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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

# Effects of ivabradine and beta-blocker therapy on dobutamine-induced ventricular arrhythmias

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## Abstract

**Background:** Indirect evidences suggest that the $I_f$ blocker ivabradine may exert an antiarrhythmic effect in ventricular myocardium in heart failure (HF) patients by inhibiting spontaneous depolarisations, but the clinical relevance of this mechanism is not known. Dobutamine (DOB) has been known to increase heart rate and the incidence of cardiac arrhythmias.

**Aim:** In this study, we evaluated the effects of ivabradine on DOB-induced ventricular arrhythmias and compared them with those of beta-blocker (BB) therapy.

**Methods:** Patients with decompensated HF requiring inotropic support, left ventricular ejection fraction < 35%, and in sinus rhythm were included in the study (ivabradine group — 29 patients, control group — 29 patients, BB group — 15 patients). All patients underwent Holter recording for 6 h before the initiation of DOB infusion. Following baseline recording, DOB was administered at incremental doses of 5, 10, and 15 μg/kg/min, with 6-h steps. Holter monitoring was continued during 18 h of DOB infusion and analysed for the median number of ventricular premature contractions (VPC), ventricular couplets, episodes of non-sustained ventricular tachycardia, and total ventricular arrhythmias in each step of the study protocol.

**Results:** The positive chronotropic effect of incremental DOB doses was blunted by beta-blockade and was totally abolished by ivabradine. The median number of VPCs, ventricular couplets, and total ventricular arrhythmias significantly increased with incremental doses of DOB in the control group ($p = 0.018$) and, to a lesser extent, in the ivabradine group ($p = 0.015$). In the BB group the absolute VPCs numbers were smaller than in the control or the ivabradine group, with the on-ivabradine VPCs numbers falling between those seen in control and BB groups. A numeric increase in VPCs with incremental DOB doses occurred in the BB group but did not reach statistical significance ($p > 0.05$), consistent with a protective effect of beta-blockade. Ivabradine reduced VPCs by 43% at 5 μg/kg/min DOB and by 38% at 10 μg/kg/min DOB against the control group (VPCs median 256 vs. 147 and 251 vs. 158) in the absence of significant differences at 15 μg/kg/min DOB between the control and ivabradine groups (overall $p > 0.05$). Thus, ivabradine administered without background beta-blockade attenuated the arrhythmogenic effect of increasing doses of DOB in the low and moderate DOB dose but not in the high DOB dose.

**Conclusions:** In patients with decompensated HF, ivabradine appears to reduce the incidence of VPCs in response to low and medium DOB dose. Whether the anti-arrhythmic effect of ivabradine is additive to the anti-arrhythmic effect of beta-blockade requires further investigation; this should also determine the clinical significance of ventricular arrhythmia attenuation with ivabradine.

**Key words:** ivabradine, heart failure, arrhythmias

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## INTRODUCTION

Sympathetic nervous system activation in chronic human heart failure (HF) has implications for both disease progression and survival [1]. Sympathetic nervous system plays a key role in the pathogenesis of arrhythmias in the failing heart [2]. Holter electrocardiographic (ECG) monitors in patients with congestive HF have demonstrated that arrhythmias occur in approximately 90% of patients and that non-sustained ven-

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tricular tachycardia (NSVT) or multifocal premature ventricular complexes are relatively common [3]. Arrhythmias have been reported to be poor prognostic predictors in patients with HF [4].

The most widely used inotropic agent, dobutamine (DOB), has been shown to provide favourable haemodynamic and clinical improvements in patients with decompensated HF syndromes [5, 6]. However, inotropic stimulation with DOB effects the cardiac conduction system and enhances myocardial contractility, but also increases heart rate (HR), increases energy expenditure, and precipitates ischaemia and myocardial necrosis [5–7].

Previously published data showed that ivabradine decreases HR and confers benefits on chronic HF [8]. However, the effects of ivabradine specifically on cardiac arrhythmias are unknown. Dobutamine has been known to increase HR and the incidence of cardiac arrhythmias especially in the setting of decompensated HF. Ivabradine inhibits $I_f$ channels that in the normal heart are expressed only in the sinoatrial node but whose pathologic expression occurs also in the ventricular myocardium in HF in humans [9]. In HF, $I_f$ activation in ventricular myocytes may translate into spontaneous depolarisations, particularly in the presence of increased sympathetic stimulation [9]. The effect of $I_f$ blockade on suppression of ventricular arrhythmias in decompensated HF has not yet been elucidated. In this study, we evaluated the effects of ivabradine on DOB-induced ventricular arrhythmias and compared it to treatment with beta-blocker (BB) therapy.

In our previous study, we showed that ivabradine treatment blunts DOB-induced increase in HR in patients presenting with decompensated HF [8]. Indirect evidence suggests that ivabradine may exert an antiarrhythmic effect in ventricular myocardium in HF patients by inhibiting spontaneous depolarisations, but the clinical relevance of this mechanism is not known [9]. Therefore, we analysed the Holter monitoring data of this study to compare the effects of ivabradine treatment with BB therapy on the incidence of ventricular arrhythmias during DOB infusion.

## METHODS

Seventy-three patients, 18 years of age or older, hospitalised with the diagnosis of decompensated HF, New York Heart Association functional class III–IV, left ventricular ejection fraction (LVEF) less than 35% as measured by transthoracic echocardiography, in sinus rhythm with a resting HR of at least 70 bpm, who were in need of inotropic support according to the decision of their physicians were included in this study. All patients were treated with DOB as an inotropic agent and randomised (in a 1:1 design) to either ivabradine (n = 29) or control (n = 29) as previously described elsewhere [8]. Patients who were included in both ivabradine and control groups were not receiving BB therapy. A nonrandomised BB group with 15 patients who were on standard background BB therapy was also included in the study. Atrial fibrillation or flutter, acute coronary syndromes, severe renal failure, hypertrophic cardiomyopathy, systolic blood pressure 90 mm Hg or less, cardiogenic shock, and pregnancy were the exclusion criteria. ECG Holter recording data from the previously published study were analysed to evaluate the effect of ivabradine on ventricular arrhythmias observed during DOB therapy [8].

Briefly, all patients underwent Holter recording for 6 h before the initiation of DOB infusion. Following baseline recordings, DOB was administered at incremental doses of 5, 10, and 15 $\mu$g/kg/min, with 6-h steps according to our research protocol. Four patients were excluded from the study because they could not tolerate higher DOB infusion doses. Holter monitoring of 69 patients was continued during 18 h of DOB infusion. Ivabradine was given twice in doses of 7.5 mg orally at the initiation of DOB and re-administered at 12$^{th}$ h of DOB infusion in 26 patients not receiving BB therapy (ivabradine group). Fifteen patients under BB therapy (BB group) and 28 patients not taking BB therapy (control group) did not receive ivabradine during DOB infusion. In the present analysis, Holter recordings were evaluated for the median number of ventricular premature contractions (VPC), ventricular couplets, episodes of NSVT, and total ventricular arrhythmias in each step of the study protocol (Fig. 1).

The research protocol was approved by the Local Ethical Committee of Eskisehir Osmangazi University, and all subjects provided their informed written consent.

### *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 ± standard deviation and median (25$^{th}$–75$^{th}$ 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 and Friedman test were used for the analysis of non-normally distributed variables. Categorical data were presented as frequencies and percentages and were analysed by Pearson's $\chi^2$, continuity correction $\chi^2$, 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 were similar among the BB, ivabradine, and control groups [8], as shown in Table 1. There was no profound difference between the BB, ivabradine, and control groups in terms of patient demographics and medication. N-terminal pro-B-type natriuretic peptide (NT- proBNP) levels, LVEF, and biochemical parameters did not differ between the

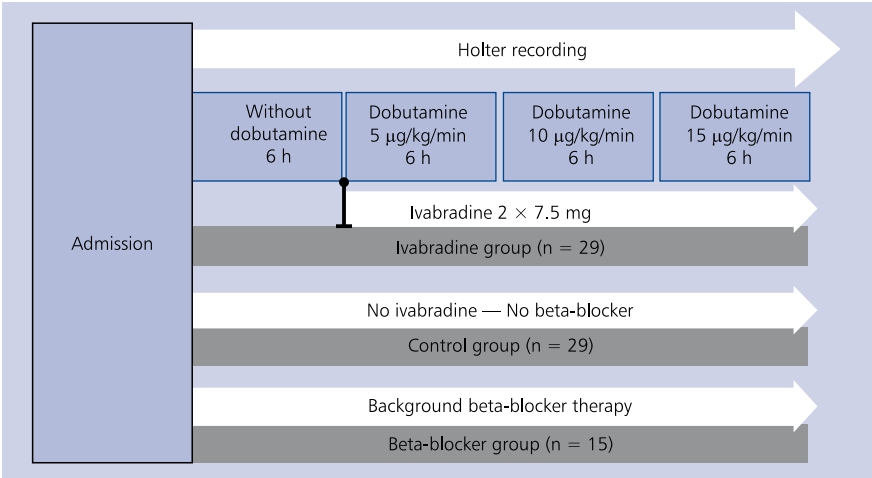


Figure 1. Design of the study

Table 1. Patient demographics and laboratory data at hospital admission

| | Control (n = 29) | Ivabradine (n = 29) | Beta-blocker (n = 15) | P |
|---|---|---|---|---|
| Age [years] | 67 ± 12 | 64 ± 8.4 | 66 ± 10 | 0.554 |
| Male gender | 21 (72%) | 19 (65%) | 10 (67%) | 0.840 |
| Diabetes | 13 (44%) | 17 (58%) | 10 (67%) | 0.335 |
| Hypertension | 23 (79%) | 21 (72%) | 10 (67%) | 0.644 |
| Hyperlipidaemia | 9 (31%) | 12 (41%) | 7 (46%) | 0.547 |
| Ischaemic heart failure | 24 (82%) | 24 (82%) | 13 (86%) | 0.472 |
| Haemoglobin [g/dL] | 12.7 ± 1.9 | 12.8 ± 2.1 | 12.0 ± 1.7 | 0.426 |
| Creatinine [mg/dL] | 1.26 ± 0.5 | 1.25 ± 0.7 | 1.29 ± 0.7 | 0.482 |
| Sodium [mg/dL] | 139 ± 4.2 | 139± 3.6 | 136 ± 4.1 | 0.135 |
| Potassium [mg/dL] | 4.69 ± 0.65 | 4.63 ± 0.67 | 4.46 ± 0.53 | 0.571 |
| NT-proBNP [pg/mL] | 6964 ± 6806 | 7145 ± 7634 | 4130 ± 5205 | 0.424 |
| LVEF [%] | 27.52 ± 5.31 | 25.69 ± 5.95 | 28.73 ± 5.77 | 0.210 |
| Medication: | | | | |
| ACEI/ARB | 18 (62%) | 21 (72%) | 10 (67%) | 0.703 |
| Nitrate | 17 (58%) | 10 (35%) | 7 (46%) | 0.183 |
| Diuretic | 20 (69%) | 22 (75%) | 12 (80%) | 0.700 |
| Spironolactone | 18 (62%) | 17 (58%) | 8 (53%) | 0.855 |
| Digoxin | 3 (10%) | 3 (10%) | 0 (0.0%) | 1.0 |

ACEI — angiotensin converting enzyme inhibitor; ARB — angiotensin receptor blocker; LVEF — left ventricular ejection fraction; NT-proBNP — N-terminal pro-B-type natriuretic peptide

groups. The majority of the study population had ischaemic HF (Table 1).

There were no statistically significant changes observed in haemoglobin levels, serum potassium, sodium, and creatinine levels after DOB therapy in the BB, ivabradine, and control groups. As expected, NT-proBNP levels were found to significantly decrease in the ivabradine and control groups, but there was no significant decrease in the BB group (respectively, $p = 0.012$, $p = 0.048$, $p = 0.078$). Although not in the BB group ($p = 0.417$), LVEF significantly increased following inotropic therapy in the ivabradine and control groups (respectively, $p = 0.013$, $p = 0.014$) (Table 2).

Mean HR gradually and significantly increased at each step of DOB infusion in both control (81 ± 11, 90 ± 16,

Table 2. Changes in clinical and laboratory parameters following dobutamine therapy

| | Control (n = 29) | | | Ivabradine (n = 29) | | | Beta-blocker (n = 15) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Before | After | p | Before | After | p | Before | After | p |
| Haemoglobin [g/dL] | 12.7 ± 1.9 | 12.7 ± 1.6 | 0.955 | 12.8 ± 2.1 | 13.0 ± 1.6 | 0.483 | 12.0 ± 1.7 | 11.8 ± 1.7 | 0.674 |
| Potassium [mg/dL] | 4.6 ± 0.6 | 4.7 ± 0.4 | 0.893 | 4.6 ± 0.6 | 4.6 ± 0.5 | 0.709 | 4.4 ± 0.5 | 4.6 ± 0.3 | 0.219 |
| Sodium [mg/dL] | 139 ± 4.2 | 137 ± 5.1 | 0.073 | 139 ± 3.6 | 137 ± 5.3 | 0.085 | 136 ± 4.1 | 136 ± 1.7 | 0.944 |
| Creatinine [mg/dL] | 1.26 ± 0.5 | 1.32 ± 0.7 | 0.509 | 1.25 ± 0.7 | 1.32 ± 0.6 | 0.107 | 1.29 ± 0.7 | 1.31 ± 0.8 | 0.397 |
| NT-proBNP [pg/mL] | 6964 ± 6806 | 3777 ± 2652 | 0.048 | 7145 ± 7634 | 4312 ± 5724 | 0.012 | 4130 ± 5205 | 2356 ± 2451 | 0.078 |
| LVEF [%] | 27.5 ± 5.3 | 28.4 ± 4.9 | 0.014 | 25.6 ± 5.9 | 26.4 ± 5.3 | 0.013 | 28.7 ± 5.7 | 29.0 ± 5.3 | 0.417 |

LVEF — left ventricular ejection fraction; NT-proBNP — N-terminal pro-B-type natriuretic peptide

Table 3. Dobutamine (DOB)-induced increase in ventricular premature contraction (VPCs) and couplets (medians)

| | VPCs | | | Couplets | | |
|---|---|---|---|---|---|---|
| | Control (median) | Ivabradine (median) | Beta-blocker (median) | Control (median) | Ivabradine (median) | Beta-blocker (median) |
| Baseline | 149 (42–340) | 132 (23–271) | 45 (7–245) | 1.5 (0–3.25) | 0.0 (0–2.0) | 4.0 (0–8.0) |
| DOB 5 μg/kg/min | 256 (55–508)[a] | 147 (30–538)‡ | 22 (11–448)[*] | 2.5 (1–5.25) | 1.0 (0–3.0) | 2.0 (0–41) |
| DOB 10 μg/kg/min | 251 (57–549)[b] | 158 (47–588)[Σ] | 96 (7–820)[#] | 1.0 (0–5.25) | 1.0 (0–4.0) | 5.0 (0–40) |
| DOB 15 μg/kg/min | 208 (44–446)[c] | 198 (47–503)[§] | 123 (21–634)[&] | 1.5 (0–5.0) | 1.0 (0–7.0) | 2.0 (0–24) |
| P | 0.01 | 0.001 | 0.112 | 0.159 | 0.003 | 0.200 |

Changes in ventricular arrhythmias during each step of dobutamine infusion. Overall increase in ventricular arrhythmias was significant in the control and ivabradine groups, whereas no significant change was observed in the beta-blocker group. Compared with baseline — in the control group: (a) p = 0.017, (b) p = 0.038, and (c) p = 0.024; in the ivabradine group: (‡) p = 0.049, (Σ) p = 0.001, and (§) p = 0.004; in the beta-blocker group: (*) p = 0.551, (#) p = 0.158, and (&) p = 0.330

Table 4. Dobutamine (DOB)-induced increase in total arrhythmias (medians)

| | Total arrhythmias | | |
|---|---|---|---|
| | Control (medians) | Ivabradine (medians) | Beta-blocker (medians) |
| Baseline | 128 (42–322) | 158 (48–312) | 49 (7.0–249) |
| DOB 5 μg/kg/min | 258 (58–469)[a] | 205 (55–722)‡ | 38 (11–565)[*] |
| DOB 10 μg/kg/min | 241 (59–446)[b] | 226 (112–739)[Σ] | 99 (7.0–900)[#] |
| DOB 15 μg/kg/min | 212 (45–438)[c] | 261 (74–493)[§] | 135 (21–847)[&] |
| P | 0.018 | 0.015 | 0.127 |

Changes in total arrhythmias during each step of dobutamine infusion. Overall increase in ventricular arrhythmias was significant in the control and ivabradine groups, whereas no significant change was observed in the ß blocker group. Compared with baseline — in the control group: (a) p = 0.047, (b) p = 0.07, and (c) p = 0.042; in the ivabradine group: (‡) p = 0.017, (Σ) p = 0.005, and (§) p = 0.024; in the beta-blocker group: (*) p = 0.510, (#) p = 0.149, and (&) p = 0.346

97 ± 14, and 101 ± 16, respectively, p = 0.001) and BB groups (75 ± 13, 82 ± 13, 86 ± 14 and 88 ± 13, respectively, p = 0.001), while no significant increase in HR was observed in the ivabradine group (82 ± 17, 82 ± 15, 85 ± 14, and 83 ± 12, respectively, p = 0.439).

The present analysis revealed that the median number of VPCs, ventricular couplets, and total ventricular arrhythmias significantly increased in the ivabradine group (p < 0.001, p < 0.003, and p < 0.015, respectively). In the control group, VPCs and total ventricular arrhythmias increased significantly (p < 0.01 and p < 0.018, respectively). However, in the BB group, no statistically significant increase was found in VPCs, couplets, and total ventricular arrhythmias (Table 3). Baseline Holter recording evaluation also shows that the median number of total arrhythmias in the BB group was less than in the control and ivabradine groups (49 [7.0–249], 128 [42–322], 158 [48–312], respectively) (Table 4).

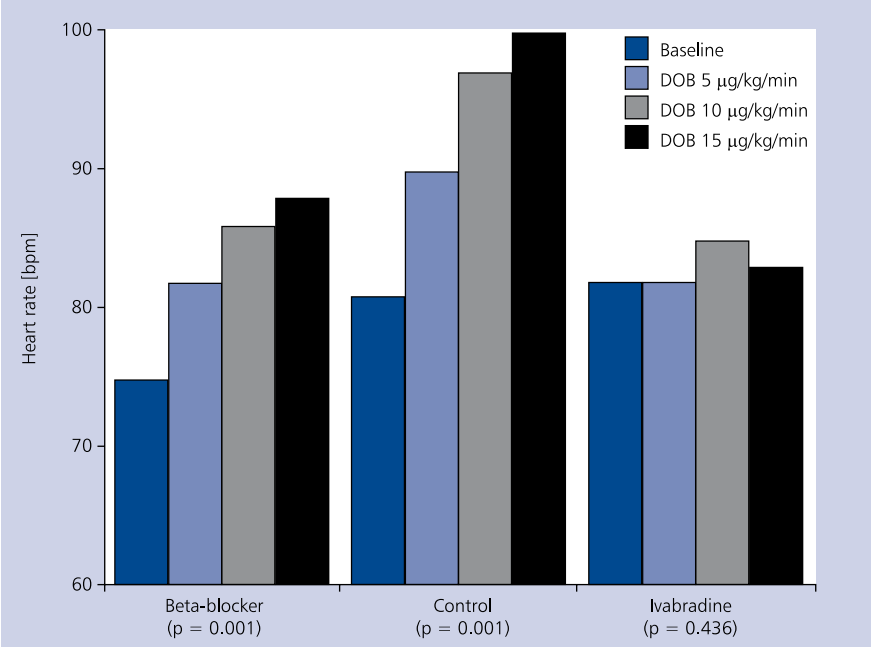


Figure 2. Dobutamine-induced (DOB)-increase in heart rate blunted by ivabradine and beta-blocker therapy fails to blunt dobutamine induced increase in heart rate

There was a profound difference between the control (n = 256 [55–508]) and ivabradine (147 [30–538]) groups in terms of the median numbers of VPCs at 5 µg/kg/min. Similarly, the median numbers of VPCs at 10 µg/kg/min were higher in the control group (n = 251 [57–549]) compared with the ivabradine group (n = 158 [47–588]). There was no difference in VPCs at 15 µg/kg/min between the control and ivabradine groups, and the overall difference did not reach statistical significance ($p > 0.05$). The incidence of NSVT did not significantly differ in the three groups (0 [BB group], 0 [ivabradine group], 1 [control group]).

## DISCUSSION

The major finding of this analysis is that ivabradine has almost no statistically significant effect on DOB-induced ventricular arrhythmias, especially in patients with decompensated HF syndromes. A significant increase in DOB-induced ventricular arrhythmias in the ivabradine group was determined from Holter monitoring records ($p = 0.018$). Unlike ivabradine, it was revealed that BB prevents DOB-induced ventricular arrhythmias in our study population. There was no significant increase in ventricular arrhythmias in the BB group ($p = 0.127$). Ivabradine effectively prevented HR increase with escalating doses of dobutamine (Fig. 2).

Moreover, compared with the control group the median number of VPCs was reduced by 43% in the ivabradine group at 5 µg/kg/min DOB dosage (respectively, n = 256 [55–508] and 147 [30–538]), and similar results were obtained at 10 µg/kg/min DOB dosage (respectively, n = 251 [57–549], n = 158 [47–588]; reduction of 38%). Ivabradine was not effective in attenuating the pro-arrhythmic effect of DOB at 15 µg/kg/min dosage. Albeit in a non-randomised fashion, beta-blockade is more effective in attenuating the pro-arrhythmic effect of DOB infusion. Further, well-designed investigations (larger study population, patient crossover design, randomised BB group, and ivabradine + BB group) are needed in order to evaluate the anti-arrhythmic effects of ivabradine and to elucidate clinical outcomes.

The commonly used inotropic agent DOB increases myocardial contractility at the expense of increased myocardial oxygen consumption and mediates its inotropic action through the stimulation of beta-adrenergic receptors [10]. Myocardial oxygen consumption has been reported to increase from baseline by almost 60% during DOB infusion [10, 11]. In animal models, DOB has been shown to reduce sub-endocardial blood flow and may cause myocardial injury. Therefore, DOB is thought to have significant potential to induce myocardial ischaemia, myocyte damage, and cardiac arrhythmias, and is associated with worse outcomes [10–13].

Moreover, ventricular premature beat frequency, couplet frequency, and ventricular tachycardia frequency are associated with mortality in patients with HF [3, 4, 14, 15]. Intravenous inotropic agents decrease ventricular refractoriness in both healthy and ischaemic myocardium [5]. The recent guidelines of the European Society of Cardiology [16] also recommend limited use of inotropic agents and highlight the inotrope-induced tachycardia in decompensated HF. Inotropes cause sinus tachycardia and may induce myocar-

dial ischaemia and arrhythmias [16]. There is long-standing concern that they may increase mortality. As well as these arrhythmogenic effects, our study reveals that BB therapy, unlike ivabradine, prevents DOB induced increase in ventricular arrhythmias.

The anti-arrhythmic effects of ivabradine are derived from several studies examining animals or small groups of patients [9]. Ng et al. [17] used ivabradine to assess the effects of HR reduction during ischaemia-reperfusion ventricular arrhythmias and assessed the potential anti-arrhythmic mechanism by optical mapping on 35 adult male rats' excised hearts. It was shown that the mean HR during ischaemia was an important determinant of reperfusion arrhythmia susceptibility, and slower HR during ischaemia delayed the development of ischaemia-induced electrophysiological changes [18]. Ivabradine reduced the incidence of reperfusion arrhythmias following regional ischaemia. However, it was revealed that the anti-arrhythmic effects of ivabradine were due to its selective HR lowering effects [18, 19]. In light of the fact that the link between beta-adrenergic and $I_f$ channel stimulation could provide a potential arrhythmogenic mechanism in the setting of enhanced sympathetic drive, such as HF or/and DOB infusion.

Cerbai et al. [18] reported that a current with electrophysiological properties of $I_f$ is consistently present in human ventricular myocytes isolated from three patients with post ischaemic dilated cardiomyopathy undergoing heart transplantation. It can be speculated that $I_f$ might represent arrhythmogenic mechanism in patients with HF [9]. Both automaticity and delay after depolarisation are observed in the ventricular trabeculae of failing human myocardium exposed to the altered extracellular environment mimicking that is present in patients with HF [20]. These alterations cannot explain the rapid ventricular tachycardias occurring in HF. However, they may induce extrasystoles, which can serve as a trigger in hearts in which the substrate for re-entry is clearly present [2, 20].

Furthermore, Kuwabara et al. [21] examined the effect of ivabradine on survival and arrhythmicity in transgenic mice, which is a useful mouse model of dilated cardiomyopathy leading to sudden death. In their study, ivabradine reduced lethal arrhythmias associated with dilated cardiomyopathy in mice, and beta-adrenergic stimulation conversely increased arrhythmogenecity [21]. Also, another study showed that $I_f$ current activity increases the pro-arrhythmogenic potential in the failing myocytes through prolongation of the repolarisation phase in ventricular action potentials [22]. These findings suggest that $I_f$ blockade is a potentially useful approach in the prevention of sudden death in patients with HF. In contrast, in the SHI*f*T study, sudden cardiac death did not appear to be affected by ivabradine [23]. However, 89% of the patients in SHI*f*T were under BB treatments, which can effectively prevent sudden cardiac death [23]. Also, a recently published post hoc subgroup analysis of the SHI*f*T study showed that reduction of cardiovascular death by ivabradine among subjects without BB treatment was not statistically significant [24].

On the other hand, therapies such as beta-adrenergic antagonism and angiotensin-converting enzyme inhibition, which diminish noradrenergic drive, augment the vagal modulation of HR, or both, prolong and improve the quality of life [1]. The impact of BB on neurohormonal imbalance remains of interest against ventricular arrhythmias. Beta-blockers are likely to be more effective in treating ventricular arrhythmias (e.g. generated in areas of myocardial scarring) compared with $I_f$ blockade, the effect of which is focused on the SAN. Therefore, BB and ivabradine can be considered complementary drugs [25]. Beta-blockers may be considered as a reasonable therapeutic option to prevent arrhythmogenic effects of DOB, especially by beta-receptor blockage. However, haemodynamic response to DOB is also known to be attenuated by BB therapy [26]. Higher doses of DOB are required for patients under BB therapy to restore its inotropic effect [26, 27]. We included patients who were already using BB without interfering dosage in BB group. Our results showed that the presence of beta-blockade prevents the increase of ventricular arrhythmias in patients with HF during DOB therapy; further investigations are needed to evaluate the anti-arrhythmic effect of ivabradine occurs on top of the effect of beta-blockade.

We excluded four (5.5%) patients from the study because of intolerance of high blood pressure and exacerbation of dyspnoea with higher doses of dobutamine. Paradoxically, progressive bradycardia with increasing doses of DOB was previously reported [28], but this di not occur in our study cohort.

### *Limitations of the study*

The study was not designed to primarily assess the clinical outcomes of DOB-induced increase in ventricular arrhythmias in patients with HF. We primarily aimed to evaluate whether ivabradine or/and BB therapy prevents the increase of ventricular arrhythmias in patients with HF during DOB therapy. Further, larger studies are needed to elucidate the clinical outcomes for this patient population.

Furthermore, the BB (n = 15) group was approximately half the size of the ivabradine group (n = 26) and control group (n = 28) because the BB group was a non-randomised, earlier group. Also, we did not evaluate whether the anti-arrhythmic effect of ivabradine occurs on top of the effect of beta-blockade. Consequently, further, well-designed investigations are needed to evaluate the antiarrhythmic effect of combined ivabradine + BB treatment, which is a desired therapy in this population.

## CONCLUSIONS

Ivabradine appears to attenuate the incidence of VPCs in response to low and medium DOB doses in patients with HF. Whether this phenomenon occurs on top of the effect of beta-blockade (i.e. independently of the anti-arrhythmic effect beta-blockade) requires further investigation.

***Conflict of interest:*** *none declared*

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# Wpływ terapii iwabradyną i beta-adrenolitykami na zaburzenia rytmu wywołane próbą dobutaminową

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## Streszczenie

**Wstęp:** Pośrednie dane z badań naukowych sugerują, że iwabradyna, lek hamujący kanały $I_f$, może działać antyarytmicznie na mięśniówkę komór u osób z niewydolnością serca poprzez hamowanie spontanicznej depolaryzacji, jednak znaczenie kliniczne tego mechanizmu nie jest znane. Wiadomo, że dobutamina (DOB) zwiększa częstotliwość rytmu serca oraz zapadalność na zaburzenia rytmu serca.

**Cel:** Celem niniejszej pracy była ocena wpływu iwabradyny na wywołane DOB arytmie komorowe i porównanie go z działaniem leków beta-adrenolitycznych.

**Metody:** Do badania włączono chorych z niewyrównaną niewydolnością serca wymagających stosowania leków o działaniu inotropowym dodatnim, z frakcją wyrzutową lewej komory wynoszącą < 35%, z rytmem zatokowym (29 chorych w grupie leczonej iwabradyną, 29 chorych w grupie kontrolnej, 15 chorych leczonych beta-adrenolitykiem). Wszystkim pacjentom 6 godzin przez rozpoczęciem infuzji DOB podłączano monitor holterowski EKG. Po uzyskaniu wstępnego zapisu chorym podawano DOB w dawkach zwiększanych stopniowo co 6 godzin i wynoszących 5, 10 i 15 μg/kg/min. Zapis holterowski kontynuowano przez 18 godzin podawania DOB, a następnie analizowano pod kątem średniej liczby przedwczesnych skurczów komorowych (VPC), par pobudzeń komorowych, epizodów nieutrwalonego częstoskurczu komorowego i liczby wszystkich zaburzeń komorowych na każdym etapie protokołu badania.

**Wyniki:** Chronotropowe dodatnie działanie wzrastających dawek DOB zostało osłabione przez leki beta-adrenolityczne i całkowicie zniesione przez iwabradynę. W grupie kontrolnej mediany liczby VPC, par pobudzeń i liczby zaburzeń rytmu ogółem zwiększały się istotnie wraz ze wzrastającymi dawkami DOB ($p = 0,018$), co było również widoczne, ale w mniejszym stopniu, w grupie przyjmującej iwabradynę ($p = 0,015$). W grupie leczonej beta-adrenolitykiem bezwzględna liczba VPC była mniejsza niż w grupie kontrolnej i u osób przyjmujących iwabradynę, przy czym liczba VPC w grupie stosującej iwabradynę miała wartość pośrednią między pozostałymi grupami. W grupie przyjmującej beta-adrenolityk odnotowano wzrost liczby VPC w miarę zwiększania dawek DOB, jednak nie osiągnął on istotności statystycznej ($p > 0,05$), co jest zgodne z ochronnymi właściwościami leków z tej grupy. Iwabradyna spowodowała zmniejszenie liczby VPC o 43% przy dawce DOB wynoszącej 5 μg/kg/min i o 38% przy dawce DOB wynoszącej 10 μg/kg/min w porównaniu z wartościami stwierdzonymi w grupie kontrolnej (mediana VPC 256 *vs*. 147 oraz 251 *vs*. 158), natomiast nie odnotowano istotnych różnic między grupą kontrolną a osobami stosującymi iwabradynę w przypadku dawki DOB wynoszącej 15 μg/kg/min ($p > 0,05$). Iwabradyna przyjmowana bez leku beta-adrenolitycznego osłabiła arytmogenne działanie wzrastających dawek DOB w przypadku dawek niskich i średnich, lecz nie powodowała takiego efektu przy wysokich dawkach DOB.

**Wnioski:** U chorych z niewyrównaną niewydolnością serca iwabradyna wpłynęła na zmniejszenie liczby VPC wywołanych niską lub pośrednią dawką DOB. Należy przeprowadzić dalsze badania w celu ustalenia, czy łączne stosowanie iwabradyny z beta-adrenolitykiem pozwoli uzyskać addytywny efekt przeciwarytmiczny. Trzeba również określić znaczenie kliniczne działania iwabradyny zmniejszającego skłonność do arytmii komorowych.

**Słowa kluczowe:** iwabradyna, niewydolność serca, zaburzenia rytmu

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