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Comparative effects of levosimendan and dobutamine infusion on p wave dispersion in patients with acute decompensated heart failure

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Aim: We aimed to evaluate the comparative effects of levosimendan and dobutamine on P-wave dispersion (PWD) in the patients with acute decompensated heart failure (ADHF).

Materials and methods: The study population consisted of 40 patients (mean age = 68 years, 23 men, NYHA class III-IV) presented with ADHF. Patients were randomized to intravenous levosimendan (n = 20) or dobutamine (n = 20) groups. The P-wave duration measurements were calculated in 12-lead surface ECG simultaneously and recorded before and after treatment. Manual measurements of P-wave duration were performed with digital calipers on a high resolution computer screen by two cardiologists not aware of the patients' clinical data.

Results: There were no significant changes in P max in the dobutamine group whereas a significant decrease was observed in the levosimendan group after the infusion. The levosimendan infusion significantly reduced PWD (from 40 msec to 30 msec, P < 0.001) but the dobutamine infusion has no effect on PWD. In hospital new onset atrial fibrillation (AF) frequency was similar among two groups.

Conclusion: Levosimendan infusion significantly reduces PWD compared to dobutamine infusion in our study population. This finding may be related to hemodynamic improvements provided by levosimendan.

Key words: Acute decompensated heart failure, dobutamine, levosimendan, P-wave dispersion

Akut dekompanze kalp yetmezlikli hastalarda levosimendan ve dopamin infüzyonunun p dalga dispersiyonu üzerine olan karşılaştırmalı etkileri

Amaç: Akut dekompanze kalp yetmezlikli (ADKY) hastalarda levosimendan ve dobutamin infüzyonunun P dalga dispersiyonu (PDD) üzerine olan karşılaştırmalı etkilerini değerlendirmeyi amaçladık.

Yöntem ve gereç: Çalışma grubu ADKY ile başvuran 40 hastadan oluşmakta idi (ortalama yaş = 68 yıl, 23 erkek, NHYA sınıf III-IV). Hastalar intravenöz levosimendan (n = 20) veya dobutamin (n = 20) gruplarına randomize edildi. P dalga süresi ölçümleri tedavi öncesi ve sonrasında alınan 12-derivasyonlu yüzey EKG'lerden hesaplandı. P dalga süresinin elle ölçümü, hastaların klinik durumu hakkında bilgi sahibi olmayan iki kardiyolog tarafından yüksek çözünürlüklü bilgisayar ekranında yapıldı.

Bulgular: İnfüzyon sonrası levosimendan grubunda P max'de anlamlı bir azalma varken, dobutamin grubunda P max'de anlamlı bir değişiklik yoktu. Levosimendan infüzyonu PDD'i anlamlı olarak azaltmıştır (40 milisaniyeden 30 milisaniyeye, P < 0,001). Fakat dobutamin infüzyonu PDD'i etkilememiştir. Hastane içi yeni atriyal fibrilasyon (AF) sıklığı iki grup arasında benzerdi.

Sonuç: Bizim çalışma grubumuzda, dobutamin infüzyonu ile karşılaştırıldığında levosimendan infüzyonu PDD'i anlamlı olarak azaltmıştır. Bu bulgu levosimendan ile sağlanan hemodinamik iyileşme ile ilişkili olabilir.

Anahtar sözcükler: Akut dekompanze kalp yetmezliği, dobutamin, levosimendan, P dalga dispersiyonu

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Introduction

Heart failure (HF) is a common medical problem associated with frequent hospital admissions and poor prognosis. Patients with HF are generally treated with diuretics and vasodilators in the long term. Positive intravenous inotropes are widely used in the short term for symptomatic improvement of the decompensated patients despite the fact that their long term usage is limited because of excess mortality (1). The positive inotropic agents improve hemodynamics and symptoms by increasing intracellular cyclic adenosine monophosphate (c-AMP) within the failing heart; but their use has been associated with an increased risk of death and other adverse cardiovascular events (2, 3).

Levosimendan is a novel agent with a dual mechanism of action developed for the treatment of decompensated heart failure. It improves cardiac contractility via increasing calcium sensitivity of the myofilaments by stabilizing calcium induced conformation of troponin C (4, 5). Levosimendan is a calcium sensitizer that increases the contractile force of the myocardium by enhancing the sensitivity of myofilaments to calcium without increasing intracellular calcium concentration at therapeutic doses. Moreover, this drug leads to coronary and peripheral vasodilation by opening ATP-sensitive potassium channels into vessel wall (6, 7). Large clinical trials have shown that levosimendan increases cardiac output and stroke volume, and reduces pulmonary capillary wedge pressure in patients with acutely decompensated chronic HF (8-10).

The clinical usefulness of phosphodiesterase (PDE) inhibitors and dobutamine, which improve cardiac output and symptoms in decompensated heart failure, is limited by adverse events especially arrhythmias. Treatment with PDE inhibitors has been associated with increased nonsustained ventricular tachycardia (VT), sudden death, and overall mortality (11, 12). Since positive inotropes have been arrhythmogenic, it is important to determine the proarrhythmic potential of any new inotropic agent intended for treatment of HF. Clinical electrophysiologic investigations showed that levosimendan has no significant potential to provoke life-threatening arrhythmias during its intravenous use in HF patients (13, 14). Despite some studies reported a higher incidence of new onset atrial fibrillation (AF) with the use of levosimendan compared to dobutamine, the controversery about that issue is still going on. In the current study we aimed to investigate the comparative effects of levosimendan and dobutamine on atrial electrophysiology via examining the P-wave dispersion (PWD) in patients with acute decompensated (ADHF) due either to coronary artery disease or to dilated cardiomyopathy.

Methods

Participants: We studied 40 patients (mean age = 68 years, 23 men) presented with ADHF symptoms (New York Heart Association class III or IV). All study participants had documented left ventricular ejection fraction (LVEF) lower than 35%. The etiology of HF were ischemic in 33 patients and nonischemic in 7 patients. All patients were receiving treatment with angiotensin converting enzyme inhibitors (ACE-I), spirinolactone, acetylsalicylic acid and diuretics at the time of randomization. Some of the patients were also treated with β adrenergic blockers, digoxin and amiodarone. Patients with recent myocardial infarction (< 8 weeks), AF, paced rhythm, hepatic or renal impairment (creatinine > 2.5 mg/dl), supine systolic blood pressure (SBP) of < 90 mmHg and with severe debilitating comorbid conditions were excluded from the study. All the patients enrolled in the study gave a written informed consent. This study was planned in accordance with the Declaration of Helsinki. The study was approved by the local ethics Committee of our Institute.

Study Protocol: Patients were randomized to intravenous levosimendan (n = 20; mean age = 69 years, 13 men) or dobutamine (n = 20; mean age = 65 years, 10 men) infusion in that controlled, randomized and prospective study. The patients were randomly assigned to two treatment arms. Treatment was allocated in a 1:1 ratio. The randomization was done using table of random numbers.

Levosimendan was administered as a continous 24 hour infusion under continuous haemodynamic monitoring. An initial loading dose of levosimendan of 12 μg/kg was infused over 10 min, followed by a continuous infusion of 0.1 μg/ kg/min for 24 hours.

Dobutamine was infused for 24 hours at an initial dose of 5 μg/kg/min without a loading dose. The infusion rates were doubled if the response was inadequate at 2 hours. Systolic and diastolic blood pressures were evaluated every 30 min during the first 2 hour infusion period and then every 60 min till the end of the 24 hour infusion. The infusion of either study drug was stopped for 30-60 min or until the following dose limiting events are resolved: symptomatic hypotension, SBP below 85 mmHg, and tachycardia (heart rate > 140/min for at least 10 min or increased by > 25 beats/min). Symptoms were evaluated by patients and physicians at baseline, 6 hours after the initiation of the treatment and at the end of the treatment.

Echocardiographic Examination: Left ventricular systolic and diastolic functions were assessed by using EASOTE 2,5 Mhz probe (ESAOTE, Genova, Italy) at the left lateral decubitus position in a standard manner at baseline and after the infusion of the drugs. M mode tracing of the left ventricle was obtained in the parasternal long axis views at a speed of 50 mm/s. Five consecutive cardiac cycles were averaged for every echocardiographic measurement. Left ventricular systolic and diastolic diameters [LVIDs, LVIDd] and left atrial systolic diameter [LAd] were calculated from the parasternal long axis view according to standard criteria. Left ventricular ejection fraction [LVEF] was measured by the software using the Teichholz formula. The peak early transmitral filling during early diastole [E], peak transmitral atrial filling velocity during late diastole [A], deceleration time [DT] (time elapsed between peak E velocity and the point where the extrapolated deceleration slope of the E velocity crosses the zero baseline), and isovolumetric deceleration time [IVRT] (time period between the end of mitral diastolic flow Doppler tracing and the starting point of aortic flow Doppler tracing) were used to assess left ventricular diastolic functions.

Surface ECG: Resting 12-lead surface ECG was recorded from all the patients before and after study drugs infusion (Hewlett Packard M1700A, Houston, USA). The ECG recordings were obtained at a paper speed of 50 mm/sec. and signal size of 10 mm/mV at sinus rhtym.

P-wave duration analyses: Dilaveris et al. showed that on-screen manual measurements were more reliable than the measurement of paper printouts in a nicely designed study (15). Therefore we performed on-screen manual measurements on the computer. The P-wave duration (P_{dur}) measurements were calculated in 12-lead surface ECG simultaneously recorded before and after treatment. After the ECG recordings had been scanned with a high-resolution scanner (HP Scanjet 8200 digital flatbed scanner C9931A, 4800 X 4800 dpi, Hewlett Packard, Houston, USA), all ECG recordings were transferred into the computer and opened with a high performance graphic program (Adobe Photoshop 7.0, Adobe Inc., USA). Manual measurements of P_{dur} were performed with digital calipers on a high resolution computer screeen by two cardiologists not aware of the patients' clinical data. The electrocardiogram gridlines were evaluated precisely to ensure accurate conversion to milliseconds and that the image was orthogonal to the measuring tool. Electrocardiograms were magnified to 4 times actual size by Adobe Photoshop software. Mean P_{dur} was calculated as the mean value in each lead by two investigators blinded to patients' clinical data. The P-wave onset was defined as the first atrial deflection from the isoelectric line and the offset was the return of the atrial signal to baseline. Mean P_{dur} was calculated as the mean value P_{dur} in each lead.

The difference between the maximum and minimum P-wave duration was defined as PWD (PWD (ms) = $P_{maximum}$ - $P_{minimum}$). Two investigators blinded to patients' clinical data calculated P-wave duration. Intra and interobserver variability were obtained from random ECG recordings of 20 patients. While intra and interobserver variability for $P_{maximum}$ were 3.8% and 4.1%, consecutively; for PWD, intra- and inter-observer variability were 2.9% and 3.8% respectively.

Statistical Analysis: Statistical analysis was performed by using the SPSS 15.0 Statistical Package Program for Windows (SPSS Inc., Chicago, Illinois, USA). Results are expressed as the median (minimum-maximum) and percentages. The statistical differences between groups were tested for significance by chi-square and Mann-Whitney *U*-tests. Wilcoxon test was used to compare continuous variables before and after drug therapy. Differences were considered significant at $P < 0.05$. Intra- and

inter-observer variability was calculated as a relative error.

Results

The two groups were identical with respect to baseline features and various medications (Table 1). None of the study participants had bronchial asthma, and none of them had body mass index > 30 kg/m^2. As listed in Table 2, NYHA class improved after the infusion of the both drugs. This improvement was identical for both groups. In both of the groups mean systolic and diastolic blood pressures (DBP) decreased to the same degree as shown in Table 1. Mean SBP decreased from 115 mmHg to 100 mmHg (P < 0.001) in levosimendan group; and it decreased from 112.5 mmHg to 100 mmHg (P < 0.001) in dobutamine group. On the other hand, mean DBP decreased from 85 mmHg to 80 mmHg in both groups (P < 0.001). The decreases in SBP and DBP were comparable among the groups. No changes were observed in serum sodium, potassium and creatinine levels. The heart rate increased significantly in the dobutamine goup after the infusion (from 95 bpm to 106 bpm, P < 0.001). However levosimendan infusion has no significant effect on the heart rate (Table 2). Although favorable changes were observed in all of the investigated echocardiographic parameters (left ventricular systolic and diastolic diameters, LVEF, E wave, A wave, E deceleration time, IVRT and E/A ratio), after the levosimendan infusion dobutamine infusion has favorable effects only on LVEF, A wave, E deceleration time and IVRT (Table 3). The left atrial diameters were identical among the study groups before drug infusions.

There were no significant changes in P_{max} in the dobutamine group whereas a significant decrease was observed in the levosimendan group after the infusion (Table 4, Figure 1). The levosimendan infusion significantly reduced PWD but the dobutamine infusion has no effect on it. Although PWD decreased from 40 msec. to 30 msec (P < 0.001) in levosimendan arm, no significant effect was found in dobutamine gruop as shown in Table 4. In hospital new onset, AF was observed in only 1 patient in the levosimendan group and 3 patients in the dobutamine group (P = 0.52).

Table 1. Baseline demographic and clinical characteristics of the study patients.

	Levosimendan (n = 20)	Dobutamine (n = 20)	P
Age (yrs)	69 (45-78)	65 (48-75)	0.15
Sex (M), n (%)	13 (65)	10 (50)	0.33
NYHA Class	4 (3-4)	4 (3-4)	1.00
Systolic blood pressure (mmHg)	115 (90-140)	112.5 (100-140)	0.75
Diastolic blood pressure (mmHg)	85 (60-100)	85 (60-100)	0.78
LVEF (%)	24 (14-35)	27 (13-35)	0.58
Drugs			
ACE-I	18 (90)	19 (95)	1.00
βAB	16 (80)	15 (75)	1.00
Diuretics	18 (90)	19 (95)	1.00
Aldosterone antagonists	17 (85)	16 (80)	1.00
Digoxin	13 (65)	11 (55)	0.52
Amiodarone	13 (65)	12 (60)	0.74
Diabetes Mellitus, n (%) 9 (45) 7 (35) 0.51			
Hypertension, n (%) 8 (40) 9 (45) 0.74			

NYHA, New York Heart Association; LVEF, Left ventricle ejection fraction; ACE-I, Angiotensin converting enzyme inhibitors; βAB, Beta adrenergic receptor blockers.
Values are presented median (minimum-maximum) or percentages.

Table 2. The comparative effects of levosimendan and dobutamine on biochemical, hemodynamic and clinical parameters.

	Levosimendan (n = 20)	Dobutamine (n = 20)	P
NHYA class			
Before	4 (3-4)	4 (3-4)	0.79
After	3 (2-4)	3 (2-4)	0.62
P	<0.001	<0.001	
Systolic blood pressure (mmHg)			
Before	115.0 (90-140)	112.5 (100-140)	0.75
After	100.0 (85-130)	100.0 (90-120)	0.67
P	<0.001	<0.001	
Diastolic blood pressure (mmHg)			
Before	85 (60-100)	85 (60-100)	0.77
After	80 (60-90)	80 (60-90)	0.38
P	0.01	0.002	
Serum Sodium (mg/dl)			
Before	131.0 (120-141)	135.0 (120-142)	0.25
After	130.0 (120-140)	132.5 (120-141)	0.28
P	0.16	0.29	
Serum Potassium (mg/dl)			
Before	4.1 (3.5-4.6)	4.1 (3.5-4.6)	0.67
After	4.2 (4-6)	4.1 (3.7-4.7)	0.25
P	0.08	0.14	
Serum Creatinine (mg/dl)			
Before	1.6 (1.2-1.8)	1.6 (1.4-1.9)	0.62
After	1.5 (1.3-1.8)	1.5 (1.4-1.8)	0.25
P	0.06	0.05	
Heart Rate (bpm)			
Before	95 (82-110)	95 (80-115)	0.86
After	97 (85-112)	106 (90-122)	0.001
P	0.06	<0.001	

Values are presented median (minimum-maximum).

Discussion

The main finding of the present study is a reduction in PWD with levosimendan infusion and no such effect of dobutamine in patients with ADHF. Arrhytmogenesis is one of the drawbacks of the positive inotropic drugs. So, it is important to determine the proarhythmic potential of any new inotropic agent intended for treatment of the heart failure. Mild arryhtmias observed during continous monitoring might reveal proclivity to induce clinically significant arrhythmic events.

The calcium sensitizing mechanism of levosimendan is functional within the sarcomere and doesn't affect myocellular transmembrane potentials or intracellular calcium level (16, 17). Therefore this novel inotropic action is thought to be devoid of proarrhythmic effects. Levosimendan has not increased the incidence of fatal arrhtymias in experimental animal models of HF (18).

Levosimendan has been previously studied in the two major trials with decompensated HF patients, the Levosimendan Infusion versus Dobutamine (LIDO) study and the Randomized Study on Safety and Effectiveness of Levosimendan in Patients with Left Ventricular Failure after an Acute Myocardial Infarct (RUSSLAN), where the drug showed outcome

Table 3. The comparative effects of levosimendan and dobutamine on echocardiographic parameters.

	Levosimendan (n = 20)	Dobutamine (n = 20)	P
LVIDd (mm)			
Before	66 (59-75)	68 (59-77)	0.22
After	63 (57-73)	67 (60-77)	0.009
P	<0.001	0.31	
LVIDs (mm)			
Before	57 (50-67)	57.5 (50-68)	0.75
After	52.5 (48-62)	57.5 (50-67)	0.001
P	<0.001	0.32	
LVEF (%)			
Before	23.5 (14-35)	27 (13-35)	0.58
After	31 (22-46)	26 (14-39)	0.04
P	<0.001	0.02	
LA Diameter (mm)	50 (58-55)	49 (45-56)	0.07
E velocity (cm/s)			
Before	84.5 (75-90)	79 (62-95)	0.09
After	84 (75-90)	79 (63-95)	0.20
P	0.003	1.00	
A velocity (cm/s)			
Before	58 (50-65)	60 (55-67)	0.12
After	60 (50-67)	60 (55-68)	0.69
P	<0.001	0.03	
E wave DT (ms)			
Before	135 (125-155)	133.5 (125-145)	0.51
After	155 (140-175)	135 (127-145)	<0.001
P	<0.001	0.02	
IVRT (ms)			
Before	60.5 (55-65)	60.0 (50-65)	0.38
After	70.5 (58-80)	61.0 (52-65)	<0.001
P	<0.001	0.02	
E/A ratio			
Before	1.4 (1.3-1.7)	1.3 (1.0-1.6)	0.05
After	1.3 (1.2-1.6)	1.3 (1.0-1.5)	0.31
P	<0.001	0.08	

LVIDd: Left ventricular internal diameter (diastolic); LVIDs: Left ventricular internal diameter (systolic); LVEF: Left ventricular ejection fraction; LA, Left atrium; E: Early rapid filling wave; A: Filling due to atrial contraction; DT, Deceleration time; IVRT: Isovolumetric relaxation time. Values are presented median (minimum-maximum).

benefits in comparison with dobutamine and placebo, respectively (10, 19).

In LIDO trial 103 patients were assigned to levosimendan and 100 patients to dobutamine (10). Under continuous hemodynamic monitoring, an initial loading dose of levosimendan of 24 μg/kg was infused over 10 min, followed by a continuous infusion of 0.1 μg kg^{-1} min^{-1} for 24 h. Dobutamine was infused for 24 h at an initial dose of 5 μg kg^{-1} min^{-1} without a loading dose. In this study levosimendan improved hemodynamic performance more effectively than dobutamine. This benefit was accompanied by lower mortality in the levosimendan group than in the dobutamine group for up to 180 days. In that study there was a higher proportion of patients with rate and rhythm disorders in the dobutamine group (13 vs. 4; P = 0.023). The incidence of AF was comparable between the groups (1 vs. 2; P = 1.0).

RUSSLAN study aimed to evaluate the safety and efficacy of levosimendan in patients with left ventricular failure complicating acute myocardial

Table 4. Comparative effects of levosimendan and dobutamine on P-wave variables.

	Levosimendan (n = 20)	Dobutamine (n = 20)	P
P maximum (ms)			
Before	107.5 (90-120)	105 (90-125)	0.90
After	92.5 (80-110)	100 (90-130)	0.002
P	<0.001	0.15	
P minimum (ms)			
Before	60 (40-80)	62.5 (40-95)	0.51
After	60 (40-85)	62.5 (40-90)	0.90
P	0.31	0.07	
P-wave dispersion (ms)			
Before	40 (25-60)	40 (25-60)	0.35
After	30 (5-50)	40 (20-60)	0.007
P	<0.001	0.08	

Values are presented median (minimum-maximum).

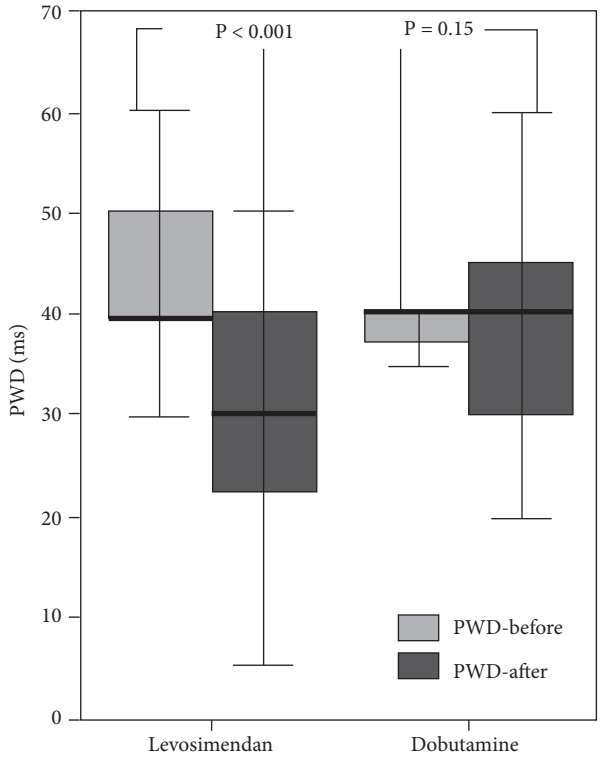

Figure 1. The comparative effects of levosimendan and dobutamine in patients with acute decompensated heart failure. PWD, P-wave dispersion.

infarction (19). The patients were allocated to placebo or one of four dose regimens of levosimendan: 6 μg . kg^{-1} loading dose +0·1 μg . kg^{-1} . min^{-1} continuous infusion; 12 μg . kg^{-1} loading dose + 0·2 μg . kg^{-1} . min^{-1} continuous infusion; 24 μg . kg^{-1} loading dose + 0·2 μg . kg^{-1} . min^{-1} continuous infusion; 24 μg . kg^{-1} loading dose + 0·4 μg . kg^{-1} min^{-1} continuous infusion. The loading dose was infused over a period of 10 min, and the continuous infusion was maintained for 5 h and 50 min. The frequency of AF and other atrial and ventricular arrythmias were similar to placebo in all of the four levosimendan regimens. The risk of arrhythmic events showed no dose-relation, and the frequency of events was comparable in all the levosimendan groups.

There are also several small-sized studies evaluating the arrhythmic potential of the levosimendan. It has been shown that the haemodynamic benefits of a 6-h levosimendan infusion in patients with HF were not at the expense of increased sympathomimetic stimulation or autonomic imbalance, which are known to be associated with an increased proarrhythmic risk (20). Toivonen and co-workers examined the electrophysiologic effects of short term levosimendan infusion in healthy subjects (21). Variables were determined in 10 patients with normal cardiac function during a preceding control phase and levosimendan infusion yielding a high therapeutic concentration of 110 (+/-22) μg/L. Levosimendan increased heart rate by 9 beats/min on average and shortened the sinus node recovery time and AH interval. At the tested cycle lengths, levosimendan shortened the effective refractory periods in the atrioventricular node by 40-63 ms, in the atrium by 22-33 ms, and in the ventricle by 5-9 ms on average.

The QT interval during spontaneous rhythm and atrial pacing remained unchanged although increased slightly when corrected to sinus rate. The observations indicated that levosimendan in short-term administration facilitates impulse formation and conduction in cardiac slow-response tissue, enhances recovery of excitability in the myocardium, and may delay ventricular repolarization. These subtle changes do not likely to cause clinically significant arrhythmias. Examination of a large database of electrophysiology recordings accrued with levosimendan has produced no evidence that the drug promotes clinically relevant arrhythmia or disturbances in cardiac conduction pathways at the recommended doses (13).

Despite the consensus on the safety profile of levosimendan in means of fatal ventricular arrhythmias, there is an ongoing debate about its effect on the frequency of AF. Two large prospective trials that evaluated the efficacy of levosimendan in patients hospitalized for ADHF have concluded that levosimendan may increase AF attacks. The second Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy (REVIVE II) study and the Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE) study showed that levosimendan may increase the frequency of AF (22, 23).

REVIVE II (n = 600 patients) was the first large, prospective, randomized, double-blind, controlled trial to compare the effects of levosimendan plus standard therapy to the effects of standard therapy alone over the clinical course of ADHF (22). Standard therapy consisted of physician-selected drugs used in ADHF (diuretics, vasodilators, and inotropes). REVIVE II was thus designed to assess prevailing clinical practice, where multiple agents are used in combination to treat ADHF. All patients had been hospitalized for worsening HF and had dyspnea at rest despite treatment with intravenous diuretics, and LVEF ≤ 35% measured within the last year. Patients were randomized to receive either a levosimendan bolus (6-12 μg/kg) followed by a stepped dose regimen of levosimendan (0.1-0.2 μg/kg/min) for 24 hours plus standard therapy or a placebo infusion for 24 hours plus standard therapy. Observations were continued for 4 days after the continuation of treatment. In this study there were more reports of hypotension (50% vs. 36%) and AF (8% vs. 2%) in the levosimendan group compared to placebo group.

The SURVIVE study compared levosimendan and dobutamine in patients with ADHF and a LVEF < 30%, who remained breathless at rest despite intravenous diuretics and vasodilators, if they had features of a low cardiac output including oliguria, cool peripheries and low arterial pressure (23). Patients had to have a systolic blood pressure in the range of 80–130 mm Hg and serum creatinine < 450 μmol/L. This was one of the highest risk populations ever enrolled in a study of HF. More than one in four patients had died within 6 months despite modern medical therapy, which is higher than in any other study of ADHF. In this study patients taking levosimendan were more likely to experience AF (9.1% vs. 6.1%; P < 0.05) and less likely to experience worsening HF (12.3% vs. 17%; P < 0.02) compared to those taking dobutamine.

On the basis of these conflicting results we tried to evaluate the effects of levosimendan on atrial electrophysiology by means of PWD. P-wave dispersion constitutes a recent contribution to the field of noninvasive electrocardiology and is defined as the difference between the longest and the shortest P-wave duration recorded from multiple different surface ECG leads. Several studies used these ECG marker in various clinical settings and particularly in the assessment of risk of AF. P-wave dispersion has proven to be a sensitive and specific ECG predictor of AF in the various clinical settings. A cutoff value of 40 msec seems to furnish the best predictive accuracy (24). In the current study the preinfusion PWDs of the groups were identical (40 msec). Although levosimendan infusion significantly decreased the PWD to 30 msec (P < 0.01), the dobutamine had no effect on PWD in our study population. Even though those results are contradictory to REVIVE II and SURVIVE, they may imply a more electrophysiologically stable atrium after the levosimendan infusion. More importantly, in the LIDO and RUSSLAN trial higher bolus and continous infusion doses of levosimendan did not result in an increase in the frequency of AF compared to dobutamine. We think that higher incidence of AF

observed in the REVIVE II and SURVIVE trial may be a consequence of the study patients' high risk. The risk of AF seems to be related with the risk status of the patients but not with the dose regimen applied.

Previous studies have shown that levosimendan treatment had a consistently better effect than dobutamine in the individual hemodynamic variables at the end of the 24 hour treatment (10, 23). Parissis et al. found that levosimendan was effective in improving left ventricular diastolic function (25). In their randomized, placebo-controlled study, 34 patients with impaired LV systolic function with NYHA class III-IV symptoms were randomized to recieve either intravenous levosimendan (n = 17) or placebo (n = 17). In the placebo group, no statistically significant differences were noted in most of the investigated echocardiographic doppler indexes, whereas E/e and E/flow propagation ratios were singnificantly elevated. This is in keeping with recent experimental findings demonstrating favorable effects of levosimendan on LV diastolic function in conscious dogs with pacing induced cardiomyopathy at rest and during exercise (26, 27). In our study levosimendan infusion improved E wave velocity and E/A ratio significantly. Other diastolic parameters such as E deceleration time and IVRT were also significantly improved by the levosimendan infusion compared with the dobutamin infusion. These findings supports the positive effects of levosimendan on LV diastolic function, which is an important determinant of atrial electrophysiology. The improvement in PWD observed in our study may be partly related to the hemodynamic changes in LV diastolic function that is induced by levosimendan infusion. On the other hand, one can propose that levosimendan may improve intratrial conduction more homogenously than dobutamine though there are no conclusive data supporting this hypothesis.

This study has a number of limitations. Small number of patients is the major limitation. Actually incidence of AF is smaller than one could expect in the current study, but it may be influenced by the number of subjects. Efforts were made to minimize hemodynamic variability among patients in order to facilitate precise examination of dose-response relationships. Thus, participating patients were required to have been clinically stable for one month and to be receiving standardized medications for HF. Although P-wave dispersion has proven to be a sensitive and specific ECG predictor of AF in the various clinical settings, no electrophysiologic study has proven up to now the suspected relationship between the dispersion in the atrial conduction times and PWD. Lastly, the methodology used for the calculation of P-wave dispersion is not standardized and more efforts to improve the reliability and reproducibility of PWD measurements are needed. To improve the precision of measurement of P-wave dispersion from 12-lead ECGs recorded and stored on paper, scanning and digitizing ECG signals from paper records using an optical scanner is a feasible and accurate alternative method (15). Concordantly we performed on-screen manual measurements to assess P-wave parameters.

In conclusion, current study demonstrated that levosimendan infusion significantly reduces PWD compared to dobutamine infusion in ADHF. This finding may be related to hemodynamic improvements provided by levosimendan but whether this translates into less proarrythmogenesis deserves further investigation.

References

1. Felker GM, O'Connor CM. Inotropic therapy for heart failure: an evidence-based approach. Am Heart J 2001; 142: 393-401.
2. Cuffe MS, Califf RM, Adams KF Jr, Benza R, Bourge R, Colucci WS et al.. Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) Investigators. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. JAMA 2002; 287: 1541-7.
3. Bayram M, De Luca L, Massie MB, Gheorghiade M. Reassessment of dobutamine, dopamine, and milrinone in the management of acute heart failure syndromes. Am J Cardiol 2005; 96: 47G-58G.
4. Haikala H, Kaivola J, Nissinen E, Wall P, Levijoki J, Lindén IB. Cardiac troponin C as a target protein for a novel calcium sensitizing drug, levosimendan. J Mol Cell Cardiol 1995; 27: 1859-66.

5. Pollesello P, Ovaska M, Kaivola J, Tilgmann C, Lundström K, Kalkkinen N et al. Binding of a new Ca2+ sensitizer, levosimendan, to recombinant human cardiac troponin C. A molecular modelling, fluorescence probe, and proton nuclear magnetic resonance study. J Biol Chem 1994; 269: 28584-90.

6. Kass DA, Solaro RJ. Mechanisms and use of calcium-sensitizing agents in the failing heart. Circulation 2006; 113: 305-15.

7. Parissis JT, Filippatos G, Farmakis D, Adamopoulos S, Paraskevaidis I, Kremastinos D. Levosimendan for the treatment of acute heart failure syndromes. Expert Opin Pharmacother 2005; 6: 2741-51.

8. Slawsky MT, Colucci WS, Gottlieb SS, Greenberg BH, Haeusslein E, Hare J et al. Acute hemodynamic and clinical effects of levosimendan in patients with severe heart failure. Study Investigators. Circulation 2000; 102: 2222-7.

9. Nieminen MS, Akkila J, Hasenfuss G, Kleber FX, Lehtonen LA, Mitrovic V et al. Hemodynamic and neurohumoral effects of continuous infusion of levosimendan in patients with congestive heart failure. J Am Coll Cardiol 2000; 36: 1903-12.

10. Follath F, Cleland JG, Just H, Papp JG, Scholz H, Peuhkurinen K et al. Steering Committee and Investigators of the Levosimendan Infusion versus Dobutamine (LIDO) Study. Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial. Lancet 2002; 360: 196-202.

11. Packer M, Carver JR, Rodeheffer RJ, Ivanhoe RJ, DiBianco R, Zeldis SM et al. Effect of oral milrinone on mortality in severe chronic heart failure. The PROMISE Study Research Group. N Engl J Med 1991; 325: 1468–75.

12. Nony P, Boissel JP, Lievre M, Leizorovicz A, Haugh MC, Fareh S et al. Evaluation of the effect of phosphodiesterase inhibitors on mortality in chronic heart failure patients. A metaanalysis. Eur J Clin Pharmacol 1994; 46: 191–6.

13. Singh BN, Lilleberg J, Sandell E-P, Ylönen V, Lehtonen L, Toivonen L. Effects of levosimendan on cardiac arrhythmias: electrophysiologic and ambulatory electrocardiographic findings in Phase II and III clinical studies in cardiac failure. Am J Cardiol 1999; 24 Suppl I: 16(I)–20(I).

14. Lilleberg J, Ylönen V, Lehtonen L, Toivonen L. The calcium sensitizer levosimendan and cardiac arrhythmias: an analysis of the safety database of heart failure treatment studies. Scand Cardiovasc J 2004; 38: 80-4.

15. Dilaveris P, Batchvarov V, Gialafos J, Malik M. Comparison of different methods for manual P-wave duration measurement in 12-lead electrocardiograms. Pacing Clin Electrophysiol 1999; 22: 1532-8.

16. Edes I, Kiss E, Kitada Y, Powers FM, Papp JG, Kranias EG et al. Effects of Levosimendan, a cardiotonic agent targeted to troponin C, on cardiac function and on phosphorylation and Ca2+ sensitivity of cardiac myofibrils and sarcoplasmic reticulum in guinea pig heart. Circ Res 1995; 77: 107-13.

17. Sorsa T, Pollesello P, Solaro RJ. The contractile apparatus as a target for drugs against heart failure: interaction of levosimendan, a calcium sensitiser, with cardiac troponin C. Mol Cell Biochem 2004; 266: 87-107.

18. Haikala H. Non-clinical studies on arrythmogenity of levosimendan. Research Report: Orion Pharma; 2003 November 11 Report No: NDO090017.

19. Moiseyev VS, Põder P, Andrejevs N, Ruda MY, Golikov AP, Lazebnik LB et al. RUSSLAN Study Investigators. Safety and efficacy of a novel calcium sensitizer, levosimendan, in patients with left ventricular failure due to an acute myocardial infarction. A randomized, placebo-controlled, double-blind study (RUSSLAN). Eur Heart J 2002; 23: 1422-32.

20. Binkley PF, Nunziata E, Hatton PS, Leier CV. The positive inotropic agent levosimendan mediates increased cardiac output without progression of sympathovagal imbalance in patients with heart failure. Circulation 2000; 102 (Suppl II): 720–1.

21. Toivonen L, Viitasalo M, Sundberg S, Akkila J, Lehtonen L. Electrophysiologic effects of a calcium sensitizer inotrope levosimendan administered intravenously in patients with normal cardiac function. J Cardiovasc Pharmacol 2000; 35: 664-9.

22. Packer M. REVIVE II: Multicenter placebo-controlled trial of levosimendan on clinical status in acutely decompensated heart failure. Program and abstracts from the American Heart Association Scientific Sessions 2005; November 13-16, 2005; Dallas, Texas. Late Breaking Clinical Trials II.

23. Mebazaa A, Nieminen MS, Packer M, Cohen-Solal A, Kleber FX, Pocock SJ et al. SURVIVE Investigators. Levosimendan vs dobutamine for patients with acute decompensated heart failure: the SURVIVE Randomized Trial. JAMA 2007; 297: 1883-91.

24. Dilaveris PE, Gialafos JE. P-wave dispersion: A novel predictor of paroxysmal atrial fibrillation. Ann Noninvasive Electrocardiol 2001; 6: 159–65.

25. Parissis JT, Panou F, Farmakis D, Adamopoulos S, Filippatos G, Paraskevaidis I et al. Effects of levosimendan on markers of left ventricular diastolic function and neurohormonal activation in patients with advanced heart failure. Am J Cardiol 2005; 96: 423-6.

26. Janssen PM, Datz N, Zeitz O, Hasenfuss G. Levosimendan improves diastolic and systolic function in failing human myocardium. Eur J Pharmacol 2000; 404: 191-9.

27. Tachibana H, Cheng HJ, Ukai T, Igawa A, Zhang ZS, Little WC et al. Levosimendan improves LV systolic and diastolic performance at rest and during exercise after heart failure. Am J Physiol Heart Circ Physiol 2005; 288: H914-22.