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Effect of gender and type 2 diabetes mellitus on heart rate recovery in patients with coronary artery disease after cardiac rehabilitation

Wpływ płci i cukrzycy typu 2 na normalizację częstości rytmu serca u pacjentów z chorobą wieńcową po rehabilitacji kardiologicznej

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Abstract

Introduction: The purpose of this study was to clarify whether type 2 diabetic patients with coronary disease are subject to similar benefits in heart rate recovery (HRR) as non-diabetic counterpatrs after cardiac rehabilitation, assessing men and women subjects separately.
Material and methods: The data used for this analysis were from an eight-week, phase-II cardiac rehabilitation including 284 patients with ischaemic heart disease who were managed at Tehran Heart Centre between July 2004 and January 2006. The heart rate parameters were compared between diabetic and non-diabetic patients before and after cardiac rehabilitation. Diabetic and non-diabetic patients had similar age and left ventricular ejection fraction.
Results: Among men, the non-diabetic patients achieved a greater improvement in peak heart rate and heart rate recovery (HRR). Additionally, lower resting heart rate was found in nondiabetic men after rehabilitation. In the women ≥ 50 years old, there was no significant difference between diabetic and non-diabetic. The non-diabetic women < 50 years old showed significantly higher peak heart rate and HRR compared with diabetic women.
Conclusions: These results indicate that the benefit of cardiac rehabilitation in HRR is significantly lower in type 2 diabetic men. Improvement of HRR is not associated with diabetic status in women ≥ 50 years old. The response to cardiac rehabilitation in women may appear to be influenced more by age at menopause rather than diabetes mellitus. **(Pol J Endocrinol 2009; 60 (6): 430–436)**

Key words: *diabetes mellitus, cardiac rehabilitation, heart rate recovery*

Streszczenie

Wstęp: Celem badania było wyjaśnienie czy pacjenci z cukrzycą typu 2 i chorobą wieńcową odnoszą podobne korzyści z rehabilitacji kardiologicznej dotyczące normalizacji częstości rytmu serca (HRR, *heart rate recovery*) jak osoby z chorobą wieńcową bez cukrzycy. Osobno oceniano mężczyzn i kobiety.
Materiał i metody: Dane wykorzystane w analizie pochodziły z 8-tygodniowego II stadium rehabilitacji kardiologicznej przeprowadzonej u 284 pacjentów z chorobą niedokrwienną serca leczonych w Tehran Heart Center w okresie pomiędzy lipcem 2004 roku a styczniem 2006 roku. Porównywano parametry opisujące częstość rytmu serca u osób z cukrzycą i bez cukrzycy, przed i po rehabilitacji kardiologicznej. Pacjenci z cukrzycą i bez cukrzycy charakteryzowali się podobnym wiekiem i zbliżoną frakcją wyrzutową lewej komory.
Wyniki: U mężczyzn bez cukrzycy uzyskano większą poprawę dotyczącą szczytowej częstości rytmu serca i normalizacji HRR. Dodatkowo po rehabilitacji, u mężczyzn bez cukrzycy stwierdzono mniejszą spoczynkową częstość rytmu serca. Nie zaobserwowano znamiennych różnic pomiędzy kobietami z cukrzycą i bez cukrzycy w wieku 50 lat i starszych. Kobiety bez cukrzycy poniżej 50. roku życia charakteryzowały się istotnie większą szczytową częstością rytmu serca i HRR w porównaniu z kobietami z cukrzycą.
Wnioski: Uzyskane wyniki świadczą o tym, że korzyści z rehabilitacji kardiologicznej dotyczące HRR są istotnie gorsze u mężczyzn z cukrzcą typu 2. Poprawa dotycząca HRR u kobiet w wieku 50 lat i starszych nie zależała od obecność cukrzycy. Wydaje się, że u kobiet odpowiedź na rehabilitację kardiologiczną w większym stopniu zależy od wieku, w którym wystąpiła menopauza niż od obecności cukrzycy.
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Słowa kluczowe: *cukrzyca, rehabilitacja kardiologiczna, normalizacja częstości rytmu serca*

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Introduction

Heart rate recovery (HRR), as a powerful tool in the investigation of autonomic modulation of the heart, was demonstrated to be a powerful predictor of all-cause mortality in healthy adults and in individuals with cardiovascular disease [1–4].

Furthermore, HRR has been shown to be inversely associated with insulin resistance, metabolic syndrome, and type 2 diabetes mellitus [5–8].

It has been well established that cardiac rehabilitation is associated with an improvement in HRR in patients with heart failure and ischaemic heart disease [9–11]. It seems that exercise training modifies the autonomic control of cardiovascular function by favourably modulating parasympathetic and sympathetic balance in patients with heart disease. However, age, gender and certain other factors may influence and interfere with the effects of exercise training on neurohumoral tone, as reflected by HRR in cardiac patients [12, 13].

To our knowledge, no previous study has specifically addressed the possible role of gender, and especially the menopausal status, regarding the relationship between diabetes and HRR after cardiac rehabilitation. The purpose of this investigation was to examine the effects of gender and type 2 diabetes mellitus on HRR response to an 8-week, hospital-based cardiac rehabilitation programme in patients with established ischaemic heart disease.

Material and methods

Our study population was drawn from a cohort of 284 patients with ischaemic heart disease (57.47 ± 11.10 years; males: 72.2%) who had enrolled in and completed a 24-session hospital-based cardiac rehabilitation between July 2004 and January 2006. The investigation was approved by the institutional review board governing the participation of human subjects in research at the Tehran University of Medical Sciences. In addition, it conforms to the principles outlined in the Declaration of Helsinki.

The inclusion criteria were selected patients with coronary artery disease who had no previous coronary artery bypass surgery, no neurologic impairment (stroke, peripheral neuropathy, or traumatic brain injury), no severe musculoskeletal disease (fracture, amputation), and no complications during hospitalization, such as severe infection, shock, arrhythmia, or prolonged ventilator dependence. Patients were excluded if they displayed uncontrolled dysrhythmia during exercise training, such as atrial flutter, fibrillation, or continuous ventricular tachycardia, or if ischaemic changes were observed on an electrocardiogram during treadmill exercise. Eligible subjects were patients who were admitted to our tertiary teaching hospital following acute myocardial infarction (AMI) or those who had undergone coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), and percutaneous transvenous mitral commissurotomy (PTMC). Confirmation of eligibility was made by checking their records for diagnosis on the day they were discharged.

Type 2 diabetic patients (n = 68) were studied in comparison with non-diabetic controls (n = 216). The demographic characteristics, atherosclerotic risk factor profiles (including smoking, hyperlipidaemia, family history of CAD, hypertension, and diabetes mellitus), and exercise treadmill parameters were extracted from the Hospital Databank and documents recorded in the Cardiac Rehabilitation Registry. Diabetes mellitus (symptoms of diabetes and plasma glucose concentration ≥ 200 mg/dl or fasting plasma glucose ≥ 126 mg/dl or 2-hp ≥ 200 mg/dl) was diagnosed based on: patients self-report of use of hypoglycaemic medications, fasting glucose measurement, and a recent patient's medical record. Information on other medications, including β-blockers, calcium chanel blockers, angiotensin-converting enzyme (ACE) inhibitors, and anti-hyperlipidaemic agents, were substantiated with use of other registries (*i.e.*, Angiography, CABG, and PTMC) and outpatient clinics.

The complete cardiac rehabilitation program was 20 minutes of cardiovascular exercise on a treadmill for 8 weeks, with a total of 24 exercise sessions (3 per week). There were approximately 20 minutes of stretching and calisthenics for warm-up, and the session finished with 20 minutes of stretching and calisthenics for cool-down. Total duration of each session was approximately 1 hour. The intensity of the aerobic exercise was patient dependent. The training intensity was increased as tolerated by the patients. Heart rate, blood pressure, and exercise intensity were monitored and supervised by a senior cardiopulmonary physical therapist during the exercise session. All patients received psychological and dietary counselling. During the psychological sessions, the patients were offered coping strategies in order to accept and live with their cardiac incident. During the dietary counselling, the subjects received education sessions on healthy nutrition and were included in a food program.

The main measurements were exercise treadmill parameters registered at the first and the last sessions of the cardiac rehabilitation program. These parameters included resting heart rate, peak heart rate achieved during treadmill exercise, post-exercise heart rate, and HRR. Heart rate recovery was defined as the decrease in heart rate from the end of peak exercise to the first minute of the recovery and cool-down period (peak heart rate subtracted by post-exercise heart rate).

Table I. *Clinical and demographic characteristics of patients*

Tabela I. *Kliniczna i demograficzna charakterystyka chorych*

	Diabetic group (n = 68)	Non-diabetic group (n = 216)	p value
Age (years)	58.91 ± 9.39	57.01 ± 11.05	0.203
Women, no.%	31 (45.6%)	48 (22.2%)	< 0.001
Hypertension, no.%	39 (57.4%)	80 (37%)	0.003
Current smoker, no.%	11 (16.2%)	57 (26.5%)	0.082
Hyperlipidaemia, no.%	47 (69.1%)	110 (50.9%)	0.009
Family history, no.%	29 (42.6%)	89 (41.2%)	0.833
LVEF (%)	51.95 ± 9.91	51.84 ± 10.32	0.940
Aspirin, no.%	62 (91.2%)	197 (91.2%)	0.994
β-blockers, no.%	56 (82.4%)	172 (79.6%)	0.623
Calcium channel blockers, no.%	15 (22.10%)	49 (22.7%)	0.914
ACEi, no.%	24 (35.3%)	69 (31.9%)	0.608
Anti-hyperlipidaemic agents, no.%	41 (60.3%)	113 (52.3%)	0.249
Diagnosis, no.%			
CABG	49 (71.1%)	129 (59.7%)	
PCI	11 (16.2%)	33 (15.3%)	0.066
Rother	8 (11.8%)	54 (25.0%)	

LVEF — left ventricular ejection fraction; ACE — angiotensin-converting enzyme inhibitors; CABG — coronary artery bypass grafting; PCI — percutaneous coronary intervention

For the categorical variables, the statistical significance of the difference between the groups was evaluated at baseline and after cardiac rehabilitation using chi-square or Fisher's exact tests. The continuous variables were expressed as the mean ± standard deviation (SD) or median (25%, 75% interquartile range), being parametrical or non-parametrical, respectively. Age and left ventricular ejection fraction (LVEF) were analyzed by Student's *t*-test. The values of the first session (*i.e.* resting heart rate$_1$, peak heart rate$_1$, end-exercise heart rate$_1$, and HRR$_1$) and the end session (*i.e.* resting heart rate$_2$, peak heart rate$_2$, post-exercise heart rate$_2$, and HRR$_2$) were analyzed and compared between and within the two groups using Mann-Whitney U and Wilcoxon Sign tests, respectively. Analyses were performed using the Scientific Package for Social Science version 15 (SPSS Inc., Chicago, IL, USA) and SAS (version 9.1; Copyright 2002–2003 by SAS Institute Inc., Cary, NC, USA). For all comparisons, a p value less than 0.05 was required, to be statistically significance.

Results

Demographic and clinical data for the sample are noted in Table I. No significant differences were observed between diabetic and non-diabetic patients concerning age, LVEF, tobacco smoking, family history of CAD, cause of recent admission (AMI, CABG, PCI, and other procedures), or cardiovascular medications (ACE inhibitors, β-blockers, Ca-channel blockers, aspirin, and hypolipidaemic agents). Moreover, the medical treatments in women < 50 or ≥ 50 years old were similar in the diabetic and non-diabetic groups (Table II). The diabetic subjects were more likely to have hypertension and hyperlipidaemia. In other words, systolic blood pressures in the first and the end sessions were significantly higher in the diabetic patients compared with the controls. Prevalence of female gender was significantly higher in the diabetic group in comparison with nondiabetics (45.6% *v.* 22.2%; $p < 0.001$).

For the men and women, the statistics of resting heart rate, peak heart rate, post-exercise heart rate, HRR, and ΔHRR are listed separately in Tables III and IV. For the men, there was no significant difference between the diabetic and non-diabetic groups in resting hart rate, peak heart rate, and HRR at the first session. After eight weeks of rehabilitation, the groups of diabetic and non-diabetic male patients showed significant increases in peak heart rate and HRR, but significant decreases in resting heart rate. The diabetic male subjects, compared with those without diabetes, showed significantly lower values for peak hart rate (122 [112.5, 131] *v.* 128 [120, 139.5]; $p = 0.019$), HRR (24 [19, 32] *v.* 30 [21, 36]; $p = 0.029$), and ΔHRR (18 [8.5, 23] *v.* 22 [15, 29]; $p = 0.030$) after cardiac rehabilitation.

Table II. *Medical treatment in women < 50 and ≥ 50 years old, comparing diabetic and non-diabetic groups*

Tabela II. *Farmakoterapia u kobiet w wieku < 50 i ≥ 50 lat, porównanie między grupami chorych na cukrzycę i osób bez cukrzycy*

	Age < 50 years		
	Diabetic group (n = 5)	Non-diabetic group (n = 9)	p value
Aspirin, no.%	4 (80%)	7 (77.8%)	0.924
β-blockers, no.%	4 (80%)	7 (77.8%)	0.924
Calcium channel blockers, no.%	1 (20%)	2 (22.2%)	0.923
ACEi, no.%	1 (20%)	2 (22.2%)	0.923
Anti-hyperlipidaemic agents, no.%	2 (40%)	4 (44.4%)	0.873
	Age ≥ 50 years		
	Diabetic group (n = 26)	Non-diabetic group (n = 39)	p value
Aspirin, no.%	24 (92.3%)	35 (89.7%)	0.723
β-blockers, no.%	22 (84.6%)	32 (82%)	0.784
Calcium channel blockers, no.%	6 (23.1%)	8 (20.5%)	0.803
ACEi, no.%	9 (34.6%)	13 (33.3%)	0.914
Anti-hyperlipidaemic agents, no.%	16 (61.5%)	21 (53.8%)	0.539

ACE — Angiotensin-converting enzyme inhibitors

Table III. *Values of treadmill exercise parameters at the first and the end sessions of cardiac rehabilitation in men*

Tabela III. *Parametry opisujące test wysiłkowy na bieżni wykonany na początku i na końcu sesji rehabilitacji kardiologicznej u mężczyzn*

	Diabetic group (n = 37)	Non-diabetic group (n = 168)	p value
Resting heart rate$_1$ [beats/min]	83 (70, 89)	79 (68, 89)	0.346
Peak heart rate$_1$ [beats/min]	98 (85.5, 109)	95 (86, 108)	0.635
Post-exercise heart rate$_1$ [beats/min]	90 (78.5, 97.5)	88 (78, 98)	0.629
Resting heart rate$_2$ [beats/min]	77 (69.5, 83.5)	78 (68, 85)	0.852
Peak heart rate$_2$ [beats/min]	122 (112.5, 131)	128 (120, 139.5)	0.019
Post- exercise heart rate$_2$ [beats/min]	95 (88.5, 107.5)	100 (90, 106)	0.471
HRR$_1$ [beats/min]	6 (5, 10)	7 (5, 10)	0.985
HRR$_2$ [beats/min]	24 (19, 32)	30 (21, 36)	0.029
ΔHRR [beats/min]	18 (8.5, 23)	22 (15, 29)	0.030

HRR — heart rate recovery

Primary analysis in women showed that HRR was significantly lower in diabetic women during the first session compared with non-diabetics, but it was similar at the end session (20 [11, 32] *v.* 18 [10, 25]; p = 0.279). Actually, both groups had a similar pattern of ΔHRR. Neither resting heart rate nor peak heart rate were significantly different between diabetic and non-diabetic women, whether at the first or the end session. After completing the rehabilitation programme, both female groups showed significant increases in peak heart rate and HRR, but significant decreases in resting hart rate. Although the average age was not significantly different between diabetic and non-diabetic female patients (59.13 ± 9.11 *v.* 58.23±10.25; p = 0.692), we performed further analyses to assess the possible role of age with respect to the menopausal effect on heart rate. By using the knowledge of age at menopause among Iranian women [14], a cutoff of < 50 years was considered for the onset of natural menopause in this population. In the women ≥ 50 years, only the first session HRR was significantly lower in diabetic patients in comparison to non-diabetics (5 [3, 10.] *v.* 8 [4, 14]; p = 0.022). However, for women under 50 years of age, the parameters of the first session were found to be similar between diabetic and non-diabetic patients, while after eight weeks of rehabilitation, peak heart rate, HRR, and ΔHRR were significantly lower in diabetic patients compared with non-diabetic patients (Table IV).

Discussion

The concept of the body's physiological response and the therapeutic benefits of physical aerobic training have rapidly increased over recent decades. Exercise training may reduce mortality and protect against adverse cardiovascular events in both healthy individuals and type 2 diabetic patients. Several biological mechanisms have been proposed to this effect, but the relative importance of these exercise-related mechanisms is still unknown. Increased parasympathetic tone is thought to be a protective mechanism of cardiac rehabilitation [15] and can be related to heart rate variability during exercise training. Vagal reactivation mediates the rate at which the heart rate recovers to normal levels after exercise [16–18]. It is known that persistently high heart rates can be a manifestation of cardiac parasympathetic dysfunction in those with type 2 diabetes and that persistently high heart rates at rest significantly correlate with increased mortality in the general population [19, 20].

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Table IV. *Values of treadmill exercise parameters at the first and the end sessions of cardiac rehabilitation in women*

Tabela IV. *Parametry opisujące test wysiłkowy na bieżni wykonany na początku i na końcu sesji rehabilitacji kardiologicznej u kobiet*

	Age < 50 years		
	Diabetic group (n = 5)	Non-diabetic group (n = 9)	p value
Resting heart rate$_1$ [beats/min]	95 (79.5, 95.5)	88 (79, 95)	0.797
Peak heart rate$_1$ [beats/min]	111 (100.5, 116.5)	100 (95, 111)	0.240
Post-exercise heart rate$_1$ [beats/min]	99 (91, 108.5)	92 (86, 107)	0.438
Resting heart rate$_2$ [beats/min]	81 (69, 89.5)	77 (72, 89)	0.699
Peak heart rate$_2$ [beats/min]	111 (107, 125)	130 (124, 138)	0.012
Post- exercise heart rate$_2$ [beats/min]	100 (92.5, 103.5)	105 (85, 108)	0.606
HRR$_1$ [beats/min]	8 (3, 16)	8 (4.5, 10.5)	1.000
HRR$_2$ [beats/min]	17 (8, 25)	31 (24, 39.5)	0.019
ΔHRR [beats/min]	4 (–1.5, 17.5)	27 (17.5, 30)	0.029
	Age ≥ 50 years		
	Diabetic group (n = 26)	Non-diabetic group (n = 39)	p value
Resting heart rate$_1$ [beats/min]	87 (79, 96)	86 (72, 92)	0.241
Peak heart rate$_1$ [beats/min]	105 (91, 112)	98 (94, 12)	0.979
Post-exercise heart rate$_1$ [beats/min]	96 (84, 102)	91 (85, 99)	0.417
Resting heart rate$_2$ [beats/min]	77 (66, 83)	74 (65, 84)	0.753
Peak heart rate$_2$ [beats/min]	110 (97, 128)	114 (101, 123)	0.529
Post- exercise heart rate$_2$ [beats/min]	89 (81, 100)	90 (82, 98)	0.902
HRR$_1$ [beats/min]	5 (3, 10)	8 (5, 14)	0.022
HRR$_2$ [beats/min]	19 (10, 27)	17 (10, 29)	0.913
ΔHRR [beats/min]	10 (4, 19)	7.5 (–6, 24)	0.627

HRR — heart rate recovery

One of the main findings of this study, based on the pre-and post-exercise training condition, is that a 24-session cardiac rehabilitation programme for patients with ischaemic heart disease leads to significant improvements in cardiovascular autonomic function of HRR, comparing pre- and post-exercise training condition. It could serve as a potential adjunct therapy in the management of CAD with or without type 2 diabetes. However, 8.4% of the present population did not show any improvement in HRR. From this small subset, 62.5% were women ≥ 50 years old. It is in agreement with the previous study by Kligfield et al. [9], who found a decrease in HRR in about 9% of the subjects after 12 weeks of rehabilitation. They studied only a group of patients > 65 years old, which was disproportionately female. In our sample, there was a strong correlation between gender and diabetes mellitus.

Therefore, we analyzed separately the role of gender and type 2 diabetes mellitus on HRR after cardiac rehabilitation. Previous studies have demonstrated that vagal modulation of heart rate during exercise is independent of age [21]. However, Hao et al. [22] showed the proportional increase in HRR after training in older patients was greater than that found in younger patients, suggesting that older patients derive much benefit from exercise training. In our study, non-diabetic and diabetic patients were matched for age in both genders, and the possible age-related effect on HRR was omitted.

Our data showed, as was expected, that a lower improvement of HRR is associated with type 2 diabetic status among male patients, according to previous studies. The lower heart rate response to exercise in diabetics could possibly result from inappropriate secretion of catecholamines in the heart [23–27]. It was also suggested that the sensitivity of the sinus node to norepinephrine is deteriorated in diabetic patients [25]. In primary analysis (data not shown), we found no significant different between diabetic and non-diabetic women pertaining to improvement of HRR. Although both groups had a similar average age, we tested another hypothesis considering ≥ 50 years old as the age of menopause for Iranian women [14]. In women under the age of natural menopause, eight-week exercise training resulted in a higher peak heart rate, HRR, and ΔHRR in non-diabetic patients compared with diabetics. However, diabetic status had no significant effect on peak heart rate and HRR in women older than the set age at menopause. Kuo et al. [28] demonstrated that women younger than 50 years old have dominant vagal and subordinate sympathetic activity compared with age-matched men. However, gender-related differences were not detected in older subjects. Given the correlation between female gender and type 2 diabetes mellitus, as well as the distinct effect of hormonal changes on autonomic balance in menopause transition, it is surprising that diabetes and menopause status share an effect on heart rate. To explain this, we propose a hypothesis which states that decreased hormonal stores cause remarkable autonomic neural dysfunction, which exceeds the effects of diabetes mellitus in patients with CAD. Consistent with these results, it was shown that there are some links between hormonal changes, insulin resistance, and higher levels of cardiovascular risk factors in women with polycystic ovary syndrome. These associations appear to be particularly strong in women who are younger [29]. In other words, one would predict that pre-menopausal women would be the most likely to benefit from a tight control of hyperglycaemia, not to develop a non-responsive status of autonomic balance. However, most human studies [12, 15, 30–32] have not demonstrated a significant difference in spontaneous autonomic activity between postmenopausal women with oestrogen replacement therapy and those without it. Until now, the role of oestrogen in the autonomic control of gender-related differences or menopausal autonomic changes has remained ambiguous.

One limitation of this study is its retrospective design with inherent bias. Although heart rate, blood pressure, and exercise intensity were monitored and supervised by a senior cardiopulmonary physical therapist for all patients, baseline and follow-up exercise stress tests were not performed and the data was recorded during treadmill exercise training. Nevertheless, these findings seem to be an indicator of parameters of exercise stress test. Ideally, however, the study needs to be confirmed in a prospectively conducted randomized trial with entry and exit exercise stress testing.

Conclusions

Exercise training within a structured programme of cardiac rehabilitation was correlated with a significant increase in peak heart rate, HRR, regardless of the clinical and demographic characteristics of patients with coronary artery disease. However, the male patients with type 2 diabetes mellitus were less likely to achieve the improvements for these parameters after cardiac rehabilitation. In women younger than menopausal age, there was a similar pattern with respect to the effects of diabetes. Despite of the lack of enough evidence concerning the association between the study outcomes and autonomic balance, heart rate might be more influenced by postmenopausal status rather than diabetes mellitus after cardiac rehabilitation in women.

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