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# Comparison of the improvement in exercise tolerance in patients undergoing a cardiac rehabilitation program treated with beta-blockers alone or ivabradine

## Porównanie poprawy tolerancji wysiłku u pacjentów poddanych rehabilitacji kardiologicznej leczonych beta-adrenolitykami lub iwabradyną

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## Abstract

**Introduction.** Ivabradine is an agent that selectively decreases heart rate (depending on the dose) and does not affect other cardiovascular parameters. In particular, it does not influence left ventricular ejection fraction and does not inhibit vascular relaxation during exercise. Due to these properties, ivabradine can be used in those patients in whom beta-blockers are contraindicated or their dose escalation is not possible. These properties also suggest that use of ivabradine during cardiac rehabilitation in patients with contraindications to beta-blockers or beta-blocker intolerance might increase exercise tolerance. The aim of the study was to evaluate whether administration of ivabradine (in addition to or instead of beta-blockers) during a cardiac rehabilitation program improved exercise tolerance in comparison to patients receiving only beta-blockers.

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**Materials and methods.** Fifty patients treated with ivabradine during cardiac rehabilitation were enrolled into this retrospective study. The control group was matched for gender, age and other comorbidities and consisted of 50 subjects. The improvement in exercise tolerance was compared between the group receiving beta-blockers alone and those on ivabradine treatment.

**Results.** The study included 100 patients — 60 males and 40 females. Our analysis of exercise test results expressed in metabolic equivalents of task (MET) suggested a positive effect of ivabradine on the improvement of exercise tolerance. The percentage improvement was significantly higher in patients on ivabradine compared to the control group (26.8% ± 27.73% vs. 11.64% ± 19.34%, p = 0.002). In addition, a larger increase in the duration of exercise test was noted in patients treated with ivabradine (52.76% ± 47.29% vs. 32.59% ± 42.94%, p = 0.0101). No difference was found between patients who were already treated with ivabradine before cardiac rehabilitation and those in whom ivabradine was initiated during the cardiac rehabilitation program.

**Conclusions.** Treatment with ivabradine during a cardiac rehabilitation program was associated with a better improvement in exercise tolerance compared to patients receiving beta-blockers alone.

Key words: ivabradine, beta-blocker, exercise, cardiac rehabilitation

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## Introduction

Advances in invasive cardiology techniques and drug therapy have resulted in a significant reduction of life years lost in patients with ischemic heart disease but also have led to an increase in the number of patients with chronic heart failure [1]. The quality of life of these patients is reduced, with difficulties encountered during routine daily activities. Thus, adequate rehabilitation should be planned following successful treatment of an acute coronary syndrome (ACS) to allow the patient to return to normal activities as much as possible. The first step of rehabilitation should be initiated during the index hospitalization and this should be continued after hospital discharge as inpatient or outpatient cardiac rehabilitation [2]. Adequate cardiac rehabilitation reduces the risk of recurrent cardiovascular events, improves the quality of life, and prolongs life [2]. It is recommended in patients with stable coronary artery disease, following invasive treatment of ACS, and in chronic heart failure [3–6]. Drug therapy of these conditions includes beta-blockers which are well studied and effective medications but their benefits cannot be offered to all patients. Contraindications to beta-blockers include asthma, chronic obstructive pulmonary disease (COPD), symptomatic bradycardia, and atrioventricular block. Even in patients without these conditions, however, beta-blockers may be poorly tolerated and cannot be used in adequate doses. In these situations, ivabradine is indicated for persisting sinus rhythm rate above 70 beats per minute. This novel drug selectively reduces heart rate and may be initiated also during cardiac rehabilitation. The aim of the study was to evaluate the effect of ivabradine on the improvement in exercise tolerance during a cardiac rehabilitation program.

## Material and methods

The study included patients treated with ivabradine and hospitalized in the Department of Cardiology at the Medical University of Lodz from December 2015 to August 2017. The study was retrospective and based on an analysis of the cardiac rehabilitation unit database. Due to retrospective nature of the study, which included only evaluation of patient medical records, ethics committee approval was not necessary.

The study group included 50 patients who fulfilled the following criteria: treatment with ivabradine, completion of the cardiac rehabilitation program with two exercise tests, on admission and at the end of hospitalization, and the presence of sinus rhythm. Table 1 shows the reasons for initiating ivabradine therapy in the study group. The control group included 50 patients who were not treated with ivabradine and was matched for age, gender, reason for admission to the cardiac rehabilitation unit, and concomitant conditions. Patients who did not complete the cardiac rehabilitation program or did not have two exercise

**Table 1.** Reasons for initiating ivabradine therapy in the study group

| Reason | Percentage [%] |
|---|---|
| Arrhythmia or conduction disturbances | 16 |
| Asthma or COPD | 20 |
| Hypotension | 10 |
| Sinus rhythm rate > 70 bpm despite maximal beta-blocker dose | 52 |
| Psoriasis | 2 |

bpm — beats per minute; COPD — chronic obstructive pulmonary disease

**Table 2.** Characteristics of the study and control groups

| | | Study group | Control group | |
|---|---|---|---|---|
| Gender | Women | 20 | 20 | p = 1 (NS) |
| | Men | 30 | 30 | |
| Age | | 63.26 ± 10.35 | 63.04 ± 10.84 | p = 0.89 (NS) |
| SBP [mm Hg] | | 129.22 ± 18.42 | 130.69 ± 11.92 | p = 0.49 (NS) |
| DBP [mm Hg] | | 77.46 ± 9.93 | 78.53 ± 9.31 | p = 0.34 (NS) |
| Left ventricular ejection fraction [%] | | 70.74 ± 11.17 | 65.23 ± 11.09 | p = 0.08 (NS) |
| Previous myocardial infarction treated percutaneously | | 20 | 19 | p = 0.30 (NS) |
| Heart failure | | 7 | 4 | |
| Previous coronary artery bypass grafting | | 10 | 19 | |
| Unstable angina treated percutaneously | | 7 | 4 | |
| Prosthetic valve implantation | | 6 | 4 | |
| Diabetes type 2 | | 22 | 16 | p = 0.21 (NS) |
| Hypertension | | 42 | 43 | p = 0.78 (NS) |

NS — not significant; SBP — systolic blood pressure; DBP — diastolic blood pressure

tests performed were excluded from the study. Overall, the analysis included 100 patients.

In all patients, a cardiac rehabilitation program was initiated according to the Polish Cardiac Society recommendations [2]. An exercise test was performed on admission and at the end of hospitalization using the following protocols: Bruce protocol (66% of patients), modified Bruce protocol (21%), 25 W/3 min protocol using a cycle ergometer (10%), or Naughton protocol (3%).

Study data were analysed using the STATISTICA 13 package (StatSoft Inc., USA). Continuous variables were expressed as mean values ± standard deviation, and categorical variables as numbers and percentages. Normal distribution of the evaluated quantitative variables was assessed using the Shapiro-Wilk W test. Study groups were compared using the Student t test (or nonparametric Mann-Whitney test, depending on data distribution) or chi-square test (or exact Fisher test). More than two variables with normal distribution and equal variances were compared using ANOVA, and the Kruskal-Wallis test was used if otherwise and for categorical variables. For all analyses, $p < 0.05$ was considered statistically significant.

## Results

Overall, we analysed a group of 40 women and 60 men aged 41–86 years. The most common reason for admission to a cardiac rehabilitation unit was previous myocardial infarction (39%). Other reasons were heart failure (11%), previous coronary artery bypass grafting (29%), unstable coronary artery disease (11%), and previous implantation of a valve prosthesis (10%). Common concomitant conditions were hypertension (85%) and diabetes type 2 (38%). Detailed characteristics of the study and control groups are shown in Table 2.

In our study, we investigated in detail results of the exercise tests expressed in metabolic equivalents of task (METs), which allow evaluation of the intensity of exercise. The reason for terminating the exercise test was patient fatigue (76%) or achieving target heart rate (24%). Exercise tolerance on admission was slightly lower in patients treated with ivabradine compared to the control group (5.71 ± ± 2.37 MET vs. 6.13 ± 2.50 MET, p = 0.43). At the end of hospitalization, exercise tolerance was slightly higher in the study group compared to the control group but the difference was not significant (7.11 ± 3.11 MET vs. 6.76 ± ± 2.74 MET, p = 0.89). The analysis of both exercise tests suggest a positive effect of ivabradine on the improvement in exercise tolerance during cardiac rehabilitation (p = 0.004, Figure 1).

A percentage change in exercise tolerance during hospitalization in relation to the result of the first exercise test was calculated using the formula:

$$ext2/ext1 \times 100\% = \Delta ext$$

where ext2 is exercise tolerance in METs during the exercise test at the end of hospitalization, ext1 is exercise tolerance in METs during the initial exercise test, and Δext is the percentage change in exercise tolerance in METs.

Our analysis of this parameter indicated a significantly higher percentage change in exercise tolerance in patients treated with ivabradine (26.8 ± 27.73 vs. 11.64 ± 19.34; p = 0.002; Figure 2).

When we compared patients in whom ivabradine was initiated during the cardiac rehabilitation program with those who were treated with ivabradine before hospitalization,

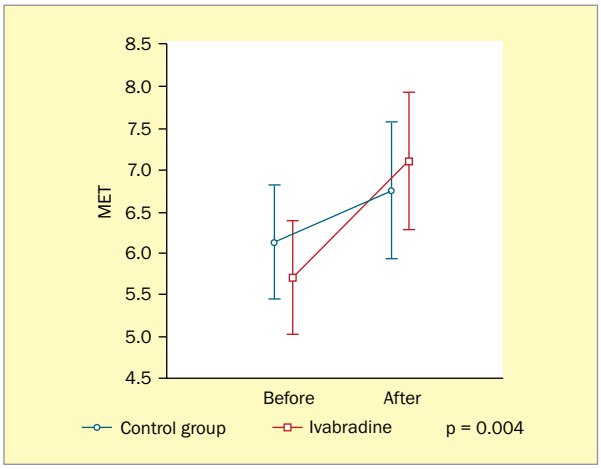


**Figure 1.** Improvement in exercise tolerance in the study and control groups during cardiac rehabilitation

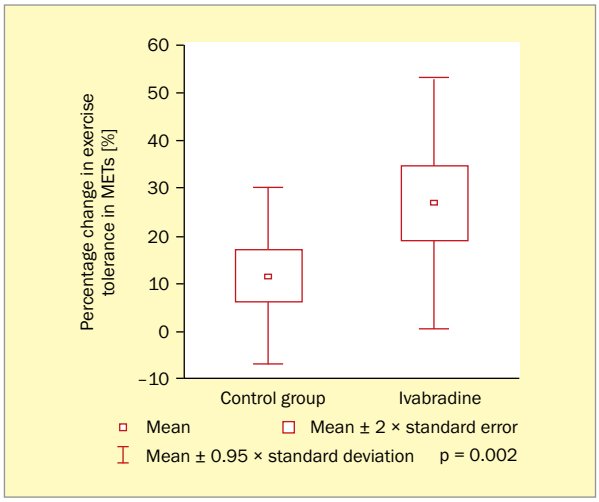


**Figure 2.** Percentage change in exercise tolerance during cardiac rehabilitation in the study and control groups

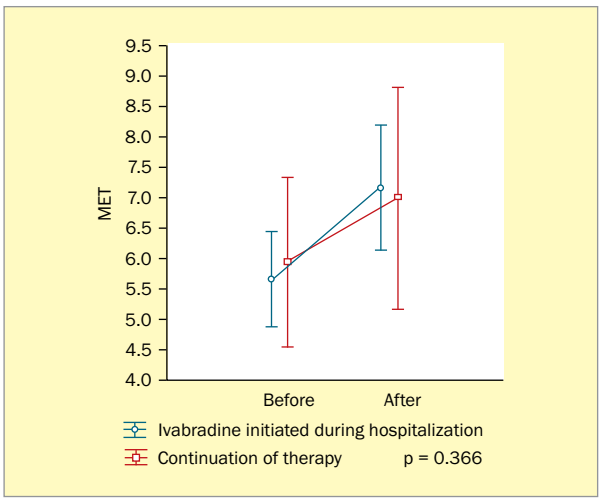


**Figure 3.** Comparison of the improvement in exercise tolerance in patients treated with ivabradine before cardiac rehabilitation and those in whom ivabradine was initiated during cardiac rehabilitation

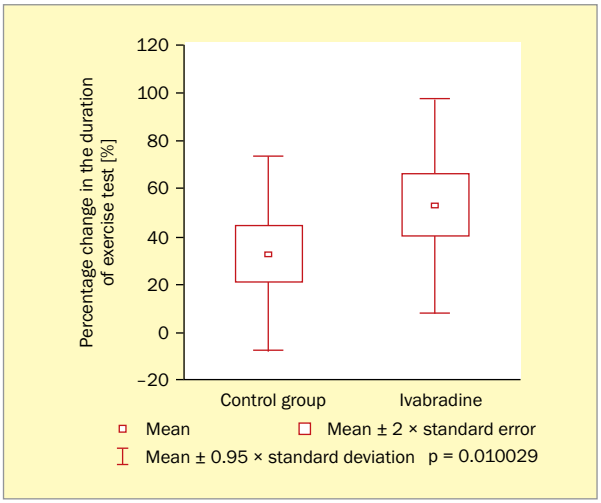


**Figure 4.** Percentage change in the duration of exercise test at the end of the cardiac rehabilitation program

we did not found significant differences in the improvement in exercise tolerance (p = 0.366, Figure 3).

Another important indicator of exercise tolerance is the duration of exercise test. Before cardiac rehabilitation, it was on average 4 minutes 51.6 seconds in patients treated with ivabradine compared to 4 minutes 33.6 seconds in the control group. At the end of the cardiac rehabilitation program, these durations were 6 minutes 50 seconds and 5 minutes 37 seconds, respectively. Our analysis of the percentage increase in the duration of exercise test suggests a beneficial effect of ivabradine on the improvement in exercise tolerance (52.76% ± 47.29 vs. 32.59% ± 42.94, p = 0.0101, Figure 4).

## Discussion

The most important result of our study is an observation that in patients receiving ivabradine during cardiac rehabilitation, either as the main medication to slow down the heart rate or in combination with a beta-blocker, the improvement in exercise tolerance is better compared to patients with similar demographic and clinical characteristics who received only beta-blockers.

Ivabradine selectively reduces heart rate by blocking the pacemaker current If in the sinus node. This drug only affects slow resting polarization without an effect on other cardiovascular system function parameters [7]. In particular, it does not affect the refraction period and cardiac conduction velocity [8], inotropic effect [9], left ventricular systolic function [9], coronary vessel contractility [9], left ventricular ejection fraction [10], and peripheral resistance. These characteristics indicate that ivabradine is an interesting alternative to beta-blockers that also affect other cardiovascular parameters in addition to the effect on the heart rate. Both beta-blockers and ivabradine improve exercise tolerance and reduce the frequency of anginal attacks

but in contrast to beta-blockers, ivabradine does not effect myocardial contractility, atrioventricular conduction, and coronary adaptation to exercise. Ivabradine may be used in patients with reduced beta-blocker tolerance or when use of these drugs or their dose escalation is not recommended, for example due to asthma or cardiac conduction abnormalities. Amosova et al. [11] showed that administration of ivabradine instead of an increase in bisoprolol dose in patients with stable angina improved exercise tolerance (as measured by the 6-minute walking test and exercise test) and increased chronotropic reserve. Similar properties of ivabradine were shown by Bagriy et al. [12] in a prospective study that evaluated the effects of initiating this medication in patients with systolic heart failure who were treated with carvedilol. Patients who received an If current inhibitor had slower resting heart rate, higher ejection fraction, and improved exercise tolerance. These studies indicate that drug treatment with ivabradine seems safe in subjects with reduced exercise tolerance and suggest it may be used during cardiac rehabilitation with the aim of improving the quality of life by increasing exercise capacity. Our study confirmed that administration of ivabradine to patients undergoing a cardiac rehabilitation program increased exercise tolerance as measured in METs and increased the duration of exercise compared to patients treated only with beta-blockers. Our results are in agreement with other studies that evaluated the effectiveness of beta-blocker and ivabradine therapy during cardiac rehabilitation. Marazia et al. [13] showed that in patients undergoing cardiac rehabilitation following coronary artery bypass grafting, addition of ivabradine to bisoprolol improved exercise capacity, resulted in an earlier recovery of systolic function, and reduced diastolic dysfunction. Few reports are available on the use of an If current inhibitor during cardiac rehabilitation following an acute coronary syndrome. In our study, we focused on evaluating patients who were matched for concomitant conditions, age, and resting heart rate. Future studies should evaluate whether the improvement in exercise tolerance is similar in patient with different specific cardiac conditions.

## Conclusions

In patients receiving ivabradine during cardiac rehabilitation, either as the main medication to slow down the heart rate or in combination with a beta-blocker, the improvement in exercise tolerance is better compared to patients with similar demographic and clinical characteristics who were treated only with beta-blockers.

## Conflict of interest(s)

The authors report no conflicts of interest.


## Streszczenie

**Wstęp.** Iwabradyna jest substancją wybiórczo zmniejszającą częstotliwość rytmu serca (zależnie od dawki), nie wpływając jednocześnie na inne parametry układu sercowo-naczyniowego. W szczególności nie wpływa na frakcję wyrzutową lewej komory ani nie hamuje wysiłkowego rozkurczu naczyń. Dzięki tym właściwości można ją zastosować u chorych, u których podawanie beta-adrenolityków jest przeciwwskazane. Opisane właściwości sugerują, że włączenie iwabradyny podczas rehabilitacji kardiologicznej u pacjentów, u których występują przeciwwskazania do leczenia beta-adrenolitykami lub do zwiększenia ich dawki, może usprawnić tę rehabilitację i w efekcie zwiększyć tolerancję wysiłkową.

Celem opisanego badania był ocena, czy włączenie iwabradyny podczas rehabilitacji kardiologicznej wpływa na zwiększenie osiąganej tolerancji wysiłkowej w porównaniu z pacjentami otrzymującymi jedynie beta-adrenolityki.

**Materiały i metody.** Pięćdziesięciu pacjentów, leczonych iwabradyną i hospitalizowanych na Oddziale Rehabilitacji Kardiologicznej Wojewódzkiego Specjalistycznego Szpitala im. dr. Władysława Biegańskiego w Łodzi, zakwalifikowano do retrospektywnego badania. Grupę kontrolną dopasowano pod względem płci, wieku oraz innych chorób towarzyszących i składała się z 50 pacjentów leczonych zgodnie z wytycznymi. Analizowano związek między przyjmowaniem iwabradyny a tolerancją wysiłku fizycznego.

**Wyniki.** W badaniu wzięło udział 100 pacjentów — 60 mężczyzn i 40 kobiet. Analiza wyników testu wysiłkowego wyrażonych w ekwiwalentach metabolicznych (MET) sugeruje korzystny wpływ iwabradyny na poprawę tolerancji wysiłku fizycznego. Procentowa poprawa była wyższa w grupie badanej niż w grupie kontrolnej (26,8% ± 27,73% *v.* 11,64% ± ± 19,34%; p = 0,002). Odnotowano również istotne wydłużenie czasu trwania próby wysiłkowej u pacjentów przyjmujących iwabradynę (52,76% ± 47,29% *v.* 32,59% ± 42,94%; p = 0,0101). Nie stwierdzono związku między pacjentami, którzy przyjmowali iwabradynę przed hospitalizacją, a pacjentami, którzy rozpoczęli terapię iwabradyną w trakcie rehabilitacji.

**Wnioski.** Pacjenci otrzymujący iwabradynę w procesie rehabilitacji kardiologicznej osiągają lepszą tolerancję wysiłku niż pacjenci otrzymujących jedynie beta-adrenolityki.


Słowa kluczowe: iwabradyna, beta-adrenolityki, wysiłek fizyczny, rehabilitacja kardiologiczna

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