Kardiologia Polska 2017; 75, 9: 893–898; DOI: 10.5603/KP.a2017.0095 ISSN 0022–9032

ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

How does ivabradine effect erectile dysfunction in patients with heart failure?

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Abstract

Background: Erectile dysfunction (ED) is the inability or insufficiency of penile erection that causes dissatisfaction during sexual intercourse. ED is seen in patients with heart failure (HF), ranging from 56% to 81% depending on the severity. Patients usually blame their cardiovascular medications for their ED. Ivabradine is used for antianginal effects, to improve exercise intolerance, and to decrease mortality in patients with HF. Most beta-blockers are known to cause ED, but unlike beta-blockers the effect of ivabradine over ED has never been evaluated.

Aim: We investigated the effect of ivabradine on ED in patients with HF.

Methods: Thirty-one patients with HF (all men) under optimal treatment for HF (except ivabradine) were recruited. Patients were evaluated with the internationally validated Sexual Health Inventory for Men (SHIM) questionnaire before the initiation of ivabradine and at the sixth month of the treatment. SHIM scores previous to treatment and at six months were compared using Wilcoxon signed rank test. A p value < 0.05 was accepted as statistically significant.

Results: At six months of follow-up after the initiation of ivabradine, a significant increase in patients with normal libido was found ($p < 0.001$).

Conclusions: This is a novel study that evaluates the effect of ivabradine on human with HF. Ivabradine improved libido in patients with HF.

Key words: heart failure, ivabradine, erectile dysfunction

Kardiol Pol 2017; 75, 9: 893–898

INTRODUCTİON

Erectile dysfunction (ED) is the inability or insufficiency of penile erection that causes dissatisfaction during sexual intercourse. It affects 40% of the male population between the ages of 40 and 69 years [1]. Because the cardiovascular disease and the ED have a similar pathophysiologic basis they also share similar aetiological risk factors, like aging, hypercholesterolaemia, hypertension, diabetes, smoking, obesity, sedentary life, and psychological stress [2–4].

Erectile dysfunction is seen in patients with heart failure (HF), ranging from 56% to 81%, depending on the severity [5]. Neurohormonal pathology, drug side effects, limited exercise capacity, and psychological factors are responsible [6]. Among those factors, drug side effects seem to be reversible. While patients usually blame their cardiovascular medications for their ED, some of them can have beneficial effects too. Thiazide diuretics, some old-generation beta-blockers (BB) [7], digoxin [8, 9], and aldosterone antagonists (spironolactone more often than eplerenone) [9, 10] are proven to cause ED. On the other hand, nebivolol, angiotensin converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB), and calcium channel blockers and statins in low doses may have neutral or positive effects on ED [7, 11, 12]. Consequently, cardiologists should be aware of the possible side effects or beneficial effects of the medications that they offer to their patients.

Ivabradine is the prototype of a novel class of selective If channel inhibitor. It is used for antianginal effects, and to improve exercise intolerance and to decrease mortality in patients with HF. Although ivabradine lacks inotropic and antiarrhythmic effects, it works similarly to BB for reducing heart rate and can be widely used if patients are intolerant to

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Received: 22.11.2016 **Accepted:** 20.03.2017 **Available as AoP:** 18.05.2017

BB, or sometimes in adjunction to BB for better and quicker dose adjustments. It basically lowers the heart rate without decreasing the ejection fraction [13, 14]. Most BBs are known to cause ED, but unlike BB the effect of ivabradine over ED has never been evaluated. We investigated the effect of ivabradine on ED in patients with HF. This article is written according to the STROBE statement checklist for observational studies.

METHODS

Study population

This study was performed between April 2015 and June 2015. The study included patients with a diagnosis of HF, who were followed by a cardiology clinic. The experimental protocol of this study was approved by the ethical committee of Kocaeli University. Written informed consent was obtained from all subjects. Thirty-one patients with HF (all men) were recruited for the study. Patients were previously diagnosed and followed-up by the department of cardiology outpatient clinic. The mean age was 53.0 ± 6.6 years, the mean disease duration after the diagnosis of HF was 38 ± 13 months. All patients were under optimal treatment for HF, including: BB (3/31 [9.6%] bisoprolol, 2/31 [6.4%] carvedilol, 26/31 [83%] metoprolol succinate), ACEI/ARB, mineralocorticoid receptor antagonist (20 [64.5%] patients were taking spironolactone 25 mg daily, and none of them was taking eplerenone), and diuretics (all patients were taking furosemide, and 12 [38%] patients were taking hydrochlorothiazides). All patients were in sinus rhythm, and none of them was taking digoxin. None of the patients was under treatment for ivabradine prior to investigation. The mean New York Heart Association (NYHA) was 1.81 (only two patients were NYHA III, and the rest were NYHA I–II).

Study protocol

After obtaining the routine history and completing the physical exam, a transthoracic echocardiography was obtained. The patients with ejection fraction under 45% with modified Simpson method from apical two- and four-chamber view are accepted to the study. A psychiatrist obtained an internationally validated Sexual Health Inventory for Men (SHIM) questionnaire and after six months of the ivabradine therapy for patients with a cardiac indication to initiate ivabradine therapy (5 mg twice a day). Because the purpose of this study was to identify the effect of ivabradine on libido and erectile dysfunction, patients were told not to start any drugs that may affect erectile dysfunction, such as phosphodiesterase inhibitors. The inclusion and exclusion criteria for the patient group are listed in Table 1.

Statistical analysis

All data were analysed using the statistical program SPSS version 15.0 (SPSS Inc., Chicago, IL). Data were expressed as mean ± standard deviation if compatible with normal distribution and expressed as median if not compatible with normal distribution. SHIM scores and the SHIM categories previous to treatment and at six months were compared using Wilcoxon signed rank test. A p value < 0.05 was accepted as statistically significant.

Table 1. Inclusion and exclusion criteria

Inclusion criteria:
1. Systolic ejection fraction less than 45% with transthoracic echocardiography
2. Patients on optimal treatment for heart failure according to the European Society of Cardiology 2012 hearth failure guidelines for at least six months, excluding ivabradine
3. Patients with heart rate > 70 bpm
Exclusion criteria:
1. Patients on any medications or herbal drugs for impotence
2. Patients who were surgically treated for benign prostate hyperplasia or patients who were surgically or medically intervened to genitalia
3. Patients younger than 35 and older than 75 years

SHIM test procedure

The SHIM questionnaire is a widely used method for understanding male sexual function [15]. It consists of five questions about erectile functions. In our study a psychiatrist evaluated ED with the internationally validated SHIM questionnaire before the ivabradine therapy and six months after. Scores are classified as 1–7 severe ED, 8–11 moderate ED, 12–16 mild to moderated ED, 17–21 mild ED, and 22–25 no ED. The SHIM questionnaire is shown in Table 2.

RESULTS

The mean age was 53 ± 6.6 years. Eighteen (61%) patients had a diagnosis of hypertension, 14 (42%) patients had a diagnosis of dyslipidaemia and were under statin treatment, 29 (94%) patients had coronary artery disease (at least > 50% coronary artery stenosis) and were accepted as ischaemic cardiomyopathy, and two patients had dilated cardiomyopathy. The mean ejection fraction was 37 ± 5%. The mean resting heart rate before ivabradine therapy was 80 ± 5 bpm and was 65 ± 3 bpm at the sixth month of ivabradine therapy. The characteristics of the patients are shown in Table 3. Two (6.4%) patients had an SHIM score between 21 and 25, indicative of no ED, nine (29%) patients had a SHIM score between 17 and 21, indicative of mild ED, seven (22%) patients had a SHIM score between 12 and 16, indicative of mild-moderate ED, six (19%) patients had a SHIM score of 8–11, indicative of moderate ED, and seven (22%) patients had a SHIM score of 7 or less, indicative of severe ED, before the initiation of ivabradine therapy. At six months of follow-up after ivabradine therapy, the SHIM scores of 22 patients increased and seven patients were promoted to an up-level category (for example from moderate ED to mild-moderate ED) according

Table 2. The Sexual Health Inventory for Men

1. How do you rate your confidence that you could get and keep an erection? Very low: 1 Low: 2 Moderate: 3 High: 4 Very high: 5
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)? No sexual activity: 0 Almost never or never: 1 A few times (much less than half the time): 2 Sometimes (about half the time): 3 Most times (much more than half the time): 4 Almost always or always: 5
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner? Did not attempt intercourse: 0 Almost never or never: 1 A few times (much less than half the time): 2 Sometimes (about half the time): 3 Most times (much more than half the time): 4 Almost always or always: 5
4. During sexual intercourse, how difficult was it to maintain your erection until completion of intercourse? Did not attempt intercourse: 0 Extremely difficult: 1 Very difficult: 2 Difficult: 3 Slightly difficult: 4 Not difficult: 5
5. When you attempted sexual intercourse, how often was it satisfactory for you? Did not attempt intercourse: 0 Almost never or never: 1 A few times (much less than half the time): 2 Sometimes (about half the time): 3 Most times (much more than half the time): 4 Almost always or always: 5

Score: Add the numbers corresponding to questions 1 through 5

to SHIM scores. The SHIM scores of two patients decreased but the ED category of them did not change. The SHIM scores of six patients did not change. After ivabradine therapy a significant increase in mean SHIM scores was noted. The mean SHIM score before ivabradine and after ivabradine was

Table 3. Patient characteristics (n = 31)

Age [years]	53.0 ± 6.6
Hypertension	18/31 (61%)
Coronary artery disease	29/31 (94%)
Dyslipidaemia	14/31 (42%)
Ejection fraction	37 ± 5%
Heart rate before (bpm)	80 ± 5
Heart rate at sixth months (bpm)	65 ± 3
SHIM score before	13.19 ± 5.31
SHIM score at sixth months	14.55 ± 5.52
ED category* before	2.77 ± 1.28
ED category* at sixth months	3.00 ± 1.29
NYHA before	1.81 ± 0.90
NYHA after	2.23 ± 0.83

*Category: 1 — severe ED, 2 — moderate ED, 3 — mild-moderate ED, 4 — mild ED, 5 — no ED; ED — erectile dysfunction; NYHA — New York Heart Association; SHIM — Sexual Health Inventory for Men

13.19 ± 5.31 and 14.55 ± 5.52, respectively ($p < 0.001$). The difference between the SHIM categories before ivabradine and after ivabradine therapy were analysed with related samples using Wilcoxon signed rank test, and a significant difference was observed ($p = 0.008$). A histogram for SHIM scores before and at the sixth month of ivabradine therapy is shown in Figure 1. The difference between the NYHA stages before ivabradine therapy and at sixth months of ivabradine therapy are also analysed with paired samples t test, and a significant difference was noted ($p < 0.000$).

DISCUSSION

Drug side effects are usually blamed for ED and an important cause of cessation of medical therapy. In hypertensive patients the effect of acebutolol, amlodipine, enalapril, chlortalidone, and doxazosin were compared with placebo in a double-blind randomised controlled trial in 912 patients. Incidence of ED in the acebutolol, amlodipine, and enalapril groups was similar to that in the placebo group, and ED increased in chlortalidone group and ED decreased in the doxazosin group. This study showed the importance of medical therapy selection. ED in HF is different than in patients with hypertension. Patients with HF, especially in the end-stage of the disease, are usually not hypertensive and sometimes hypotensive, and the requirement of an enough ejection fraction to fill the corpora cavernosa of the penis might be a major determinant. The effect on libido BB, ACEIs/ARBs, diuretics, and calcium channel blocking agents are all studied in patients with hypertension, but not on HF. Among those, the BBs can improve stroke volume, but all of these agents lower arterial blood pressure and can worsen the penile arterial blood flow in normotensive patients. Only sildenafil is proven to be effective in ED in patients with HF in large randomised controlled trials [16, 17].

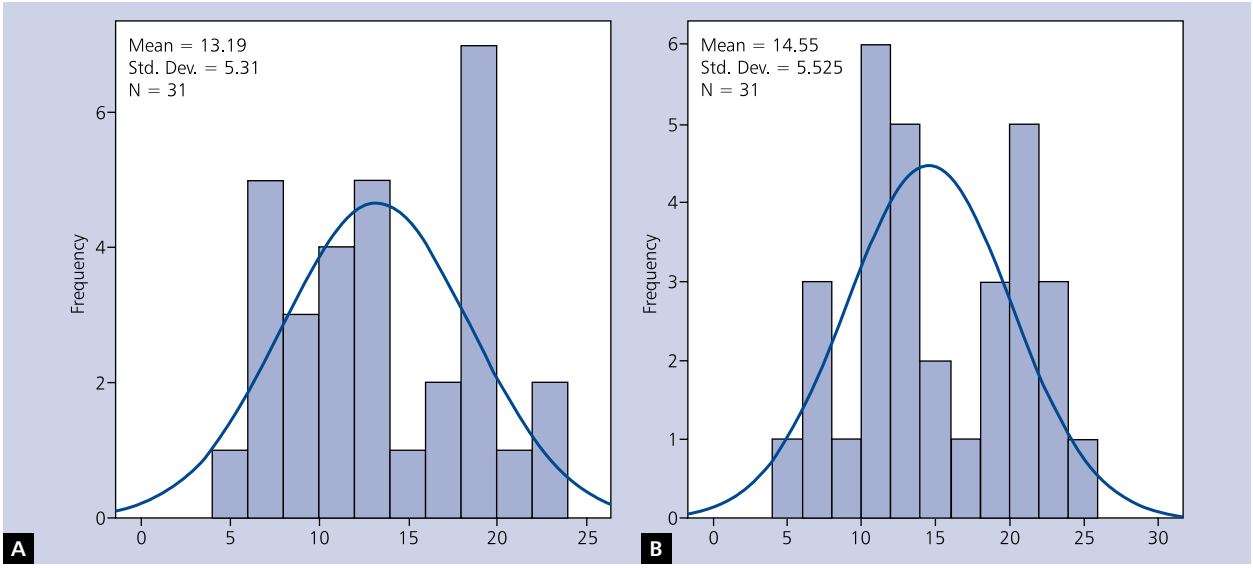

Figure 1. The Sexual Health Inventory for Men scores before (**A**) and at the sixth month (**B**) of ivabradine therapy

Vural et al. [18] also showed the effect of cardiac resynchronisation therapy (CRT) on ED in HF patients in a small group. Similarly, ivabradine increases stroke volume, and this may be the mechanism of better sexual function in patients with HF that we showed in this study. The current science showed that the ED in patients with HF can be improved by filling the corpora cavernosa of the penis by both agents that act locally by dilating the arteries of the penis (sildenafil) or by increasing the cardiac output and eventually increasing the blood in the penile artery (CRT and ivabradine).

On the other hand, endothelial dysfunction or atherosclerosis can be blamed. Baumhakel et al. [19] studied the effect of ivabradine in mice with corpora cavernosa strips and showed that ivabradine preserved endothelial function of the corpora cavernosa of the penis in previously induced endothelial dysfunction with high fat diet. They also showed that treatment with ivabradine did not increase the potency of muscarinergic stimulation, but the efficacy of endothelium-dependent relaxation was increased. The effect of ivabradine on erectile function in humans has not been evaluated. The study on mice explained a mechanism, which is through the positive effect of endothelial function of ivabradine. The results of the study by Baumhakel et al. [19] can be interpreted to humans to explain the pathology of the positive effects of ivabradine, but our study was not designed to explain the pathology and our study lacks investigations to show a mechanism. However, most patients (29/31) had significant coronary artery disease in the background of their HF, and there was a significant increase in their libido. It is possible to say that ivabradine helps to increase libido in patients with HF, but it is early to say the mechanism.

The weakness of our study was that the erectile function was not evaluated by objective methods, like penile Doppler ultrasound. But we believe that that 'feeling of satisfaction' of the patients is more important than ultrasonographic proof and it is actually that matters on their side too.

CONCLUSIONS

In conclusion, this is a novel study that evaluates the effect of ivabradine on humans with HF. Ivabradine seems to improve libido in patients with HF but has to be verified with a larger population.

Acknowledgements

We would like to thank the urology doctors for their support for the recruitment of patients.

Conflict of interest: *none declared*

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Cite this article as: Aydın F, Bektur S, Taşdelen Y, et al. How does ivabradine effect erectile dysfunction in patients with heart failure? Kardiol Pol. 2017; 75(9): 893–898, doi: 10.5603/KP.a2017.0095.

Wpływ iwabradyny na zaburzenia erekcji u pacjentów z niewydolnością serca

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Streszczenie

Wstęp: Zaburzenia erekcji (ED) to całkowita lub częściowa niezdolność do osiągnięcia wzwodu uniemożliwiająca odbycie satysfakcjonującego stosunku płciowego. Częstość ED u chorych z niewydolnością serca (HF) wynosi 56–81%, w zależności od stopnia ciężkości choroby. Pacjenci zwykle uważają, że przyczyną ED są przyjmowane przez nich leki nasercowe. Iwabradyna jest lekiem stosowanym ze względu na swoje przeciwdławicowe działanie oraz w celu poprawienia tolerancji wysiłku i zmniejszenia śmiertelności u chorych z HF. Wiadomo, że większość beta-adrenolityków powoduje ED, jednak w przeciwieństwie do tej grupy leków nigdy nie badano wpływu iwabradyny na ED.

Cel: Celem pracy była ocena wpływu iwabradyny na ED u osób z HF.

Metody: Do badania włączono 31 chorych z HF (sami mężczyźni) stosujących optymalne leczenie pozwalające uzyskać kontrolę choroby (oprócz iwabradyny). Przed zastosowaniem iwabradyny i po 6 miesiącach terapii oceniano sprawność seksualną pacjentów za pomocą kwestionariusza SHIM (*Sexual Health Inventory for Men*). Porównano ocenę wg kwestionariusza SHIM przed leczeniem i po 6 miesiącach terapii, wykorzystując test znakowanych rang Wilcoxona. Jako poziom istotności statystycznej przyjęto wartość $p < 0,05$.

Wyniki: Po 6 miesiącach obserwacji stwierdzono, że leczenie iwabradyną spowodowało poprawę sprawności seksualnej u mężczyzn z prawidłowym libido ($p < 0,001$).

Wnioski: To nowatorskie badanie oceniające wpływ iwabradyny u mężczyzn z HF. Iwabradyna spowodowała poprawę sprawności seksualnej u chorych z HF.

Słowa kluczowe: niewydolność serca, iwabradyna, zaburzenia erekcji

Kardiol Pol 2017; 75, 9: 893–898

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Praca wpłynęła: 22.11.2016 r. **Zaakceptowana do druku:** 20.03.2017 r. **Data publikacji AoP:** 18.05.2017 r.