastolic dysfunction, expressed by the E/E′ ratio, was significantly related to the degree of functional mitral regurgitation expressed by EROA, and to the plasma levels of BNP (Fig. 1a and b). Regarding bioimpedance data, the general hemodynamic pattern was that of a state of low-cardiac output, high peripheral resistances and high fluid content; thus, this patients'

Table 2 Impedance cardiography variables

Variable	Units	Measurement/calculation
Blood flow indexes		
Stroke volume	ml	VI × LVET × VEPT (Z-MARC algorithm)
Stroke index (SI)	ml/m^2	SV/BSA
Cardiac output	l/min	SV × HR
Cardiac index	$l/min/m^2$	CO/BSA
Resistances		
Systemic vascular resistance (SVR)	$dyne \times s \times cm^{-5}$	[(MAP − CVP)/CO] × 80
Systemic vascular resistance index (SVRI)	$dyne \times s \times cm^{-5}/m^2$	[(MAP − CVP)/CI] × 80
Contractility		
Velocity index	/1000/s	1000 × 1st time $derivative_{max}$/baseline impedance
Acceleration index (ACI)	$/100/s^2$	100 × 2nd time $derivative_{max}$/baseline impedance
Pre-ejection period	ms	ECG Q wave to aortic valve opening
Left ventricular ejection time	ms	Aortic valve opening to closing
Systolic time ratio	–	PEP/LVET
Systolic time ratio index (STRI)	/s	STR/RR interval
Cardiac work		
Left stroke work index (LSWI)	$g \times m/m^2$	(MAP − PCWP) × SI × 0.0136
Left cardiac work index (LCWI)	$kg \times m/m^2$	(MAP − PCWP) × CI × 0.0144
Fluid status		
Thoracic fluid content (TFC)	/kΩ	1000 × 1/baseline impedance

BSA, body surface area; CI, cardiac index; CO, cardiac output; CVP, central venous pressure (estimated value of 10 mmHg); ECG, electrocardiography; HR, heart rate; LVET, left ventricular ejection time; MAP, mean arterial pressure; RR interval, 60/heart rate; PCWP, pulmonary capillary wedge pressure (estimated value of 10 mmHg); PEP, pre-ejection period; SI, stroke index; STR, systolic time ratio; SV, stroke volume; VEPT, volume of electrically participating tissue; VI, velocity index; Z-MARC, impedance modulating aortic compliance.

Fig. 1



Severity of diastolic dysfunction expressed by E/E′ and its relationship with plasma levels of brain natriuretic peptide (a) and the degree of mitral regurgitation (b) in baseline conditions before levosimendan infusion. BNP, brain natriuretic peptide; E/E′, ratio between E and E′ waves on Doppler and tissue Doppler; EROA, effective regurgitant orifice area.

group could have been considered as 'cold and wet' according to a widely used hemodynamic classification [20]. Indeed, in 18 of the 20 patients (89%) the TFC was above 35/kΩ, a value considered at high risk for clinical instability in a large series of observations [21]; moreover, TFC values were significantly related to BNP levels ($R = 0.63$, $P < 0.01$).

Drug infusion and washout

No side effects were reported either during or after administration of the drug; in particular no change in renal function and electrolytes levels was observed. The day after infusion, NYHA class was improved from 3.19 ± 0.66 to 1.72 ± 0.13 ($P < 0.05$). Table 3 shows the effects of the infusion of levosimendan on variables under study. The last column also shows the values of each variable 4 weeks after infusion.

At Doppler echocardiography, improvement in systolic function and a slight reduction in ventricular volumes ($P < 0.05$) were observed. Remarkable effects were observed on left ventricular diastolic function and on the severity of mitral regurgitation. The restrictive pattern of left ventricular filling, observed at baseline in 16 out of the 20 patients (80%), was reversed into a pseudonormal filling pattern in five, an abnormal relaxation pattern in five, and a normal pattern in six patients ($P < 0.01$; Fig. 2). The E/E′ ratio was reduced by 32% ($P < 0.01$), an effect related to a sustained decrease in BNP levels (Fig. 3). Finally, a striking reduction in EROA was observed (from 36 ± 7 to $27 \pm 5\,mm^2$, $P < 0.01$).

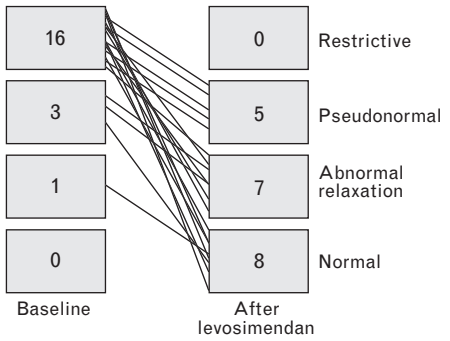
Impedance cardiography after levosimendan infusion showed improved hemodynamics in all patients, increased cardiac index, stroke volume and ACI, reduced peripheral resistances and TFC ($P < 0.001$; Table 3). Overall, 10 of the 20 patients (50%) regained a normal hemodynamic pattern and could be classified as 'warm and dry' whereas 10 still showed a slight increase in TFC and could be defined as 'warm and wet' [20]. The recovery in stroke index was related to that in ACI, that

Table 3 Effects of levosimendan on study variables

	Baseline	After LEVO infusion	After 4 weeks from LEVO infusion
NYHA class	3.19 ± 0.66	1.72 ± 0.13^{a}	2.11 ± 0.14^{a}
SAP (mmHg)	114 ± 8	107 ± 14^{a}	115 ± 11^{b}
EF (%)	27.2 ± 4.3	31.0 ± 4.0^{a}	30.0 ± 4.1
LVEDV (ml)	217 ± 55	204 ± 41^{a}	208 ± 42^{b}
EROA (mm^2)	36.3 ± 7.0	26.6 ± 5.3^{a}	$31.1 \pm 5.0^{b,a}$
E/A	2.82 ± 0.89	1.69 ± 0.85^{a}	2.01 ± 0.74^{a}
Restrictive filling pattern (%)	15 of 20 (80%)	None	6 of 20 (21%)^{b,a}
E/E′	22.7 ± 1.6	13.1 ± 0.6^{a}	$16.8 \pm 7.3^{b,a}$
BNP (pg/ml)	629 ± 378	333 ± 139^{a}	$424 \pm 275^{b,a}$
Stroke index (ml/m^2)	41.5 ± 17.1	52.8 ± 15.7^{a}	$48.3 \pm 9.3^{b,a}$
Systemic vascular resistance (dyne × s × cm^{-5})	1570 ± 423	1087 ± 299^{a}	$1457 \pm 517^{b,a}$
Thoracic fluid content (/kΩ)	46.1 ± 8.4	38.7 ± 7.5^{a}	43.7 ± 9.3^{b}
Acceleration index (/100/s^2)	59.0 ± 17.5	79.1 ± 23.5^{a}	$74.7 \pm 13.9^{b,a}$

Data are ± 1 SD. BNP, brain natriuretic peptide; E/A, ratio between velocity of the E and A wave on Doppler transmitral flow; E/E′, ratio between E and E′ waves on Doppler and tissue Doppler; EF, ejection fraction; EROA, effective regurgitant orifice area; LEVO, levosimendan; LVEDV, left ventricular end-diastolic volume; NYHA, New York Heart Association; SAP, systolic arterial pressure. [a] *P* less than 0.05 versus baseline. [b] *P* less than 0.05 versus drug infusion.

Fig. 2

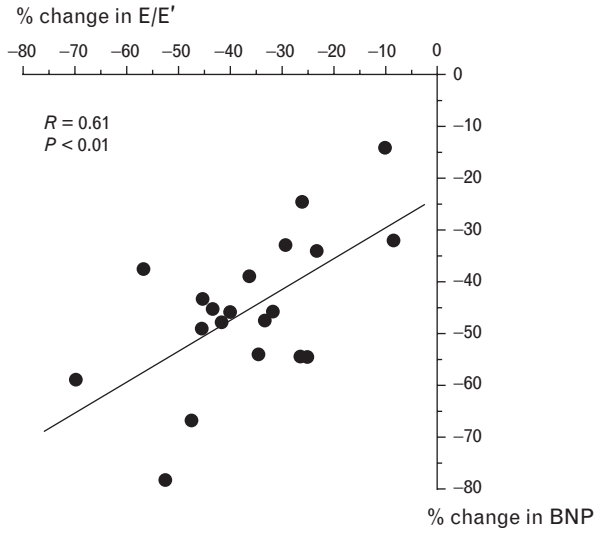


Improvement in diastolic function (expressed by the multiparametric analysis of both Doppler and tissue Doppler imaging echocardiography) after the infusion of levosimendan.

is, an index of inotropic state [18,19] ($R = 0.62$, $P < 0.01$). On the contrary, the decline of peripheral vascular resistances was related to the decrease of EROA and to the improvement of diastolic function expressed by the reduction in E/E′ (Fig. 4a,b).

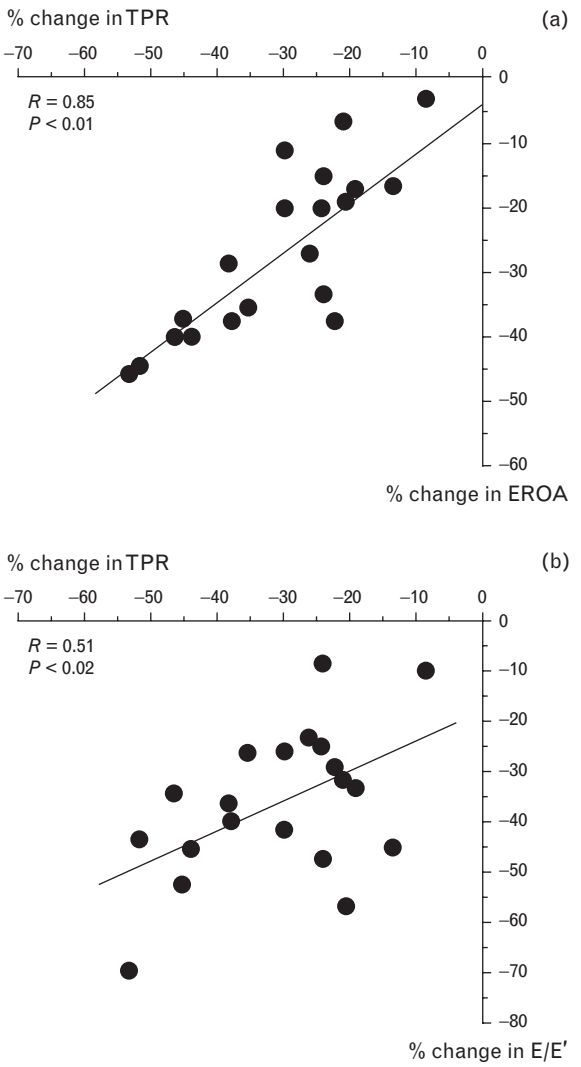
At the evaluation 4 weeks after levosimendan infusion, all variables tended to return to baseline values (Table 3). However, some clinical and hemodynamic improvement persisted. For instance, at echocardiography EROA and diastolic function still scored better than at baseline, and at bioimpedance cardiography ACI, stroke index and peripheral resistances were still different with regard to baseline ($P < 0.05$).

Fig. 3



Significant relationship between changes in brain natriuretic peptide levels and in E/E′ values after the infusion of levosimendan. BNP, brain natriuretic peptide; E/E′, ratio between E and E′ waves on Doppler and tissue Doppler.

Fig. 4



Significant relationship between changes in total peripheral resistances and changes in brain natriuretic peptide levels (a) and in E/E′ values (b) after the infusion of levosimendan. EROA, effective regurgitant orifice area; TPR, total peripheral resistances.

Discussion

In this pilot investigation, levosimendan was administered acutely in selected patients with chronic advanced heart failure and moderate to severe functional mitral regurgitation. According to the current recommendations, at variance from those enrolled in large randomized studies on levosimendan [10], these patients did not need inotropic support [9,22]. However, encouraging results on the use of levosimendan in a similar clinical setting have already been reported [9,23]. The concomitant use of noninvasive hemodynamic monitoring allowed us, at the same time, to avoid right heart catheterization (which would have been inappropriate in these patients [22]), and to follow the effects of the drug in

more detail as compared with mere blood pressure monitoring.

The favorable effects of levosimendan on systolic function and neurohormonal balance are well known [23], and recent reports indicate that levosimendan may also improve left ventricular diastolic function [24]. Our data confirm these findings; in fact, the most relevant effect of the acute infusion was the pronounced change in indexes describing left ventricular diastolic function. In most patients, transmitral flow velocity pattern showed a decrease in ratio between velocity of the E and A waves on Doppler transmitral flow (E/A ratio), a prolongation of deceleration time, a reversal of the restrictive pattern of left ventricular filling; moreover, combined TDI and mitral Doppler study showed a reduction in E/E′. These changes were associated with an acute modulation of neurohormonal control, as shown by the reduction in BNP levels, to an improvement in inotropism, indicated by the parallel changes in ACI and stroke index, and to a reduction in peripheral ventricular resistances. As diastole is a sequence of interrelated events influenced by changes in loading conditions and in myocardial intrinsic properties [25], it was beyond the purpose of this study to determine whether the improved diastolic phase was a consequence of the calcium sensitizing properties or of the vasodilating affects of the drug. We can only call attention to the relationship between changes in total peripheral resistances and E/E′, suggesting the relevance of load manipulations on left ventricular relaxation properties [26]. Finally, the small reduction in ventricular volumes, in our opinion, cannot be ascribed to reverse remodeling – a time-requiring phenomenon – but rather to the hemodynamic improvement induced by the drug.

The reduction of the severity of functional mitral regurgitation, acutely induced by levosimendan, could be of clinical relevance, as in patients with mitral regurgitation, the favorable effect of medical therapy is associated with a decrease in EROA of a magnitude similar to the one we observed [27]. At baseline, we found a significant correlation between EROA and indexes of diastolic dysfunction, and the subsequent reduction in EROA was related to the degree of improvement in diastolic function. However, changes in EROA and in peripheral resistances were also significantly related. As functional mitral regurgitation is a multifactorial condition, linked to a variety of local abnormalities and is negatively affected by afterload [5], any improvement in these factors could have determined its partial reversal. We may thus conclude that both the calcium sensitizing and the vasodilating properties of levosimendan would play a role in the reduction of functional mitral regurgitation, but changes in afterload were likely to be more relevant after the acute exposure.

Four weeks after the acute infusion of the drug, we performed a further examination, anticipating a complete disappearance of the pharmacological activity of both levosimendan and its metabolites [13,14,28]. The observation that a slight improvement was still detectable in some variables was somewhat surprising, and only speculations can be made to explain this finding. A tempting hypothesis would be that the combination of the acute favorable hemodynamic change with the improvement in systolic and diastolic function, leading to the reduction of the degree of functional mitral regurgitation, could have interrupted one of the several vicious circles favoring progression and worsening of advanced chronic heart failure.

The limitations of the study must be acknowledged. First, the sample size was small and we did not compare the drug with a placebo. A placebo effect could have determined at least some of the observed effects, for instance the reduction in NYHA class, even if our patients were used to drug infusions (diuretics, nitrates) and, as detailed in the Methods, received no anticipation of a specific beneficial effect. In fact, pilot studies such as ours are just setting out a working hypothesis that should be confirmed or disproven by large placebo-control investigations. Second, hemodynamic parameters were derived from a noninvasive tool, providing only indirect estimates of these variables. Validation of ICG was beyond the aims of our study, and we mostly focused on changes in hemodynamic parameters, which have been shown to be reliably assessed by this noninvasive approach [19], rather than on their absolute values.

In conclusion, the acute infusion of levosimendan in patients with advanced chronic heart failure and relevant functional mitral regurgitation improved left ventricular diastolic function, reduced mitral regurgitation and modulated neurohormonal activation. These effects may reflect the combination of calcium sensitizing and vasodilating properties, and partially persisted after 1 month of washout. Large randomized studies evaluating the effects of chronic, periodic treatment with the drug are warranted. Indeed, repeated and prolonged use of levosimendan may induce a reversal of some unfavorable features of advancing heart failure, and could represent an additional useful therapeutic approach in selected patients [29].

Acknowledgements

We are grateful to Donatella Boffetta RN and Ada Spiezia RN for care of the patients during the infusion of levosimendan, and to Ellen Tosazzi BS for help in collecting clinical data.

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