Original article

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Ivabradine treatment prevents dobutamine-induced increase in heart rate in patients with acute decompensated heart failure

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Background **Ivabradine is a heart rate (HR)-lowering agent acting by inhibiting the I_f-channel. Dobutamine does increase the HR and has some deleterious effects on myocardium. So, we aimed to evaluate whether ivabradine treatment blunts a dobutamine-induced increase in HR.**

Methods **The main study population consisted of 58 acute decompensated heart failure patients requiring inotropic support with left-ventricular ejection fraction below 35%, who were randomized to ivabradine ($n = 29$) or control ($n = 29$). All patients underwent Holter recording for 6 h and then dobutamine was administered at incremental doses of 5, 10 and 15 μg/kg/min, with 6-h steps. Holter recording was continued during dobutamine infusion. Ivabradine 7.5 mg was given at the initiation of dobutamine and readministered at 12 h of infusion. Also, a nonrandomized beta-blocker group with 15 patients receiving beta-blocker was included in the analysis. Control and beta-blocker groups did not receive ivabradine.**

Results **In the control group, mean HR gradually and significantly increased at each step of dobutamine infusion (81 ± 11, 90 ± 16, 97 ± 14 and 101 ± 16 b.p.m., respectively; $P = 0.001$), whereas no significant increase in HR was observed in the ivabradine group (82 ± 17, 82 ± 15, 85 ± 14 and 83 ± 12 b.p.m., respectively; $P = 0.439$). Mean HR was also found to significantly increase during dobutamine infusion in the beta-blocker group (75 ± 13, 82 ± 13, 86 ± 14 and 88 ± 13 b.p.m., respectively; $P = 0.001$). The median increase in HR from baseline was significantly higher in the control group compared to those in the ivabradine group (5 vs. 2 b.p.m.; $P = 0.007$ at first step, 13 vs. 5 b.p.m.; $P = 0.001$ at second step and 18 vs. 6 b.p.m.; $P = 0.0001$ at third step of dobutamine, respectively).**

Conclusions **Ivabradine treatment prevents dobutamine-induced increase in HR and may be useful in reducing HR-related adverse effects of dobutamine.**

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Introduction

Elevated heart rate (HR) shortens diastole, impairs ventricular loading, decreases ventricular efficiency, reduces myocardial blood supply, increases myocardial oxygen consumption and oxidative stress, and has been shown to be associated with poor clinical outcomes in patients with heart failure. Higher resting HR has been found to be a strong marker of mortality and morbidity in patients with chronic heart failure with reduced left-ventricular ejection fraction (LVEF), as well as heart failure with preserved LVEF.[1–3] Risk of in-hospital mortality has also been reported to be significantly higher in patients presenting with acute heart failure who have an elevated resting HR.[4]

The most widely used inotropic agent, dobutamine has been known to provide favorable hemodynamic and clinical improvements by increasing myocardial contractility and decreasing filling pressures in patients with acute heart failure syndromes.[5,6] However, it is also well known that dobutamine does increase HR, myocardial oxygen consumption, and intracellular calcium concentration, and therefore may lead to precipitate ischemia, cause myocardial cell damage, and increase cardiac arrhythmias and eventually be associated with increased mortality.[7–9] Dobutamine-induced increase in HR is probably responsible for some part of deleterious effects of this inotropic agent.

Ivabradine, which is a novel HR-lowering agent acting by inhibiting the I_f-current in the sino-atrial node, has been shown to improve clinical outcomes in chronic heart failure patients with reduced systolic function, in sinus ryhthm and an elevated resting HR.[10] However, the effects of ivabradine in the setting of acute heart failure and specifically on dobutamine-induced increase in HR are unknown. The aim of this study was to evaluate whether ivabradine treatment blunts dobutamine-

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induced increase in HR in patients presenting with acute decompensated heart failure.

Methods

Study population

Fifty-eight patients, 18 years of age or older, hospitalized with the diagnosis of acutely decompensated heart failure, New York Heart Association functional class III–IV, LVEF less than 35% as measured by transthoracic echocardiography, in sinus rhythm with a resting HR of at least 70 beats per minute (b.p.m.), who were in need of inotropic support according to the decision of their physicians, were included in this study. In general, patients with low-output heart failure who do not respond to optimal pharmacologic therapy with oxygen, diuretics and vasodilators, as evidenced by persistent dyspnea, those with clinical evidence of hypoperfusion and worsening renal and liver functions as evidenced by oliguria, increases in creatinine and liver transaminase levels and evidence of elevated cardiac filling pressures have been considered to be in need of inotropic therapy. All patients were treated with dobutamine as an inotropic agent and randomized (in a 1 : 1 design) to either ivabradine ($n = 29$) or control ($n = 29$). Patients who were included in both ivabradine and control groups were not receiving beta-blocker therapy. A nonrandomized beta-blocker group with 15 patients who were on standard background beta-blocker therapy was also included in the study as further explanatory post-hoc investigation. Atrial fibrillation or flutter, acute coronary syndromes, severe renal failure, hypertrophic cardiomyopathy, SBP 90 mmHg or less, cardiogenic shock, and pregnancy were the exclusion criteria.

Study design and protocol

The present study was a single-center, randomized, placebo-controlled trial performed in a tertiary university hospital cardiology department. From December 2010 to January 2012, 58 patients who were intended to be treated with dobutamine were enrolled in the main study population and consecutively randomized to ivabradine or control group. Also, 15 patients receiving beta-blocker therapy were added to the study in a nonrandomized fashion. The study protocol was approved by the institutional ethics committee, and all patients gave written informed consent before enrollment.

Patients who were judged to be in need of inotropic support underwent Holter recording for 6 h before the initiation of dobutamine infusion. Following baseline Holter recording, dobutamine infusion was started and administered at incremental doses of 5, 10 and 15 μg/kg/min, with 6-h steps. Holter monitoring was continued during 18 h of dobutamine infusion. Ivabradine 7.5 mg was given orally at the time of the initiation of dobutamine and readministered at 12 h of dobutamine infusion in the ivabradine group. Control and beta-blocker groups did not receive ivabradine treatment. Holter recordings were analyzed for mean HR change for each 6-h step of study protocol. At randomization and throughout the study, participants were expected to receive optimal medical therapy for acute heart failure, including oxygen therapy, intravenous diuretic and vasodilator therapy in addition to their own oral medication such as angiotensin-converting enzyme inhibitor or angiotensin receptor blockers, mineralocorticoid receptor antagonist or digoxin.

Baseline demographic data and medications were documented in all patients. N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, hemoglobin levels, serum potassium, sodium and creatinine levels were measured during admission and after 24–48 h of initiation of inotropic therapy. Patients' functional status was assessed by 6-min walk distance. In addition to mean HR change, changes in functional status and laboratory variables have been analyzed in the ivabradine and control groups in order to determine any effect of ivabradine treatment on clinical improvements in patients with acute decompensated heart failure.

Statistical analysis

The statistical analysis was performed using the Statistical Package for Social Sciences software 20.0 (IBM SPSS 20, SPSS Inc, Chicago, Illinois, USA) and SigmaStat 3.5 (Systat Software Inc., California, USA). The variables were expressed as mean ± SD and median (25−75 percentiles). The variables were tested for normal distribution by normality test of Shapiro-Wilk. Independent-sample *t*-test, paired-sample *t*-test, two-way analysis of variance (ANOVA) and two-way repeated-measures ANOVA were used for the analysis of normally distributed variables. Mann–Whitney *U*-test was used for the analysis of non-normally distributed variables. Categorical data were presented as frequencies and percentages and were analyzed by Pearson's chi-square, continuity correction chi-square and Fisher's exact tests. *P*-values less than 0.05 were considered as statistically significant.

Results

Clinical characteristics and laboratory findings obtained at admission are shown in Table 1. There was no profound difference between ivabradine and control groups in terms of patient demographics and medication. NT-proBNP levels, LVEF, 6-min walk distance and biochemical parameters did not differ between both groups. The majority of the study population had heart failure from ischemic cause.

Changes in mean heart rate during dobutamine therapy

Baseline mean HR before dobutamine infusion was similar in both groups. In the control group, mean HR gradually and significantly increased at each step of dobutamine infusion (Table 2). However, in the

Table 1 Patient demographics and laboratory data at hospital admission

	Control ($n=29$)	Ivabradine ($n=29$)	P
Age (years)	67 ± 12	64 ± 8.4	0.076
Male sex (*n*)	21(72%)	19 (65%)	0.777
Diabetes (*n*)	13 (44%)	17 (58%)	0.431
Hypertension (*n*)	23 (79%)	21 (72%)	0.759
Hyperlipidemia (*n*)	9 (31%)	12 (41%)	0.581
Ischemic heart failure (*n*)	24 (82%)	24 (82%)	1.0
Hemoglobin (g/dl)	12.7 ± 1.9	12.8 ± 2.1	0.765
Creatinine (mg/dl)	1.26 ± 0.5	1.25 ± 0.7	0.405
Sodium (mg/dl)	139 ± 4.2	139 ± 3.6	1.0
Potassium (mg/dl)	4.69 ± 0.65	4.63 ± 0.67	0.723
NT-proBNP (pg/ml)	6964 ± 6806	7145 ± 7634	0.930
LVEF (%)	27.52 ± 5.31	25.69 ± 5.95	0.222
6-MWD (m)	106 ± 51	123 ± 79	0.406
Medication			
ACEI/ARB (*n*)	18 (62%)	21 (72%)	0.576
Nitrate (*n*)	17 (58%)	10 (35%)	0.114
Diuretic (*n*)	20 (69%)	22 (75%)	0.769
Spironolactone (*n*)	18 (62%)	17 (58%)	1.0
Digoxin (*n*)	3 (10%)	3 (10%)	1.0

6-MWD, 6-min walk distance; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; LVEF, left-ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide.

ivabradine group, no significant change was observed in mean HR with incremental doses of dobutamine. Mean HR during the two highest doses of dobutamine infusion was found to be significantly lower in the ivabradine group than those in the control group. Two-way ANOVA also showed a significant overall increase in mean HR in the control group ($P<0.001$), but no significant change was observed in the ivabradine group ($P=0.439$). In addition, overall increase in mean HR in the control group was significantly different from that in the ivabradine group (Fig. 1).

The median HR in the control group as compared to those in the ivabradine group was found to increase from baseline by 5 (1.5–12.5) vs. 2 (−6.0–6.5) b.p.m. ($P=0.007$) at the first step of dobutamine infusion, 13 (7.5–23.0) vs. 5 (−10.0–14.0) b.p.m. ($P=0.001$) at the second step of dobutamine infusion; and 18 (13.5–26.5) vs. 6 (−11.5–10.5) b.p.m. ($P=0.0001$) at the third step of dobutamine infusion, respectively (Fig. 2). The percentage of HR increase at each step of dobutamine infusion was also found to be significantly higher in the control group when compared to those in the ivabradine group [6.85 (1.72 to 15.0) vs. 2.4 (−6.4 to 8.8)%; $P=0.012$ at the first step, 16.2 (9.1 to 25.8) vs. 6.6 (−10.3 to 17.7)%; $P=0.002$ at the second step, 23.4 (15.2 to 31.1) vs. 7.8 (−12.7 to 16.4)%; $P=0.001$ at the third step of dobutamine infusion, respectively) (Fig. 3).

Changes in clinical and laboratory variables following dobutamine therapy

There were no statistically significant changes observed in hemoglobin levels, serum potassium, sodium and creatinine levels after dobutamine therapy in both the ivabradine and control groups (Table 3). As had been expected, NT-proBNP levels have been found to significantly decrease, and LVEF and 6-min walk distance significantly increased following inotropic therapy in both the ivabradine and control groups (Table 3). However, the magnitude of change in 6-min walk distance (71 ± 56 vs. 60 ± 37 m; $P=0.477$), NT-proBNP [1660 (562 to 5347) vs. 1641 (748 to 2826) pg/ml; $P=0.797$) and LVEF [1.0 (−0.5 to 2.0) vs. 1.0 (−1.0 to 2.0)%; $P=0.981$] did not differ between the ivabradine and control groups.

Changes in mean heart rate during dobutamine therapy in the nonrandomized beta-blocker group

Patient demographics, medications, NT-proBNP levels, LVEF, 6-min walk distance and biochemical parameters were similar among beta-blocker, ivabradine and control groups (data not shown). Mean HR was found to significantly increase at each step of dobutamine infusion in the beta-blocker group (75 ± 13, 82 ± 13, 86 ± 14 and 88 ± 13 b.p.m., respectively; $P=0.001$) (Fig. 4). This increase in HR was significant even at the first step and at the second step of dobutamine infusion as compared to baseline HR ($P=0.009$ and $P=0.0001$, respectively), and was also significant at the third step of dobutamine as compared to baseline HR ($P=0.0001$) or HR values at the first step ($P=0.013$). The mean HR increase was 6.6 ± 5.8 b.p.m. at the first step, 10.4 ± 9.3 b.p.m. at the second step and 13.0 ± 7.7 b.p.m. at the third step of dobutamine therapy, and all these increases in HR were significantly higher than those in the ivabradine group ($P=0.006$, $P=0.001$ and $P=0.001$, respectively, for each step of dobutamine infusion). Also, the percentages of HR increase were 9.1 ± 7.6% at the first step, 14.6 ± 11.6% at the second step and 18.0 ± 10.1% at the third step of dobutamine, and again all these increases were significantly higher than those in the ivabradine group ($P=0.013$, $P=0.002$ and $P=0.001$, respectively, for each step of dobutamine infusion).

Discussion

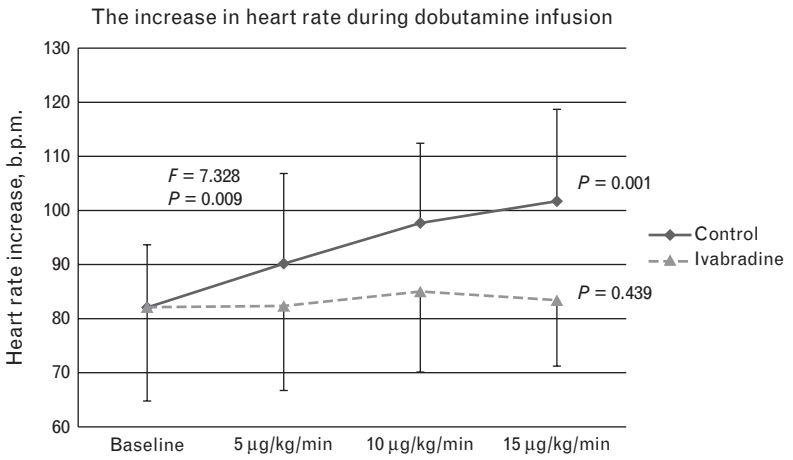
The findings of the control group of this study confirmed that HR during dobutamine therapy gradually and significantly increased from baseline by up to 23% with the incremental doses of dobutamine. The results of our

Table 2 Changes in mean heart rate during dobutamine infusion

	Control group mean heart rate (b.p.m.)	Ivabradine group mean heart rate (b.p.m.)	P
Baseline	81.9 ± 11.7	82.1 ± 17.3	0.958
Dobutamine 5 μg/kg/min	90.3 ± 16.6*	82.4 ± 15.7	0.069
Dobutamine 10 μg/kg/min	97.7 ± 14.8*,***	85.1 ± 14.9	0.002
Dobutamine 15 μg/kg/min	101.7 ± 16.9**,†	83.5 ± 12.4	0.001
P (two-way ANOVA)	0.001	0.439	

* $P=0.001$. ** $P=0.0001$ compared with baseline. *** $P=0.006$. † $P=0.0001$ compared with dobutamine 5 μg/kg/min. ANOVA, analysis of variance.

Fig. 1

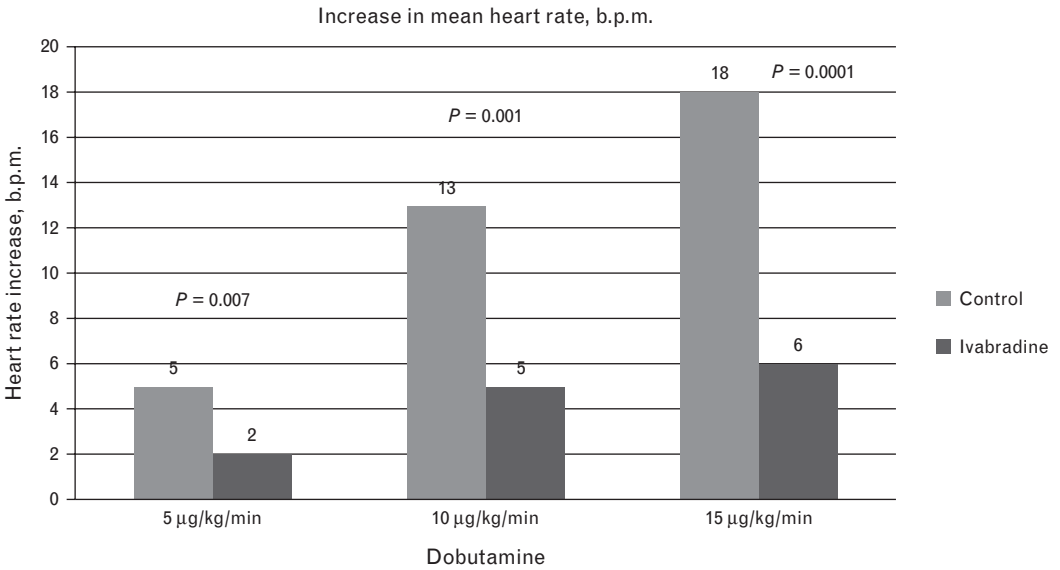


Two-way ANOVA analysis shows a significant overall increase in mean heart rate in the control group and no significant change in the ivabradine group ($P = 0.001$ and $P = 0.439$, respectively). In addition, overall increase in mean heart rate in the control group was significantly different from those in the ivabradine group ($F = 7.328$, $P = 0.009$). ANOVA, analysis of variance.

study mainly demonstrated that dobutamine-induced increase in HR was blunted by ivabradine treatment in patients hospitalized with acute decompensated heart failure.

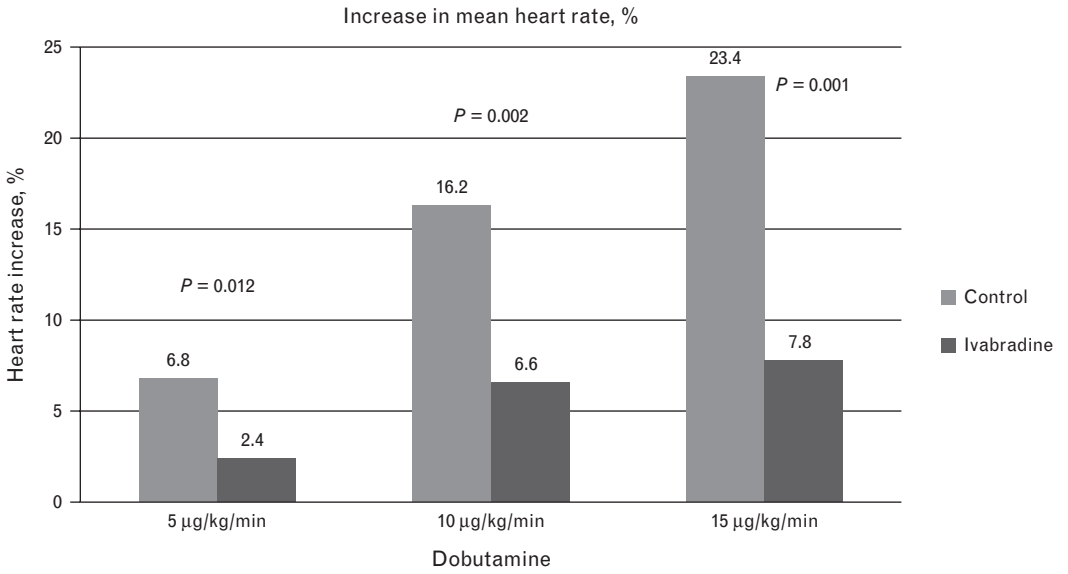
Resting HR has long been recognized as a strong predictor of mortality and morbidity in a wide spectrum of cardiovascular diseases including hypertension, myocardial infarction, coronary artery disease as well as heart failure.[1–4,11–14] The results of The Cardiac Insufficiency Bisoprolol Study II (CIBIS II) trial[1] and the placebo arm of the morBidity mortality EvAlUaTion of the If inhibitor ivabradine in patients with coronary disease and left-ventricULar dysfunction (BEAUTIFUL) study[2] indicated that higher HR is a strong marker of mortality and rehospitalization in patients with chronic heart failure or asymptomatic left-ventricular systolic dysfunction. Elevated HR is also reported to be a strong prognostic marker for patients hospitalized with acute heart failure. In the Acute Decompensated Heart Failure National Registry[4] in patients presenting with acute decompensated heart failure requiring intravenous vasoactive

Fig. 2



Increase in mean heart rate from baseline during each step of dobutamine infusion.

Fig. 3



The percentage of increase in mean heart rate from baseline during each step of dobutamine infusion.

medications, including inotropic support with dobutamine or milrinone, risk of in-hospital mortality was found to be significantly increased in those with a HR above 84 b.p.m. Also, in post-MI patients developing heart failure, total mortality from day 2 to 1 year was reported to be more than twice in patients who have an admission HR above 90 b.p.m. as compared to those with an admission HR below 90 b.p.m. (39 vs. 18%).[12]

Heart rate reduction with the use of beta-blocker therapy is associated with a marked improvement in clinical outcomes, and this improvement has been reported to be strongly associated with the magnitude of HR reduction.[15,16] Also, the recently published Systolic Heart failure treatment with the If inhibitor ivabradine Trial (SHIFT) study[10] suggested that a pure HR reduction by ivabradine provides a significant improvement in cardiovascular outcomes in chronic systolic heart failure patients with a HR above 70 b.p.m. Furthermore, patients with a HR below 60 b.p.m. at 28 days on ivabradine treatment had more clinical benefit than did patients with higher HR.[17] Although little is known about the potential beneficial effect of HR reduction in the setting of acute heart failure, in a recently published study with 421 patients with acute heart failure, the extent of HR reduction achieved by heart failure treatment during hospitalization was found to be an important predictor for the clinical outcome [hazard ratio 0.89 (0.84–0.96), $P < 0.001$].[18] Furthermore, high HR in patients hospitalized with acute decompensated heart failure has been reported to be an independent predictor of left-ventricular reverse remodeling and better prognosis in response to optimal pharmacotherapy.[19]

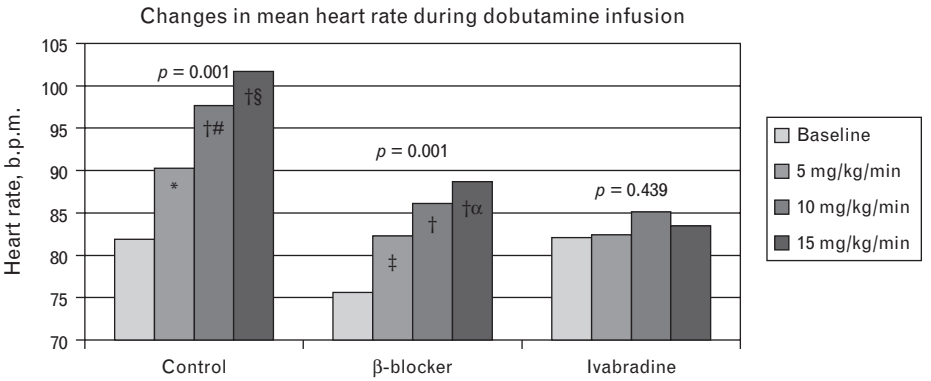
The commonly used inotropic agent dobutamine increases myocardial contractility at the expense of increased myocardial oxygen consumption and mediates its inotropic action through the stimulation of beta-adrenergic receptors.[7] Myocardial oxygen consumption has been reported to increase from baseline by almost 60% during dobutamine infusion.[20] In animal models, dobutamine has been shown to reduce subendocardial blood

Table 3 Changes in clinical and laboratory parameters following dobutamine therapy

	Control ($n = 29$)			Ivabradine ($n = 29$)		
	Before	After	*P*	Before	After	*P*
Hemoglobin (g/dl)	12.7 ± 1.9	12.7 ± 1.6	0.955	12.8 ± 2.1	13.0 ± 1.6	0.483
Potassium (mg/dl)	4.6 ± 0.6	4.7 ± 0.4	0.893	4.6 ± 0.6	4.6 ± 0.5	0.709
Sodium (mg/dl)	139 ± 4.2	137 ± 5.1	0.073	139 ± 3.6	137 ± 5.3	0.085
Creatinine (mg/dl)	1.26 ± 0.5	1.32 ± 0.7	0.509	1.25 ± 0.7	1.32 ± 0.6	0.107
NT-proBNP (pg/ml)	6964 ± 6806	3777 ± 2652	0.048	7145 ± 7634	4312 ± 5724	0.01
LVEF (%)	27.5 ± 5.3	28.4 ± 4.9	0.014	25.6 ± 5.9	26.4 ± 5.3	0.013
6-MWD (m)	106 ± 51	166 ± 52	0.001	123 ± 79	195 ± 96	0.001

6-MWD, 6-min walk distance; LVEF, left-ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Fig. 4



Changes in mean heart rate during each step of dobutamine infusion. Overall increase in heart rate was significant in the control and beta-blocker groups, whereas no significant change was observed in the ivabradine group. (*) $P=0.001$, (‡) $P=0.009$ and (†) $P=0.0001$ compared with baseline. (α) $P=0.013$, (#) $P=0.006$ and (§) $P=0.0001$ compared with dobutamine 5 μg/kg/min.

flow and may cause myocardial injury.[21] Therefore, dobutamine is thought to have a significant potential to induce myocardial ischemia, myocyte damage and cardiac arrhythmias, and associated with worse outcomes.[22,23]

Dobutamine is also well known to cause rapid dose-dependent increases in HR.[7] Dobutamine-induced increase in HR results in further increases in myocardial oxygen consumption and energy expenditure.[20–23] The other consequences of elevated HR such as shortening diastole, impairing ventricular loading or reducing coronary blood supply also adversely affect cardiac efficiency during dobutamine infusion. Hence, dobutamine-induced increase in HR may have some deleterious effects in patients with acute heart failure syndrome, particularly in those with ischemic heart failure. Therefore, it makes sense to prevent dobutamine-induced increase in HR in order to reduce deleterious effects of this inotropic agent.

Ivabradine is a selective I_f-channel inhibitor that results in HR reduction without affecting contractility and with little or no adverse cardiovascular side effects.[10] I_f-channels are located in the sino-atrial node, controlled by intracellular cyclic adenosine monophosphate (cAMP) and thus activated by beta-adrenergic stimulation.[24] Beta-adrenergic receptor stimulation is known to increase intracellular cAMP by activating adenylate cyclase, and cAMP positively shifts the I_f-channel activation curve.[24,25] This shift provides more inward current at diastolic potentials, increasing the slope of the diastolic depolarization and accelerating HR.[24,25] Therefore, I_f-channel inhibition would be expected to be an ideal target in preventing dobutamine-induced increase in HR.

Beta-blocker may be considered to be a reasonable therapeutic option to attenuate the HR response to dobutamine. However, hemodynamic response to dobutamine is also known to be attenuated by beta-blocker therapy.[26] The higher doses of dobutamine are required in patients under beta-blocker therapy to restore its inotropic effect. We aimed to see the only HR-lowering effect of ivabradine on the dobutamine-induced increase in HR, independent of beta-blocker therapy. For this reason and for the assessment of real effect of ivabradine on dobutamine-induced increase in HR, the main study population of the present study consisted of patients not receiving beta-blocker therapy. However, in order to understand whether the effect of beta-blocker treatment was comparable with ivabradine treatment with regard to preventing HR increase during dobutamine therapy, a nonrandomized beta-blocker group was included in the analysis and the results showed that even in the presence of beta-blockade, HR was increased significantly by dobutamine therapy and that beta-blocker therapy failed to prevent HR increase in response to dobutamine.

Study limitations

It is very important to know whether preventing dobutamine-induced increase in HR by ivabradine treatment also provides better clinical outcomes. Although our findings revealed no clear advantages of ivabradine treatment over standard medical care in the improvements in 6-min walk distance, NT-proBNP levels or LVEF, the aim of this study was not to primarily assess clinical outcomes of ivabradine therapy in patients with acute heart failure, but we simply aimed to evaluate whether ivabradine treatment blunts dobutamine-induced increase in HR which is thought to be responsible for some part of detrimental effects of this inotropic agent. Further larger studies designed to specifically assess clinical outcomes of ivabradine treatment are necessary for this patient population.

Conclusion

The study clearly showed that ivabradine treatment blunts dobutamine-induced increase in HR in patients

presenting with acute decompensated heart failure, and may be useful in reducing HR-related deleterious effects of dobutamine. However, further studies will be needed to determine whether preventing dobutamine-induced increase in HR by ivabradine treatment also provides better clinical outcomes.

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