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Effects of a Single, 24-Hour, Low-Dose Intravenous Dobutamine Infusion on Left Ventricular Myocardial Performance Index in Congestive Heart Failure: A Prospective, Nonrandomized Study

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ABSTRACT

Background: Dobutamine, a predominantly beta-adrenergic sympathomimetic agent, is used for improving left ventricular (LV) systolic performance with different dosing regimens in patients with congestive heart failure (CHF). Myocardial performance index (MPI) is an indicator of LV global function that is correlated with LV end-diastolic pressure, and it is increased in CHF.

Objective: The purpose of this study was to examine the effects of a single, 24-hour, low-dose, IV dobutamine infusion on LV systolic and diastolic function and on MPI in CHF as an indicator of LV global function, as well as the adverse effects (AEs) of the infusion.

Methods: This prospective, nonrandomized study was conducted at the Department of Cardiology, Baskent University Hospital, Ankara, Turkey. Adult patients with LV ejection fraction (EF) <35%, sinus rhythm, and symptomatic CHF were treated using a standard protocol for at least 4 weeks. At the end of this period, patients with symptomatic CHF and EF <35% underwent echocardiography that included measuring isovolumic relaxation and contraction times (IRT and ICT, respectively) and LV ejection time (ET), and calculating LV MPI using the formula MPI = (IRT + ICT)/ET. Dobutamine 2.5 μg/kg·min was then infused intravenously for 24 hours. Echocardiography was repeated 24 hours later and values were compared with preinfusion data. Patients were observed and monitored for CHF symptoms and AEs for 24 hours.

Results: Forty-three patients were enrolled in the study, and 31 (22 men, 9 women; mean [SD] age, 67.55 [11.78] years) continued after the 4-week standard-treatment period. Mean (SD) heart rate (74.93 [20.15] vs 80.23 [13.74] bpm, respectively), systolic blood pressure (129.00 [19.23] vs 126.67 [23.79] mm Hg), and diastolic blood pressure (75.80 [11.26] vs 74.96 [8.30] mm Hg) were sta-

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tistically similar before and after the infusion. The mean (SD) end-diastolic volume was statistically similar to the preinfusion value (215.87 [76.74] vs 211.08 [65.51] mL); however, the mean (SD) end-systolic volume was significantly reduced (163.80 [63.86] vs 146.74 [53.12] mL; $P = 0.01$). Mean (SD) EF (25.33% [7.77%] vs 30.45% [7.63%]; $P = 0.001$) and stroke volume (SV) (54.92 [22.30] vs 63.59 [23.91] mL; $P = 0.04$) increased significantly. The mean (SD) early:late diastolic flow velocity (E/A ratio) (1.58 [1.36] vs 1.65 [1.27]), IRT (107.03 [35.37] vs 100.42 [34.32] ms), ICT (96.61 [34.27] vs 86.35 [44.80] ms), ET (240.65 [33.28] vs 243.48 [33.54] ms), and MPI (0.81% [0.28%] vs 0.78% [0.31%]) did not change significantly after dobutamine infusion. No AEs were observed.

Conclusions: In this study of adult patients with symptomatic CHF, a single, 24-hour, low-dose, IV dobutamine infusion (2.5 μg/kg·min) was associated with decreased LV end-systolic volume and increased SV and EF. However, LV diastolic function parameters, isovolumic time intervals, ET, and MPI were statistically similar to preinfusion values. The infusion was well tolerated. (*Curr Ther Res Clin Exp.* 2005;66:35–44) Copyright © 2005 Excerpta Medica, Inc.

Key words: heart failure, dobutamine, myocardial performance index.

INTRODUCTION

Dobutamine, a predominantly beta-adrenergic sympathomimetic agent, is known to acutely increase left ventricular (LV) systolic function and to reduce symptoms in chronic and/or refractory congestive heart failure (CHF). Unfortunately, dobutamine has been associated with increased mortality when used in the long term, which limits its clinical use.[1,2] Based on a MEDLINE search (key terms: *dobutamine, congestive heart failure, infusion, diastolic function*, and *acute*; years: 1997–2005), few data concerning the acute effects of IV dobutamine infusion therapy on LV diastolic function are available.[3] Studies examining the acute differences in LV myocardial performance index (MPI) during dobutamine stress echocardiography (DSE) have shown that LV MPI can change acutely within minutes during dobutamine infusion periods.[4,5] At the time of the literature search, no data were available concerning the effects of a single, 24-hour, low-dose, IV dobutamine infusion used for therapeutic purposes on LV MPI, and the optimal infusion dose, frequency, and protocol for improving LV MPI were unknown. We hypothesized that such an infusion could be used to establish a stable plasma drug level and to create more prominent and continuous therapeutic effects of dobutamine compared with short infusion times. The effects of dobutamine are also known to be dose dependent, and the minimum effective dose of the drug (2.5 μg/kg·min) is associated with few arrhythmogenic adverse effects (AEs).[1] Thus, dobutamine would be an attractive therapeutic option if it had a beneficial effect on LV global function and MPI.

The aim of this study was to examine the effects of a single, 24-hour, low-dose (2.5 μg/kg·min) IV dobutamine infusion on LV systolic and diastolic function and on MPI as an indicator of global function, as well as the AEs of the infusion.

PATIENTS AND METHODS

This prospective, nonrandomized study was conducted at the Department of Cardiology, Baskent University Hospital, Ankara, Turkey. The ethics committee at the university approved the investigational protocol. Verbal informed consent was obtained from all eligible patients.

Inclusion and Exclusion Criteria

Patients aged 18 to 90 years presenting to the Department of Cardiology between December 2001 and June 2003 were prospectively enrolled. Inclusion criteria were ejection fraction (EF) <35%, sinus rhythm, and symptomatic CHF (defined as 3 of the following criteria: dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, peripheral edema, and pulmonary venous congestion on chest radiography).

Exclusion criteria were significant valvular regurgitation, uncontrolled hypertension (systolic/diastolic blood pressure, >160/>90 mm Hg), beta-blocker use, pregnancy, and poor echocardiographic visualization.

Study Drug Administration

All patients received a standard oral treatment regimen for CHF, which included digitalis (0.25 mg QD), furosemide (40–80 mg QD), and enalapril (5–10 mg/d, in 2 divided doses), for 4 weeks. After 4 weeks, patients with rhythms other than sinus rhythm were withdrawn from the study, and patients with symptomatic CHF and EF <35% continued in the study. These patients were placed on bed rest in a coronary care unit and were observed and monitored for CHF symptoms and AEs for 24 hours. In addition to standard echocardiography, isovolumic relaxation and contraction times (IRT and ICT, respectively) and ejection time (ET) were measured, and LV MPI was calculated (equation follows). Dobutamine 2.5 μg/kg · min was then infused intravenously for 24 hours. None of the medications were discontinued or changed during the infusion period. At the end of this single infusion, echocardiography was repeated and data were compared with preinfusion values.

Echocardiographic Assessment

Echocardiography was performed using the Acuson Sequoia Echo 256 sonography device (Acuson Corporation, Mountain View, California) and a 3.5-MHz transducer (model 3V2c, Acuson Corporation) with second-harmonic imaging at the left lateral decubitus position. Classic echocardiographic windows with electrocardiographic monitoring were used. All echocardiograms were videotaped for off-line analysis, which was performed by 2 investigators who were blinded to whether patients were being examined before or after dobutamine infusion.

Two-dimensional Doppler echocardiography was performed according to the techniques described by the American Society of Echocardiography.[6,7] The mean of 3 consecutive cardiac cycles was used for all echocardiographic vari-

ables. Measurements of LV systolic function were determined using the modified Simpson's rule for biplanar imaging.[6]

Myocardial Performance Index

The intervals used to derive the LV MPI are shown in the **figure**. Each interval was measured on 3 consecutive beats, and the mean was calculated. Interval a was the period from the end of the Doppler A (late diastolic flow) wave to the beginning of the E (early diastolic flow) wave of the next cardiac cycle. Interval a was obtained from the scan plane (apical 4-chamber view) for the left ventricle with a pulse-wave Doppler signal placed between the mitral valve leaflet tips. The LV ET (interval b for the left ventricle) was measured from the apical long-axis scan plane with a pulse-wave Doppler signal placed just inferior to the aortic valve at the LV outflow tract. The formula for calculating LV MPI was calculated as follows:

$$MPI = (a - b)/b = (IRT + ICT)/ET$$

The **figure** shows the equations used to derive the IRT and ICT of the left ventricle.

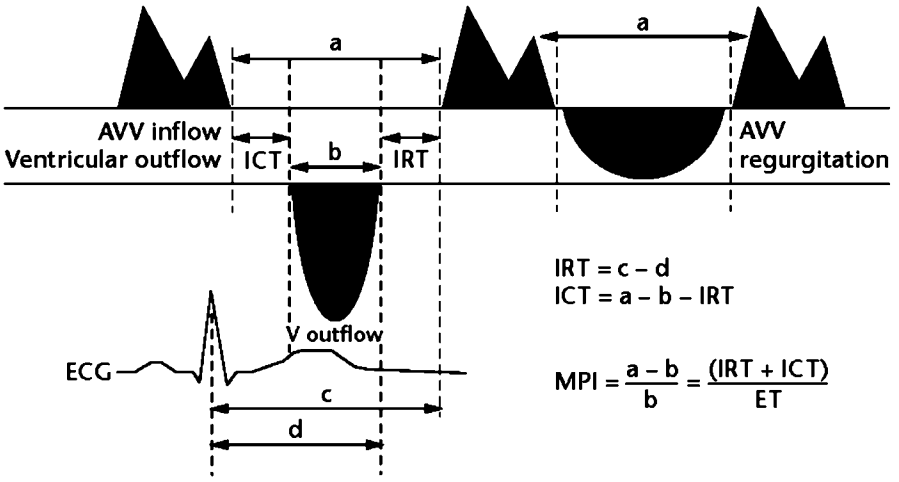

Figure. The myocardial performance index (MPI) is calculated from the following Doppler intervals: a, the interval from cessation to onset of mitral valve inflow (ms); and b, the left ventricular ejection time (ET) (ms). Alternatively, the duration of mitral valve regurgitation is considered equal to interval a. Isovolumic relaxation time (IRT) is calculated using c, the interval between the peak of the R wave and the onset of mitral inflow, and d, the interval between the peak of the R wave and cessation of left ventricular outflow. The MPI is calculated as the sum of IRT and isovolumic contraction time (ICT), divided by ET. ICT and IRT are derived as shown by the equations in the bottom right corner of the figure. AVV = atrioventricular valve; ECG = electrocardiogram; V = ventricular.

Statistical Analysis

Data analysis was performed using SPSS version 9.0 (SPSS Inc., Chicago, Illinois). Continuous variables were expressed as mean (SD). Differences before and after infusion were assessed using the paired *t* test. $P < 0.05$ was considered statistically significant.

RESULTS

Of the patients who were screened for the study, 43 were enrolled, and 31 (22 men, 9 women; mean [SD] age, 67.55 [11.78] years) continued after the 4-week standard-treatment period (**Table I**). Most of the patients were men with ischemic cardiomyopathy (n = 14). All 31 patients had dilated cardiomyopathy and New York Heart Association class III or IV disease (ie, marked or total limitation of physical activity).

Before dobutamine infusion, the mean heart rate was normal (60–100 bpm), and the mean systolic and diastolic blood pressures were within the accepted ranges (<160/<90 mm Hg) (**Table II**). The mean EF was below normal (normal value, >50%) and the mean end-diastolic and end-systolic volumes were above normal (normal values, <120 and <50 mL, respectively). No significant diastolic dysfunction was identified in any of the patients, and the mean LV MPI was increased compared with previously accepted normal values.

After 24-hour dobutamine infusion, all of the patients experienced improved symptoms, and no AEs were observed. Heart rate and systolic and diastolic blood pressures were statistically similar to preinfusion values. Mean end-systolic volume decreased significantly ($P = 0.01$), and mean stroke volume (SV) and EF increased significantly ($P = 0.04$ and 0.001, respectively) compared with preinfusion values. Neither the diastolic function parameters nor MPI changed significantly.

Table I. Baseline demographic and clinical characteristics of the study patients (N = 31).

Characteristic	Value
Age, mean (SD), y	67.55 (11.78)
Sex, no. (%)	
Male	22 (71.0)
Female	9 (29.0)
Type of dilated cardiomyopathy, no. (%)	
Ischemic	21 (67.7)
Idiopathic	10 (32.3)
NYHA disease class, no. (%)	
III*	16 (51.6)
IV†	15 (48.4)

NYHA = New York Heart Association.
*Marked limitation of physical activity.
†Total limitation of physical activity.

Table II. Echocardiographic findings in patients receiving dobutamine infusion (N = 31). Data are mean (SD).

Variable	Before Infusion	After Infusion	*P*
HR, bpm	74.93 (20.15)	80.23 (13.74)	NS
SBP, mm Hg	129.00 (19.23)	126.67 (23.79)	NS
DBP, mm Hg	75.80 (11.26)	74.96 (8.30)	NS
EF, %	25.33 (7.77)	30.45 (7.63)	0.001
End-diastolic volume, mL	215.87 (76.74)	211.08 (65.51)	NS
End-systolic volume, mL	163.80 (63.86)	146.74 (53.12)	0.01
SV, mL	54.92 (22.30)	63.59 (23.91)	0.04
E, cm/sec	73.48 (28.57)	63.77 (23.74)	NS
A, cm/sec	66.00 (30.46)	56.93 (31.21)	NS
E/A ratio	1.58 (1.36)	1.65 (1.27)	NS
Deceleration time, ms	156.45 (73.49)	164.13 (85.31)	NS
IRT, ms	107.03 (35.37)	100.42 (34.32)	NS
ICT, ms	96.61 (34.27)	86.35 (44.80)	NS
ET, ms	240.65 (33.28)	243.48 (33.54)	NS
LV MPI, %	0.81 (0.28)	0.78 (0.31)	NS

HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; EF = ejection fraction; SV = stroke volume; E = early diastolic flow velocity; A = late diastolic flow velocity; IRT = isovolumic relaxation time; ICT = isovolumic contraction time; ET = ejection time; LV MPI = left ventricular myocardial performance index.

DISCUSSION

MPI is an easily determined, repeatable, quantitative echocardiographic measurement that can be used to determine LV global function.[8] More favorable function is found if the isovolumic phases are short and ejection time is long.[9] In one study that compared the MPI values of patients with dilated cardiomyopathy with those of healthy controls,[8] the mean (SD) MPI value in healthy controls was 0.39 (0.05). MPI has been found to be correlated with LV end-diastolic pressure[10] and invasive measurements of it (ie, using cardiac catheterization).[11] MPI has been found to be independent of heart rate and blood pressure.[4] MPI quantitatively reflects ventricular function in patients with complex ventricular geometry (ie, Ebstein's anomaly, LV aneurysm). In the absence of a geometric solution as the basis for the assessment of ventricular systolic function, this nongeometric index is appealing for the assessment of left and right ventricular function.[12] Thus, it has clinical advantages in determining LV function compared with other measurements.[8]

MPI has been found to be increased, whereas systolic and diastolic function are poorer, in patients with CHF compared with healthy subjects, and MPI is associated with shortened ET and/or increased IRT and ICT.[8] In a study of patients with dilated cardiomyopathy, the mean (SD) MPI was 0.59 (0.10).[13] MPI also has

been found to be valuable in determining the severity of CHF[14] and prognosis in dilated cardiomyopathy.[15,16]

Clinical studies have shown that the acute, subacute, and long-term effects of dobutamine on cardiac function, symptoms, and clinical findings differ based on dose, infusion time, and the patient's condition. De Wolf et al[17] found, in 39 anthracycline-treated patients and 32 healthy controls, that improvement in EF paralleled progressively increasing doses of dobutamine in DSE (0.5–5.0 μg/kg·min at 10-minute intervals for 35 minutes). The improvement in EF was more prominent in healthy subjects. In another study, 4-hour IV infusion per week did not change resting LV function (pre-ejection period/ET and cardiac index [CI]), but exercise performance and clinical status improved.[18] Eryol et al[19] found that IV dobutamine infusion (1–10 μg/kg·min for 72 h/mo), in combination with conventional therapy for CHF, created improved LV EF, cardiac output, and CI, and caused lower pulmonary capillary wedge pressures in the first and second months of treatment, but these findings were reversed at 3 months.

The acute effects of IV dobutamine infusion on LV MPI have been explored in a few studies that used DSE. Harada et al[4] studied 15 patients with surgically treated ventricular septal defect or Kawasaki disease and found that dobutamine (5 μg/kg·min for 15 minutes) increased ET and decreased IRT, ICT, and MPI on DSE. Parthenakis et al[5] studied 42 patients with dilated cardiomyopathy and found that dobutamine was associated with decreased IRT and ICT and hence improved MPI after peak dosage (10 μg/kg·min) was reached at the end of 12 minutes of DSE. The findings of Norager et al[20] suggested that during low-dose DSE for 6 minutes, MPI worsens in patients with no LV functional reserve, and that the opposite is true for patients who have functional reserve and healthy controls. Gorgulu et al[21] showed that low-dose dobutamine infusion (5 μg/kg·min for 5 minutes) was associated with decreased MPI and increased IRT in a group of 31 patients with normal LV systolic function. Elbl et al[22] found that subclinical cardiac dysfunction with anthracycline chemotherapy was associated with higher resting MPI values and a blunted MPI response during DSE (5–10 μg/kg·min). However, according to the literature search, no data were available concerning the effects of therapeutic dobutamine infusion on MPI. Theoretically, dobutamine might improve not only systolic but also diastolic function and may create a favorable effect on global function as represented by MPI. However, the effects of dobutamine are related to the dose and infusion interval of the drug, beta-adrenergic receptor density, and myocardial properties.

In the present study, we selected the smallest therapeutic dobutamine infusion dose, to eliminate arrhythmogenic AEs. The data showed that a single, 24-hour, low-dose, IV dobutamine infusion decreased LV end-systolic volume and increased EF but did not improve IRT, ICT, ET, diastolic function parameters, or global function as represented by MPI. The decreased LV end-systolic volume found may be explained by improved myocardial contractility due to dobutamine treatment. As a result, SV is increased. However, the improvement in diastolic myocardial function is more difficult than improvement in systolic function. The difference

in myocardial calcium metabolism and a change in myocardial compliance are necessary to establish this improvement. Sometimes it is more complex to improve diastolic function than systolic function in severe CHF. Capomolla et al[23] reported that dobutamine was associated with improved LV systolic function but also impaired diastolic function, and increased the severity of mitral valve regurgitation.

Although some of the early studies showed that short infusions with progressively increasing doses of dobutamine during DSE improved systolic and diastolic parameters and global function as represented by MPI values,[4,5] later studies suggest that improved MPI is attributable to the functional reserve of the myocardium.[20–22] Regardless, the results of both early and late studies[4,5,20–22] are due to higher doses of dobutamine used during DSE compared with the low dose used in our study. Obviously, different doses, infusion protocols, and myocardial conditions may cause different results. The results of the previously mentioned studies cannot be compared directly with ours because our data are valid for only the dose, interval, and patient group used. Higher doses or longer infusion intervals may improve isovolumic time intervals, ET, and MPI, but may cause arrhythmogenic AEs and may limit the clinical use of dobutamine.

Study Limitations

Because MPI cannot be used to assess rhythms other than sinus rhythm,[24] the results of this study cannot be generalized to all patients with CHF. Thus, the data are valid only for patients with CHF in sinus rhythm. The effect of increased or decreased preload on LV MPI is controversial.[25] All of the patients were receiving regular diuretic therapy, and patients with severe valvular regurgitations were excluded. Thus, we conclude that preload was stable and did not affect our data.

The present study was also limited because we were unable to measure isovolumic time intervals and ET in the same cardiac cycle. The sample data were too small to generate confidence in the outcome. Furthermore, these data must be verified in a larger, randomized study to clarify the most effective drug dose, treatment duration, and frequency of infusion.

Because our aim was to observe the adverse and echocardiographic effects during the study period, no follow-up period was studied, no data concerning long-term mortality were available, and a control group was not used. Instead, baseline (preinfusion) values were used as controls.

These data are valid only in adult patients with ischemic and idiopathic dilated cardiomyopathy in sinus rhythm. MPI was not improved, but benefits on LV end-systolic volume, SV, and EF were observed. More investigations are needed to determine the optimal dobutamine infusion dose and treatment duration that improves not only systolic function but also diastolic and global function (as represented by MPI).

CONCLUSIONS

In this study of adult patients with symptomatic CHF, a single, 24-hour, low-dose, IV dobutamine infusion (2.5 μg/kg · min) was associated with decreased LV

end-systolic volume and increased SV and EF. However, diastolic function parameters, isovolumic time intervals, and LV ET and MPI were statistically similar to preinfusion values. The infusion was well tolerated.

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