# Acute Effects of Levosimendan and Dobutamine on QRS Duration in Patients with Heart Failure

*Osman Can Yontar, Mehmet Birhan Yilmaz, Kenan Yalta, Alim Erdem, Izzet Tandogan*
*Cumhuriyet University, Faculty of Medicine, Department of Cardiology, Sivas - Turkey*

## Abstract

**Background: Levosimendan is a novel inotropic agent that enhances cardiac contractility without increasing cellular calcium intake, so that it is not supposed to cause intracellular calcium overload and related arrhythmias. In patients with heart failure, prolonged QRS duration is associated with increased risk of mortality and sudden cardiac death. Structural changes in the left ventricle may lead to asynchronous contraction, causing conduction delay and a prolonged QRS on the surface electrocardiogram.**

**Objective: We aimed to compare the acute effects of levosimendan and dobutamine on QRS duration in patients with severe heart failure and sinus rhythm.**

**Methods: Sixty consecutive patients with ischemic heart failure were enrolled for the study and randomized into two groups for levosimendan (n=37) or dobutamine (n=23) infusions. 67.2 % were male; mean age was 66.4±9.2 years for all patients. Baseline QRS durations in levosimendan and dobutamine groups were, 120.44 ± 23.82 ms *vs* 116.59 ± 13.80 ms respectively. Baseline ejection fractions were both depressed (23.15 ± 8.3% *vs* 24.56 ± 7.5%).**

**Results: In the levosimendan group, QRS duration shortened from baseline value to 116.47 ± 24.56 msec (p=0.006), whereas dobutamine group showed no significant change (p=0.605). Both drugs caused an increase in ejection fraction, but only the levosimendan group showed significance (27.95 ± 8.9% p=0.003 *vs* 26.67 ± 7.6%, p=0.315).**

**Conclusion: We suggest that the administration of levosimendan, not dobutamine, shortens QRS duration on the surface ECG, possibly by means of providing collective contraction in the left ventricle muscle fibers. The molecular basis of this effect remains to be clarified. (Arq Bras Cardiol 2010;95(6):738-742)**

**Keywords: Heart failure; levosimendan; cardiotonic agents; dobutamine/adverses effects.**

## Introduction

Levosimendan is a novel inotropic agent that improves cardiac contractility without increasing myocardial oxygen consumption. Unlike other inotropic agents, levosimendan does not increase cellular calcium intake, so that it does not cause intracellular calcium overload and related arrhythmias[1]. Levosimendan binds to the N-terminal domain of troponin C and stabilizes the troponin molecule with subsequent prolongation of its effect on contractile proteins[2]. Studies have shown that 24-h infusion of levosimendan in patients with severe left ventricular dysfunction improves cardiac functions and relieves symptoms, as well as decreased short-term morbidity and mortality[3-5].

The QRS complex duration has been shown to be of prognostic importance in patients with heart failure. In this group of patients, prolonged QRS duration is associated with increased risk of mortality and sudden cardiac death[6]. A graded increase in mortality was correlated with ascending degrees of QRS prolongation. Increase in QRS duration is also correlated with impaired left ventricle systolic function[7]. Structural changes in the left ventricle may lead to asynchronous contraction, yielding conduction delay and a prolonged QRS on the surface electrocardiogram (ECG). In our study, we aimed to compare the acute effects of levosimendan and dobutamine on QRS duration in patients with severe heart failure and sinus rhythm.

**Mailing address: Osman Can Yontar •**
Sivas Numune Hastanesi, Kardiyoloji, Sivas-Turkiye - 58070 - Sivas
E-mail: drcanyontar@gmail.com
Manuscript received December 15, 2009; revised manuscript received March 06, 2010; accepted May 26, 2010.

## Material and methods

### 1. Study population

A total of sixty consecutive patients in normal sinus rhythm with ischemic heart failure presenting New York Heart Association class III or IV symptoms and left ventricular systolic dysfunction of ischemic origin were enrolled into our study after giving their informed consent and assigned to levosimendan or dobutamine administration at the discretion of their primary physician. Exclusion criteria were: pregnancy and lactation; acute or chronic infectious or inflammatory diseases, recent myocardial infarction (< 8 weeks) or active

myocardial ischemia; systolic blood pressure < 85 mmHg, hypersensitivity to levosimendan or any of its metabolites, severe renal failure (creatinine > 2.5 mg/dl), hepatic failure, 2nd or 3rd-degree atrioventricular blocks, overt bundle branch blocks, history of ventricular tachycardia or ventricular fibrillation, heart failure due to restrictive or hypertrophic cardiomyopathy or to uncorrected stenotic valvular disease. The investigation conforms to the principles outlined in the Declaration of Helsinki.

Patients received a loading dose of levosimendan (3 to 6 μg/kg) followed by a continuous infusion of 0.1 μg/kg per minute for 50 minutes; the rate was increased to 0.2 μg/kg per minute for an additional 23 hours as tolerated. Dobutamine was given at a 2.5 μg/kg, rate, which was subsequently increased to 5 μg/kg as tolerated, up to a 24-hour-period. Patients were also receiving similar and efficient doses of ACE-inhibitors, beta blockers, furosemide and spironolactone before admission. During admission the furosemide dose was fixed at 80 mg per day and was not increased. Moreover, other drugs' doses were not allowed to change.

Each patient's primary physician decided to administer the inotropic agent. All the patients were submitted to electrocardiography and echocardiography, before and 24 hours after the start of administration. Patients were hospitalized at coronary care unit and were monitored by means of ECG, 24-hour urine output, blood pressure. Additionally, all patients' biochemical work up was performed before and after the inotrope administration. During infusions, no nephrotoxic agent was allowed (nesiritide is not available in the country) and no increase in the dose of continuous loop diuretics (only furosemide is available in the country), as well as no change in the intravenous fluid administration, unless the patient had hypotension, were allowed. Other drug therapy and discharge decisions, determined by patient's status, were left to the discretion of the primary physicians, who were totally blinded to the study outcomes, including clinical parameters. The study was approved by the institutional ethics committee and written informed consent was obtained before randomization.

### 2. Electrocardiography

Patients' electrocardiographic examination was performed with the available ECG equipment (ELI-250, Mortara Instruments, Wisconsin, USA) at baseline and 24 hours after the start of the administration. ECGs were recorded at a speed of 50 mm/second. QRS duration was measured manually using a digital caliper and magnifying lens in the electrocardiograms performed on admission. QRS duration was determined in the single lead which had the longest QRS. Maximal QRS width in any lead was measured from the first to the last sharp vector crossing the isoelectric line. Electrocardiographic data were analyzed by 2 independent observers blinded to all other patient's data, and an average of two measurements was accepted as final result.

### 3. Echocardiography

Patients' echocardiographic examination was performed with available ultrasound equipment (GE-Vivid 4 with a 3.5 MHz transducer, Wisconsin, USA) Left ventricular ejection fraction (LVEF) was measured by Simpson's rule[8]. Examination was performed by two blinded echocardiographists, thirty minutes before and twenty four hours after the start of the administration and an average of two values were obtained for each examination.

### 4. Statistical analysis

Parametric data were expressed as means (Standard deviation) and categorical data as percentages. SPSS 15.0 (SPSS, Inc., Chicago, Illinois) was used to perform statistical procedures. Independent parametric data were evaluated by Mann Whitney U test. Temporal change of parametric data was evaluated by Wilcoxon's signed rank test, and categorical data via Chi square test. Correlation was evaluated by Spearman's correlation test. A p value ≤0.05 was accepted as significant.

## Results

Sixty patients were enrolled in the study and randomized into two groups. Two patients died (due to pump failure) during inotrope infusions, one for each group. The remaining fifty-eight patients (levosimendan n=36, dobutamine n=22) underwent complete treatment and statistical evaluation. All patients had NYHA Class IV symptoms before the infusions. In the whole group, 67.2 % were male (n: 39), 32.8 % were female (n: 19). Mean age for all patients was 66.4±9.2 years (66.1±10.5 for levosimendan, 67.0±6.9 for dobutamine). All patients' baseline rhythms were sinus before inotrope administration, with no alteration after that. In the levosimendan group, baseline mean QRS duration was 120.44±23.82 ms. Following infusion, mean QRS duration significantly decreased to 116.47±24.56 ms (p = 0.006) on the 24th hour. On the other hand, dobutamine infusion yielded no significant effect on QRS duration (Table 1 and 2, figure 1).

After both infusions, ejection fractions in both groups increased. Left ventricular systolic and diastolic diameters did not show any significant change in both groups (Table 1). No significant correlation was detected between ejection fraction and QRS duration (r:0,398, p=0.082) in the levosimendan group. Additionally, heart rate slightly increased in levosimendan group, but showed no significant change compared to baseline values (Table 1). Patients' baseline body weights were similar, no difference occurred between both groups, after the administration of the drug. Moreover, absolute weight loss, which is a surrogate for improved edematous state, was similar in both groups (Table 1). No patient experienced electrolyte abnormality, both before and after the infusions.

## Discussion

Heart failure is one of the most frequent causes of morbidity and mortality in a global scale. Despite improvements in medical therapies and surgical methods, its prevalence keeps rising[9]. QRS duration complex has been shown to be of prognostic importance in patients with heart failure. In this group of patients, prolonged QRS duration is associated with increased risk of mortality and sudden cardiac death.

Bode-Schnurbus et al[10] showed significant mortality and sudden cardiac death difference in patients with heart failure who had implantable cardioverter-defibrillators when compared by QRS prolongation, defined as ≥ 150 msec[10]. In their retrospective study, Xiao et al[11] found that abnormal conduction, demonstrated as prolonged PR interval and QRS duration, of dilated cardiomyopathy patients appears to be a high risk for mortality[11]. Iuliano et al[6] conducted a retrospective analysis of 669 chronic heart failure patients according to QRS duration < 120 ms or ≥ 120 ms. They showed a significant increase in mortality and sudden death in patients with prolonged QRS duration. In a subgroup of patients with LVEF < 30%, QRS prolongation was associated with a significant increase in mortality (51.6% *versus* 41.1%, p < 0.01) and sudden death (28.8% *versus* 21.1%, p < 0.02)[4]. These results were supported by another study, conducted by Shenkman et al[7], in which 3,471 chronic heart failure patients were enrolled for the study. Prolonged QRS duration of 120 to 149 milliseconds was associated with an increased mortality at 60 months (p < 0.001)[7].

**Table 1 - Comparison of both groups**

| | Dobutamine (n=22) | Levosimendan (n=36) | p |
|---|---|---|---|
| Age (Years) | 67.0±6.9 | 66.1±10.5 | 0.721 |
| Beta blocker | 22/22 | 36/36 | 1.000 |
| ACE-inhibitor or Angiotensin receptor blocker | 22/22 | 36/36 | 1.000 |
| Digoxin | 11/22 | 14/36 | 0.309 |
| Spironolactone | 22/22 | 36/36 | 1.000 |
| Median furosemide dose (mg/day) | 80 | 80 | 1.000 |
| SBP before (mmHg) | 112.9±15.7 | 120.3±22.5 | 0.240 |
| SBP after (mmHg) | 109.0±15.4 | 112.8±17.3 | 0.464 |
| DBP before (mmHg) | 70.5±9.6 | 72.8±9.3 | 0.441 |
| DBP after (mmHg) | 69.0±9.7 | 71.2±10.6 | 0.484 |
| Weight before infusion (kg) | 68.6±2.5 | 67.2±12.0 | 0.698 |
| Weight after infusion (kg) | 65.0±1.7 | 65.3±11.8 | 0.923 |
| Absolute weight loss (kg) | 2.8±1.8 | 2.9±2.5 | 0.862 |
| Blood urea nitrogen before infusion (mg/dl) | 25.0±9.5 | 25.7±8.4 | 0.909 |
| Blood urea nitrogen after infusion (mg/dl) | 23.0±16.9 | 33.4±17.7 | 0.538 |
| Creatinine before infusion (mg/dl) | 1.0±0.3 | 1.1±0.2 | 0.566 |
| Creatinine after infusion (mg/dl) | 1.1±0.3 | 1.2±0.3 | 0.718 |
| Hemoglobin before infusion(mg/dl) | 11.2±2.0 | 12.1±2.1 | 0.513 |
| Hemoglobin after infusion (mg/dl) | 12.0±2.8 | 11.8±1.8 | 0.957 |

*ACE - angiotensin-converting enzyme; DBP - diastolic blood pressure; SBP - systolic blood pressure.*

In the light of the aforementioned studies, we decided to investigate the acute effects of levosimendan on QRS duration measured in surface ECG, in a group of patients who had severely depressed left ventricle functions. The drug caused an increase in left ventricle ejection fraction, as expected (p = 0.003), with a mild decrease in left ventricle diastolic diameters, without significance. QRS duration measured in surface ECG was also found to be decreased after drug administration (120.44±23.82 ms *versus* 116.47±24.56 ms, p = 0.006). A possible explanation of this novel effect might be a unique property of levosimendan, which enables the myocardium to contract as a syncytium through improved calcium handling. In our study group, we did not observe any arrhythmia or hypotensive effect, mostly associated with the high loading dose of levosimendan yielding arrhythmic and possibly mortal complications following infusion[12]. We believe that this finding has not been fully investigated[13] and it could be worth further investigating within this concept.

In the SURVIVE[12] study, levosimendan showed greater benefit in patients who received beta blocker therapy. Patients with acutely decompensated heart failure carry high risk for mortality and the use of beta blocking agents was suggested. This is a controversy regarding the use of beta adrenergic inotropes like dobutamine. Regarding this issue, a study in Brazil[14] showed that beta adrenergic agonist-resistant patients responded well (55.8% of patients) to levosimendan administration. These data are important regarding the use of inotropic agents in patients who receive beta-blocker therapy and are beta-adrenergic agonist-resistant.

**Table 2 - Temporal change of parameters in both arms**

| Parameter | Levosimendan | | | Dobutamine | | |
|---|---|---|---|---|---|---|
| | Before administration | 24 hours after administration | p | Before administration | 24 hours after administration | p |
| HR (beats/min) | 73±6.7 | 77±5.5 | 0.182 | 68±3.0 | 67±2.3 | 0.184 |
| LVEF (%) | 23.15±8.3 | 27.95±8.9 | 0.003 | 24.56±7.5 | 26.67±7.6 | 0.315 |
| LVEDD (mm) | 64.95±9.2 | 64.53±9.5 | 0.504 | 62.00±6.2 | 63.33±5.1 | 0.184 |
| LVESD (mm) | 62.29±9.5 | 62.29±9.0 | 1.0 | 61.00±8.4 | 62.00±7.0 | 0.5 |
| QRS duration (ms) | 120.44±23.82 | 116.47±24.56 | 0.006 | 116.59±13.80 | 115.59±12.24 | 0.605 |

*HR - heart rate; LVEF - left ventricle ejection fraction; LVEDD - left ventricle end diastolic diameter; LVESD - left ventricle end systolic diameter.*

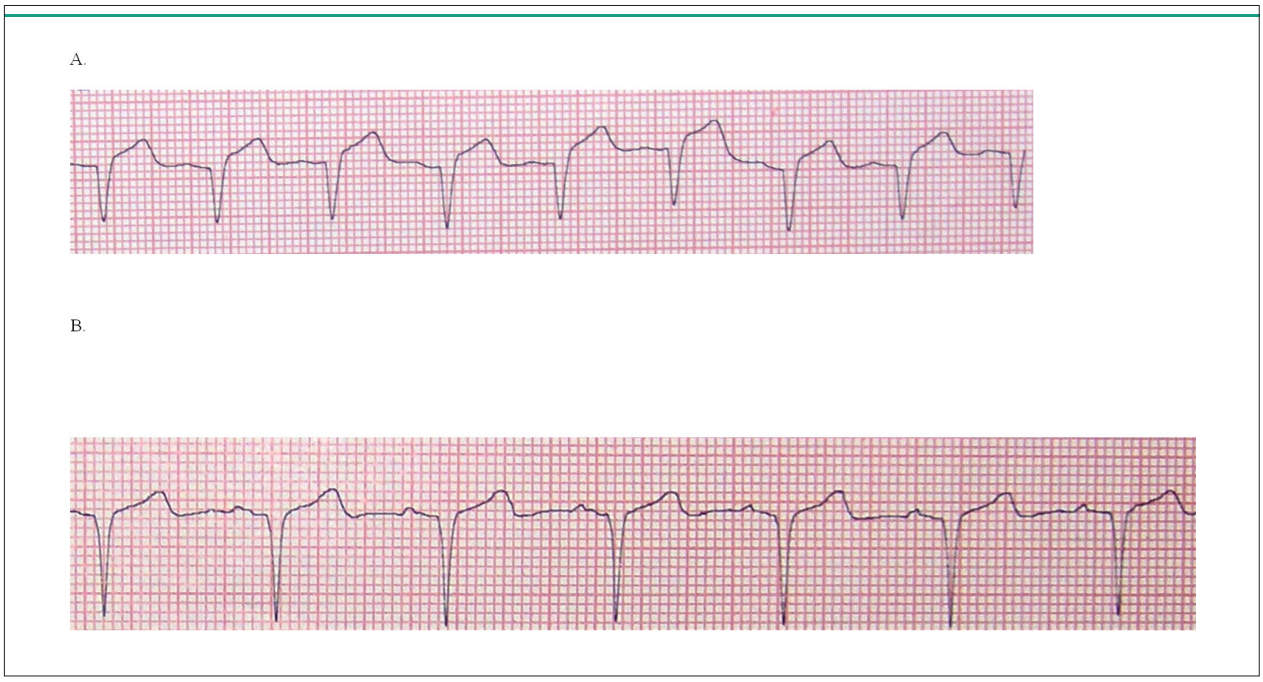


*Figure 1 - Shortening of QRS duration on the surface electrocardiogram, A: 102 ms before levosimendan administration B: 93 ms after levosimendan administration.*

In terms of limitations, it is possible to speculate a causal link between relative decrease in left ventricular size and shortening of QRS duration. However, we did not observe such change in QRS duration among patients in the dobutamine arm, which also yielded almost similar improvements associated with the left ventricle. Hence, we suggest this could possibly be associated with the molecular properties of levosimendan. Another limitation is that baseline QRS width is greater in levosimendan group than dobutamine group. The baseline mean left ventricle diastolic diameter is also greater in the levosimendan group, so we may claim that levosimendan patients had slightly more severe heart failure to a certain degree and this may be related to the difference between baseline QRS durations. On the other hand, among a group of patients with ischemic heart failure, effect of dobutamine might have two phases. Effect at the initial phase might be towards the side of QRS shortening during the first few minutes or hours, because ischemic and nonischemic myocardial regions would probably contract to similar extent. However, ischemic regions cannot sustain increased contraction tempo due to extended beta mimetic stimulation; therefore the latter phase effect might result with poorer response than first phase just like those seen (biphasic response) during dobutamine stress echocardiography. This would lead contraction delay between myocardial regions.". However, this issue remains as a limitation. In this study, PR and QT durations were not mentioned, not because of lack of data, but because it is beyond the aim of this study; hence these could be a matter of another study, as we aimed to assess the possible relationship between myocardial cellular contraction and depolarization, not the conduction. That is the reason why we excluded those with overt bundle branch block, in whom it is not reasonable to expect to revert the QRS duration up on therapeutic interventions, due to established destruction of the conduction system.

In conclusion, we suggest that the administration of levosimendan, but not dobutamine, shortens QRS duration in the surface ECG, possibly by means of providing collective contraction in the left ventricle muscle fibers. The molecular mechanism responsible for this effect remains to be clarified with further trials enrolling a sufficient number of patients.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

### Sources of Funding

There were no external funding sources for this study.

### Study Association

This study is not associated with any post-graduation program.

## References

1. McBride B, White M. Levosimendan: implications for clinicians. J Clin Pharmacol. 2003; 43 (10): 1071-81.
2. Endoh M. The therapeutic potential of novel cardiotonic agents. Expert Opin Investig Drugs. 2003; 12 (5): 735-50.
3. Moiseyev VS, Poder P, Andrejevs N, Ruda MY, Golikov AP, Lazebnik LB, et al. 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 (18): 1422-32.
4. Cavusoglu Y, Tek M, Birdane A, Ata N, Demirustu C, Gorenek B, et al. Both levosimendan and dobutamine treatments result in significant reduction of NT-proBNP levels, but levosimendan has better and prolonged neurohormonal effects than dobutamine. Int J Cardiol. 2008; 127 (3): e188-91.
5. Tavares M, Andrade AC, Mebazaa A. Levosimendan use in several scenarios of acute heart failure. Arq Bras Cardiol. 2008; 90 (3): 231-5.
6. Iuliano S, Fisher SG, Karasik PE, Fletcher RD, Singh SN. Department of Veterans Affairs Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure. QRS duration and mortality in patients with congestive heart failure. Am Heart J. 2002; 143 (6): 1085-91.
7. Shenkman HJ, Pampati V, Khandelwal AK, McKinnon J, Nori D, Kaatz S, et al. Congestive heart failure and QRS duration: establishing prognosis study. Chest. 2002; 122 (2): 528-34.
8. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. American Society of Echocardiography's Nomenclature and Standards Committee; Task Force on Chamber Quantification; American College of Cardiology Echocardiography Committee; American Heart Association; European Association of Echocardiography, European Society of Cardiology. Recommendations for chamber quantification. Eur J Echocardiogr. 2006; 7 (2): 79-108.
9. Cowie MR, Mosterd A, Wood DA, Deckers JW, Poole-Wilson PA, Sutton GC, et al. The epidemiology of heart failure. Eur Heart J. 1997; 18 (2): 208-25.
10. Bode-Schnurbus L, Böcker D, Block M, Gradaus R, Heinecke A, Breithardt G, et al. QRS duration: a simple marker for predicting cardiac mortality in ICD patients with heart failure. Heart. 2003; 89 (10): 1157-62.
11. Xiao HB, Roy C, Fujimoto S, Gibson DG. Natural history of abnormal conduction and its relation to prognosis in patients with dilated cardiomyopathy. Int J Cardiol. 1996; 53 (2): 163-70.
12. 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 (17): 1883-91.
13. 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 (6): 1903-12.
14. Bocchi EA, Bilas-Boas F, Moreira M, Barreto AC, Lage S, Albuquerque D, et al. e Grupo de estudos de insuficiencia cardiaca da Sociedade Brasileira de Cardiologia. Study BELIEF et al. Levosimendan in decompensated heart failure patients: efficacy in a Brazilian cohort. Results of the BELIEF study. Arq Bras Cardiol. 2008; 90 (3): 182-90.