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ORIGINAL ARTICLE

Heart rate recovery in hypertensive patients: relationship with blood pressure control

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Delayed heart rate recovery (HRR) post treadmill exercise testing reflects autonomic dysfunction and is related to worse cardiovascular outcome. The present study compared HRR in normotensive subjects and hypertensive patients taking antihypertensive medications with controlled blood pressure (BP) and uncontrolled BP. A total of 279 consecutive patients with ($n = 140$, HP) and without ($n = 139$, N-HP) essential hypertension who were hospitalized in our department during May 2012 to March 2016 were included in this study. All subjects underwent treadmill exercise testing. Hypertensive patients were divided into controlled BP ($n = 88$) and uncontrolled BP ($n = 52$) groups according to their BP prior to treadmill exercise testing. Body mass index, triglyceride level and incidence of diabetes mellitus (DM) were significantly higher in the HP group than in the N-HP group, and HDL-c and HRR were significantly lower. Male gender, higher creatinine value and lower cholesterol and HDL-c were associated with lower HRR in the N-HP group, and higher triglyceride, lower LDL-c, and HDL-c were associated with lower HRR in the HP group. More frequent, $\geqslant 3$, antihypertensive drug use, less monotherapy use and high incidence of smokers and lower HRR were found in hypertensive patients with uncontrolled BP compared to hypertensive patients with controlled BP. The present results demonstrate that uncontrolled BP following antihypertensive medication is associated with lower HRR in hypertensive patients.

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INTRODUCTION

Hypertension remains a major public health problem that is associated with considerable morbidity and mortality.[1] The rate of decline in heart rate (HR) after exercise (HR recovery, or HRR) reflects the status of vagal tone activation and sympathetic tone withdraw post exercise. Lower HRR represents an autonomous imbalance and is related to a worse cardiovascular outcome.[2] Previous studies have shown reduced HRR in hypertensive patients.[3,4] The impact of BP control on HRR in hypertensive patients is not fully understood. Beta-blockers are widely used to lower BP in hypertensive patients and exert a direct impact on HR. Previous studies have shown that HRR maintained its prognostic value in heart failure patients, regardless of beta-blocker use.[5] Karnik *et al.*[6] demonstrated that beta-blockers do not affect HRR in patients with a negative exercise stress echocardiography result and that HRR may be used for mortality prediction in these patients. HRR is improved in the presence of beta-blockers in patients with a positive exercise stress echocardiography result.[6] The impact of beta-blockers on hypertensive patients has not been reported. The present study compared the HRR between hospitalized normotensive subjects and hypertensive patients and between hypertensive patients with controlled and uncontrolled BP in the absence and presence of beta-blockers.

PATIENTS AND METHODS

Study population

A total of 279 consecutive hospitalized patients with ($n = 140$) and without ($n = 139$) diagnoses of essential hypertension who underwent treadmill exercise tests and achieved the submaximal goal HR [$(220 - \text{age}) \times 0.85$] during May 2012 to March 2016 were included in this retrospective study. Patients with acute coronary syndrome, old myocardial infarction, complete left bundle branch block, WPW syndrome, atrial fibrillation, valvular heart disease and known non-ischemic cardiomyopathy were excluded. Patients treated with digitalis were also excluded. The local hospital ethics committee approved the study protocol, and written consent was obtained from each participating patient. All hypertensive patients received antihypertensive medication. Venous blood samples were obtained for lipid measurements following an overnight fast.

Treadmill exercise test

The treadmill exercise test was performed as previously described on a GE T2100 treadmill machine equipped with CASE6.5 software and exercise ECG test system according to the ACC/AHA 2002 guideline update for exercise testing.[7] Symptom-limited Bruce's protocol was used, and a surface 12-lead ECG was continuously monitored. BP was measured and recorded at rest, the end of each stress stage, peak stress, and recovery until six minutes after exercise or ST segment returned to the baseline level.[8,9] The exercise was stopped at the time of submaximal goal HR [$(220 - \text{age}) \times 0.85$]. The treadmill test was performed according to the Bruce plan: the initial speed was of the treadmill was 1.7 km h^{-1}, slope 10°; the second speed was 2.5 km h^{-1}, slope 12°; the third speed was 3.4 km h^{-1}, slope 14°; and the fourth speed was 4.2 km h^{-1}, slope 16°. The speed increased every 3 min. HR and BP at rest and after exercise were measured in a sitting position using the method proposed by the American Heart Association.[10] HRR1 for the treadmill exercise test was the difference between the maximum HR in motion and the HR one minute after the test. Abnormal HRR1 was defined as $\leqslant 24$ beats per minute.[11] The HR and HRR at 2, 3, 4 and 5 min after exercise were also analyzed.

Figure 1 shows HR and HRR changes after exercise.[4] The overall kinetics of HR or HRR during the transition from exercise peak to rest 1–5 min was described using the following mono-exponential function:[4]

$$\text{HR(or HRR)}(t) = a0 + a1 \times \left(1 - e^{-t/T}\right)$$

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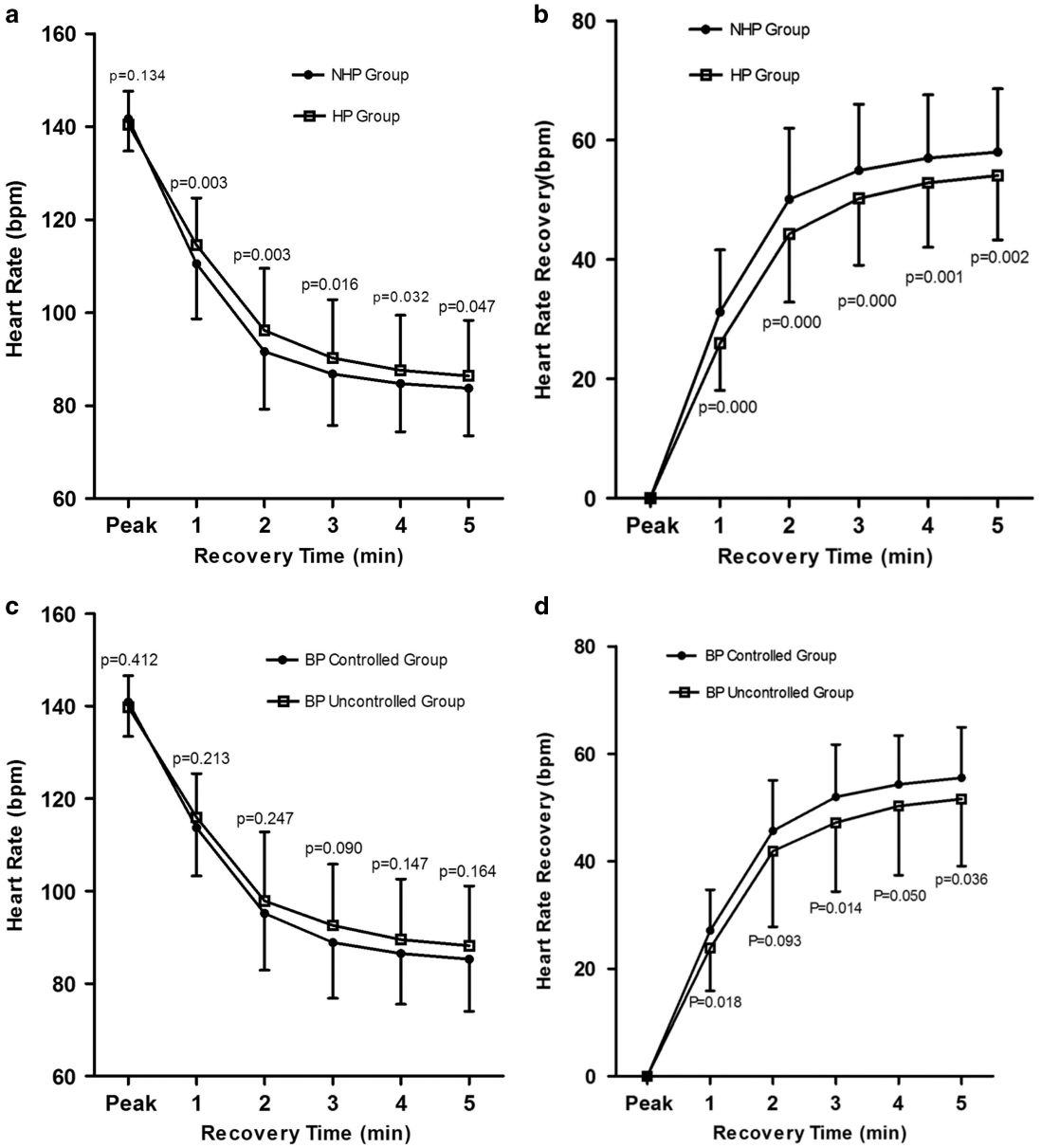

Figure 1. (**a**, **b**) HR change and HRR change post-exercise for the HP and NHP groups; (**c**, **d**) HR change and HRR change post-exercise for the BP uncontrolled and BP controlled groups. *P*-values at individual data points represent the *P*-value between groups at that specific time point. The data are shown as the mean ± s.d.

where *a*0 is the pre-recovery value of HR (or HRR) of exercise peak and *a*1 is the amplitude of the change in HR (or HRR) from *a*0. T is the recovery time constant (mean response time) and represents the time required to attain 63% of the steady-state amplitude. The model parameters were estimated using least-squares nonlinear regression, in which the best fit was defined by minimizing the residual sum of squares and minimal variation of residuals.

Follow-up

Patients were followed up for 3–48 months, with an average follow-up time of 18.8 ± 11.7 months, by phone call or home/clinic visit.

Statistical analysis

Continuous data are expressed as the mean ± standard deviation. Student's *t*-test was used for comparisons between groups. The chi-square test was used to compare the rates. The risk factors for hypertension were determined using multivariate logistic regression model after adjusting for age and gender. *P*-values < 0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS 19.0 software (Armonk, NY, USA).

RESULTS

Clinical features of patients in N-HP and HP groups

Table 1 shows the clinical characteristics between N-HP and HP patients. Body mass index (BMI), triglyceride level and incidence of DM were significantly higher in the HP group than in the N-HP group, and HDL-c and HRR were significantly lower. BP was significantly higher in the HP group than the N-HP group before treadmill exercise, at peak exercise and 1 and 5 min post exercise. HR was significantly higher and HRR was significantly lower in the HP group than the N-HP group at 1–5 min after exercise. The percent of manual labour was similar between the N-HP and HP

groups, and education status was better in the HP group than in the N-HP group.

Multiple regression analysis showed that history of DM, higher BMI, TG values, education level, and reduced HRR post exercise were risk factors and that higher HDL-c was a protective factor of HP after adjusting for gender and age (Table 2). Figure 1a and b show the HR and HRR changes post exercise in the N-HP and HP groups.

Clinical features and risk factor comparison between N-HP and HP patients with normal and reduced HRR

Table 3 shows the clinical features of N-HP and HP patients with normal or reduced HRR. Male gender, smoking, BMI and creatinine values were higher in non-HP subjects, and CHOL and HDL-c values were lower in the reduced HRR group compared with the normal HRR group. TG was higher in HP subjects, while LDL-c and HDL-c were lower in the reduced HRR group compared to the normal HRR group.

Clinical features of hypertensive patients with controlled and uncontrolled BP

The incidence of smokers, CCB use and patients with reduced HRR were significantly higher in hypertensive patients with uncontrolled BP compared with hypertensive patients with controlled BP. The incidence of monotherapy was higher and $\geqslant 3$ drug therapy regimens was lower in hypertensive patients with controlled BP compared with hypertensive patients with uncontrolled BP. HRR1, HRR3 and HRR5 were significantly lower and peak exercise BP and BP at 1 min post exercise was significantly higher in hypertensive patients with uncontrolled BP compared to hypertensive patients with controlled BP. The percentages of manual labour occupation and education level were similar between hypertensive patients with uncontrolled and controlled BP (Table 4). Figures 1c and d show the HR and HRR changes post exercise in hypertensive patients with controlled and uncontrolled BP.

Clinical features of hypertensive patients with or without beta-blockers

We divided the hypertensive patients into without beta-blockers group and with beta-blockers group to observe the potential impact of beta-blockers on HRR in hypertensive patients (Table 5). Our results demonstrated that the clinical characteristics, including HRR, were comparable between the groups, which suggest that HRR was not significantly affected by beta-blockers in hypertensive patients.

Follow-up results

Two patients were lost to follow-up, one patient in the HP group and the other in the N-HP group. There were no deaths or acute myocardial infarctions during the follow-up. Three of the 97 patients (3.1%) in the N-HP group with normal HRR and two of the 41 patients (4.9%) in the N-HP group with reduced HRR were hospitalized due to cardiac reasons. Three of the 74 patients (4.1%) in the HP group with normal HRR and three of the 65 patients (4.6%) in the HP group with reduced HRR were hospitalized due to cardiac reasons. The incidence of re-hospitalization due to cardiac reasons was similar among groups.

DISCUSSION

This study found that HRR was significantly lower in hypertensive patients compared with non-hypertensive patients. HRR was also significantly lower in hypertensive patients with uncontrolled BP compared with hypertensive patients with controlled BP. Our data

Table 1. Clinical characteristic of N-HP patients and HP patients

	N-HP (n = *139*)	*HP* (n = *140*)	P-*value*
Age (yr)	57.17 ± 6.14	58.72 ± 7.29	0.056
Male gender (*n*, %)	49/139 (35.3%)	58/140 (41.4%)	0.289
BMI (kg/m^2)	23.16 ± 3.43	25.18 ± 3.48	0.000
Smoker (*n*, %)	32/139 (23.0%)	45/140 (32.1%)	0.088
Manual labour (*n*, %)	84/139 (60.4%)	90/140 (64.3%)	0.506
Education (n, *%)*			0.013
Primary school and below (*n*, %)	29/139 (20.9%)	12/140 (8.6%)	
Middle school (*n*, %)	44/139 (31.7%)	46/140 (32.9%)	
High school (*n*, %)	56/139 (40.3%)	62/140 (44.3%)	
University and above (*n*, %)	10/139 (7.2%)	20/140 (14.3%)	
CAD (*n*, %)	47/139 (33.8%)	45/140 (32.1%)	0.767
DM (*n*, %)	12/139 (8.6%)	27/140 (19.3%)	0.010
Dyslipidemia (*n*, %)	102/139 (73.4%)	116/140 (82.9%)	0.056
Creatinine (μM)	64.89 ± 14.34	66.18 ± 14.71	0.459
CHOL (mM)	4.89 ± 0.94	4.75 ± 1.07	0.235
TG (mM)	1.59 ± 1.37	2.14 ± 1.71	0.003
LDL-c (mM)	2.95 ± 0.80	2.84 ± 0.98	0.294
HDL-c (mM)	1.20 ± 0.37	1.07 ± 0.32	0.001
HR before Ex (b.p.m.)	79.68 ± 11.58	80.91 ± 12.21	0.386
Peak HR (b.p.m.)	141.73 ± 6.95	140.46 ± 7.17	0.134
HR1 (b.p.m.)	110.55 ± 11.88	114.54 ± 10.11	0.003
HRR1 (b.p.m.)	31.19 ± 10.43	25.92 ± 7.86	0.000
HRR1 $\leqslant$ 24 b.p.m. (*n*, %)	41/139(29.5%)	65/140 (46.4%)	0.004
HR2 (b.p.m.)	91.63 ± 12.41	96.19 ± 13.32	0.003
HRR2 (b.p.m.)	50.09 ± 11.88	44.27 ± 11.49	0.000
HRR2 $\leqslant$ 42 b.p.m. (*n*, %)	34/139 (24.5%)	63/140 (45.0%)	0.000
HR3 (b.p.m.)	86.81 ± 11.05	90.25 ± 12.57	0.016
HRR3 (b.p.m.)	54.91 ± 11.10	50.21 ± 11.20	0.000
HR4 (b.p.m.)	84.76 ± 10.39	87.63 ± 11.85	0.032
HRR4 (b.p.m.)	56.97 ± 10.61	52.83 ± 10.80	0.001
HR5 (b.p.m.)	83.72 ± 10.22	86.38 ± 11.97	0.047
HRR5 (b.p.m.)	58.01 ± 10.59	54.08 ± 10.80	0.002
SBP before Ex (mm Hg)	119.47 ± 12.27	130.49 ± 14.34	0.000
DBP before Ex (mm Hg)	75.43 ± 8.19	80.76 ± 8.93	0.000
SBP peak (mm Hg)	156.30 ± 22.96	175.13 ± 20.20	0.000
DBP peak (mm Hg)	73.50 ± 11.23	80.20 ± 11.33	0.009
SBP at 1 min post Ex (mm Hg)	134.66 ± 18.06	150.11 ± 21.39	0.000
DBP at 1 min post Ex (mm Hg)	75.42 ± 7.75	79.39 ± 10.09	0.016
SBP at 5 min post Ex (mm Hg)	124.65 ± 17.84	138.26 ± 16.77	0.000
DBP at 5 min post Ex (mm Hg)	76.25 ± 7.57	80.94 ± 9.50	0.000
Time for Ex (minute)	4.52 ± 1.86	4.24 ± 1.72	0.203
Exercise tolerance (Mets)	6.34 ± 1.69	6.36 ± 1.77	0.911
Ejection fraction	0.62 ± 0.06	0.63 ± 0.07	0.541
medication			
Aspirin use (*n*, %)	77/139 (55.4%)	90/140 (64.2%)	0.130
Statin use (*n*, %)	92/139 (66.2%)	98/140 (70.0%)	0.494
Bata-blockers use (*n*, %)	42/139 (30.2%)	70/140 (50.0%)	0.001
ACEI use (*n*, %)	6/139 (4.3%)	39/140 (27.9%)	0.000
ARBs use (*n*, %)	0/139 (0.0%)	41/140 (29.3%)	0.000
CCB use (*n*, %)	16/139 (11.5%)	93/140 (66.4%)	0.000
Diuretics use (*n*, %)	0/139 (0.0%)	12/140 (8.6%)	0.000

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARBs: angiotensin receptor blockers; BMI, body mass index; CAD, coronary artery disease; CCB, Calcium Channel Blockers; CHOL, cholesterol; DBP, diastolic blood pressure; DM, diabetes mellitus; Ex, treadmill exercise; HDL-c, high density lipoprotein cholesterol; HP, hypertensive; HR, heart rate; HRn, heart rate at n minute post exercise; HRR, heart rate recovery; HRRn, heart rate recovery at n minute post exercise; LDL-c, low density lipoprotein cholesterol; Mets, metabolic equivalents (1MET = 3.5 ml kg^{-1} per minute of oxygen consumption); N-HP, normotensive; SBP, systolic blood pressure; TG, triglyceride; yr, year.

indicate that more intensive BP control is essential to improve the autonomous balance and outcome for hypertensive patients and HRR, which is an inexpensive and easily available biomarker. HRR should be monitored to guide anti-hypertensive therapy. To the best of our knowledge, this study is the first report describing the association between HRR and BP in hypertensive patients receiving anti-hypertensive therapy.

Reduced HRR and hypertension

The present study found that HRR was reduced in hospitalized patients with hypertension compared with hospitalized patients without hypertension, which is consistent with previous studies.[3,4] Multiple regression analysis demonstrated that besides history of DM, higher BMI and TG values, reduced HRR1–HRR5 were also important risk factors of hypertension after adjusting for gender and age. Notably, our results showed that HRR1, HRR3 and HRR5 were significantly lower in hypertensive patients with uncontrolled BP than in hypertensive patients with controlled BP. This novel finding suggests that optimal BP after anti-hypertensive medication is related to an improved sympathetic/vagal balance in hypertensive patients. As expected, the percent of patients using a combined drug therapy regimen was higher in hypertensive patients with uncontrolled BP, and the percent of monotherapy use was more often seen in hypertensive patients with controlled BP. These results indicate that the sympathetic/vagal imbalance in patients with uncontrolled BP might serve as a reason for the uncontrolled BP despite the use of medications according to the current guideline.[12] Strategies that aim to improve sympathetic/vagal imbalance might be important to treat patients with uncontrolled BP in addition to guideline-conforming antihypertensive medications.

Risk stratification for patients with severe cardiovascular diseases, such as in chronic heart failure patients (NYHA II or III) with left ventricular ejection fraction $\leqslant 40\%$[13] could be already made by lower HRR ($\leqslant$18 per minute), and higher HRR might be applicable to patients with relatively 'mild' cardiovascular diseases, as in the case of uncomplicated essential hypertension shown in this study and in patients with stable heart failure ($\leqslant$24/minute).[14] The mean HRR in the present study cohort was 31 ± 10 for non-hypertensive patients and 26 ± 8 for hypertensive patients. We used HRR $\leqslant 24$ beats/minute as the cutoff value for HRR, following Gharacholou *et al*.[11] We examined the results by defining HRR $\leqslant 18$ beats per minute as the cutoff value for HRR and found that abnormal HRR was 11.5% in the non-hypertension group and 20.0% in the hypertension group. Abnormal HRR was 18.2% in the BP controlled group and 23.1% in the BP uncontrolled group.

Potential impact of beta-blockers, gender, smoking, BMI, triglyceride level, manual labour occupation, and education status on HRR in hypertensive patients

Previous studies explored the potential impact of beta-blockers on HRR in heart failure patients[5] and ischemic patients,[6] but studies investigating the impact of beta-blockers on HRR in hypertensive patients are scant. Our results showed comparable results between hypertensive patients receiving beta-blockers and hypertensive patients who were not treated with beta-blockers (Table 5), which suggest that HRR post exercise was not significantly affected by beta-blockers in this patient cohort.

As there were 19% more smokers and 14% more males in the uncontrolled hypertensive group compared to the hypertensive patients with controlled BP group, gender and smoking status might be linked to the reduced HRR in the uncontrolled hypertensive group. We examined the HRR after adjusting for gender and smoking, and the results showed that HRR1 $\leqslant 24$ remained a risk factor for uncontrolled BP (Table 6). Therefore, the difference in HRR between hypertensive patients with controlled and uncontrolled BP is unlikely induced by gender and smoking. Notably, the BMI was significantly higher in hypertensive patients compared to non-hypertensive patients, but the BMI was near the normal range in this study patient cohort. Therefore, caution is required in the interpretation of the present data, and future studies are warranted to explore the association between HRR and hypertension, including goal BP control in obese hypertensive patients. Our results showed relatively high triglyceride levels, although 67–75% of the patients received a lipid-lowering medication (statin). the underlying reasons for this result are not fully clear, but poor drug compliance might be a possible reason for this result. Another factor might be the impact of dietary habits because dietary carbohydrate content is generally very high in the Chinese population, which might be another reason to explain the high triglyceride levels despite statin use. Future studies should explore the lipid-lowering efficacy of statins in various dietary plans. The percent of patients with a manual labour occupation was similar between the N-HP and HP groups. Therefore, the impact of manual labour occupations on the development of hypertension in this patient cohort might be minimal. The

Table 2. Multivariate logistic regression results for risk of HP

	B	*s.e.*	*Wald*	P-*value*	*Exp*	*95% CI lower limit*	*95% CI upper limit*
BMI (kg m^{-2})	0.194	0.041	22.600	0.000	1.214	1.121	1.316
Education			10.345	0.016			
Middle school (*n*, %)	0.930	0.407	5.215	0.022	2.534	1.141	5.629
High school (*n*, %)	1.062	0.397	7.137	0.008	2.891	1.327	6.229
University and above (*n*, %)	1.613	0.534	9.116	0.003	5.018	1.761	14.296
DM (*n*, %)	0.951	0.377	6.357	0.012	2.588	1.236	5.422
TG (mM)	0.321	0.108	8.834	0.003	1.379	1.116	1.704
HDL-c (mM)	−1.221	0.405	9.116	0.003	0.295	0.133	0.651
HRR1 (b.p.m.)	0.059	0.015	16.196	0.000	1.061	1.031	1.092
HRR1 $\leqslant 24$ (%)	0.653	0.258	6.389	0.011	1.921	1.158	3.188
HRR2 (b.p.m.)	0.043	0.012	13.162	0.000	1.044	1.020	1.068
HRR2 $\leqslant 42$ (%)	0.959	0.278	11.860	0.001	2.608	1.512	4.501
HRR3 (b.p.m.)	0.036	0.012	8.887	0.003	1.036	1.012	1.060
HRR4 (b.p.m.)	0.033	0.012	7.221	0.007	1.034	1.009	1.059
HRR5 (b.p.m.)	0.031	0.012	6.459	0.011	1.032	1.007	1.057

Abbreviations: BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; HDL-c, high-density lipoprotein cholesterol; HP, hypertensive; HRR, heart rate recovery; HRRn, heart rate recovery at n minute post exercise; TG, triglyceride.

Table 3. Clinical characteristics of N-HP and HP patients with normal HRR1 and abnormal HRR1

	N-HP		*HP*	
	Normal HRR1 (n = *98*)	*Reduced HRR1* (n = *41*)	*Normal HRR1* (n = *75*)	*Reduced HRR1* (n = *65*)
Age (yr)	56.82 ± 5.95	58.02 ± 6.56	58.51 ± 7.30	58.97 ± 7.33
Male gender (*n*, %)	28/98 (28.6%)	21/41 (51.2%)*	26/75 (34.7%)	32/65 (49.2%)
BMI (kg m^{-2})	22.78 ± 3.63	24.07 ± 2.71*	24.94 ± 3.50	25.46 ± 3.48
Smoker (*n*, %)	18/98 (18.4%)	14/41(31.4%)*	19/75 (25.3%)	26/65(31.4%)
Manual labour (*n*, %)	56/98(57.1%)	28/41 (51.2%)	51/75 (68.0%)	39/65 (60.0%)
*Education (*n*, %)*				
Primary school and below (*n*, %)	23/98 (23.5%)	6/41 (14.6%)	7/75 (9.3%)	5/65 (7.7%)
Middle school (*n*, %)	30/98 (30.6%)	14/41 (34.1%)	27/75 (36.0%)	19/65 (29.2%)
High school (*n*, %)	40/98 (40.8%)	16/41 (39.0%)	31/75 (41.3%)	31/65 (47.7%)
University and above (*n*, %)	5/98 (5.1%)	5/41 (12.2%)	10/75 (13.3%)	10/65 (15.4%)
CAD (*n*, %)	30/98 (30.6%)	17/41(41.5%)	21/75 (28.0%)	24/65 (40.0%)
DM (*n*, %)	8/98 (8.2%)	4/41(9.8%)	11/75(14.7%)	16/65 (24.6%)
Dyslipidemia (*n*, %)	74/98 (75.5%)	28/41(68.3%)	62/75(82.6%)	54/65 (83.1%)
Creatinine (μM)	62.21 ± 12.99	71.31 ± 15.50*	64.92 ± 14.21	67.63 ± 15.24
CHOL (mM)	5.03 ± 0.92	4.56 ± 0.89*	4.89 ± 1.10	4.59 ± 1.01
TG (mM)	1.43 ± 0.92	1.98 ± 2.05	1.95 ± 1.80	2.37 ± 1.59†
LDL-c (mM)	3.05 ± 0.83	2.72 ± 0.69	2.99 ± 1.05	2.68 ± 0.88†
HDL-c (mM)	1.27 ± 0.39	1.06 ± 0.25*	1.13 ± 0.30	1.01 ± 0.32†
HR before Ex (b.p.m.)	78.05 ± 11.51	83.56 ± 10.93*	77.51 ± 10.49	84.85 ± 12.94†
Peak HR (b.p.m.)	141.93 ± 6.74	141.24 ± 7.51	141.03 ± 6.94	139.80 ± 7.42
HR1 (b.p.m.)	105.76 ± 9.62	122.02 ± 8.43*	109.21 ± 8.35	120.68 ± 8.37†
HR2 (b.p.m.)	87.83 ± 10.94	100.73 ± 11.00*	91.51 ± 11.48	101.58 ± 13.33†
HRR2 (b.p.m.)	54.10 ± 10.63	40.51 ± 8.95*	49.52 ± 9.71	38.22 ± 10.40†
HRR2 ⩽ 42 b.p.m. (*n*, %)	11/98 (11.2%)	23/41 (56.1%)*	16/75 (21.3%)	47/65 (72.3%)†
HR3 (b.p.m.)	83.52 ± 10.04	94.68 ± 9.33*	85.65 ± 10.72	95.55 ± 12.54†
HRR3 (b.p.m.)	58.41 ± 10.07	46.56 ± 8.83*	55.37 ± 9.72	44.25 ± 9.80†
HR4 (b.p.m.)	82.34 ± 9.62	90.54 ± 9.98*	83.60 ± 9.52	92.28 ± 12.61†
HRR4 (b.p.m.)	59.59 ± 10.11	50.71 ± 9.12*	57.43 ± 9.38	47.52 ± 9.91†
HR5 (b.p.m.)	81.38 ± 9.76	89.32 ± 9.17*	82.40 ± 10.17	90.97 ± 12.31†
HRR5 (b.p.m.)	60.55 ± 10.51	51.93 ± 8.07*	58.63 ± 9.53	48.83 ± 9.79†
SBP before Ex (mm Hg)	118.27 ± 12.75	122.34 ± 10.64	127.92 ± 14.22	133.46 ± 14.00†
DBP before Ex (mm Hg)	74.74 ± 8.49	77.07 ± 7.26	80.03 ± 9.02	81.62 ± 8.82
SBP peak (mm Hg)	157.98 ± 21.94	149.58 ± 26.65	174.33 ± 23.57	176.33 ± 14.63
DBP peak (mm Hg)	73.81 ± 11.13	72.25 ± 12.05	81.00 ± 21.25	79.00 ± 10.19
SBP at 1 min post Ex (mm Hg)	132.91 ± 17.65	140.85 ± 18.88	148.06 ± 23.58	152.42 ± 18.74
DBP at 1 min post Ex (mm Hg)	74.96 ± 7.96	77.08 ± 6.99	80.00 ± 10.79	81.18 ± 8.39
SBP at 5 min post Ex (mmHg)	123.33 ± 17.81	127.84 ± 17.74	136.29 ± 18.67	139.88 ± 15.04
DBP at 5 min post Ex (mm Hg)	75.57 ± 7.58	77.92 ± 7.38	80.64 ± 10.79	81.18 ± 8.39
Time for Ex (minute)	4.40 ± 1.74	4.79 ± 2.11	4.29 ± 1.71	4.20 ± 1.74
Exercise tolerance (Met)	6.19 ± 1.60	6.70 ± 1.88	6.41 ± 1.65	6.31 ± 1.90
Ejection fraction medication	0.62 ± 0.06	0.62 ± 0.05	0.63 ± 0.07	0.63 ± 0.06
Aspirin use (*n*, %)	54/98 (55.1%)	23/41 (56.1%)	49/75 (65.3%)	41/65 (63.1%)
Statin use (*n*, %)	68/98 (69.4%)	24/41 (58.5%)	50/75 (66.7%)	48/65 (73.8%)
Beta-blockers (*n*, %)	29/98 (29.6%)	13/41 (31.7%)	36/75 (48.0%)	34/65 (52.3%)
ACEI use (*n*, %)	4/98 (4.1%)	2/41 (4.9%)	24/75 (32.0%)	15/65 (23.1%)
ARBs use (*n*, %)	0/98 (0.0%)	0/41 (0%)	20/75 (26.7%)	21/65 (32.3%)
CCB use (*n*, %)	10/98 (10.2%)	6/41 (14.6%)	47/75 (62.7%)	46/65 (70.8%)
Diuretics use (*n*, %)	0/98 (0.0%)	0/41 (0%)	4/75 (5.3%)	8/65 (12.3%)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARBs: angiotensin receptor blockers; BMI, body mass index; CAD, coronary artery disease; CCB, Calcium Channel Blockers; CHOL, cholesterol; DBP, diastolic blood pressure; DM, diabetes mellitus; Ex, treadmill exercise; HDL-c, high density lipoprotein cholesterol; HP, hypertensive; HR, heart rate; HRn, heart rate at n minute post exercise; HRR, heart rate recovery; HRRn, heart rate recovery at n minute post exercise; LDL-c, low density lipoprotein cholesterol; Mets, metabolic equivalents (1MET = 3.5 ml kg^{-1} per minute of oxygen consumption); N-HP, normotensive; SBP, systolic blood pressure; TG, triglyceride; yr, year. *$P < 0.05$ vs N-HP normal HRR; †$P < 0.05$ vs HP normal HRR.

education level was slightly higher in the HP group compared to the N-HP group. The underlying reasons for higher hypertension in this small study cohort could not be explained, and it is beyond the scope of the present study. The percentages of labour occupation and education level were similar between hypertensive patients with controlled and uncontrolled BP. Therefore, these factors might not be related to the lower HRR found in hypertensive patients with uncontrolled BP.

Clinical implications

The present study suggests that reduced HRR, which is a simple and inexpensive biomarker, is related to hypertension and reflects suboptimal BP control in hypertensive patients. Therefore, monitoring HRR during antihypertensive therapy might be an essential strategy to improve the autonomous balance and outcome for hypertensive patients.

Study limitations

First, the present retrospective study results were derived from a small patient cohort based on a single center database. Our results need to be validated by a larger patient cohort from multi-center database. Second, the outcome during the short-term (18.8 ± 11.7 months) follow-up was similar among groups. A longer follow-up period is warranted to observe the impact of reduced HRR on outcomes in this patient cohort. Third, a

Table 4. Clinical characteristic of HP patients with controlled and uncontrolled BP

	BP controlled (n = 88)	*BP uncontrolled (n = 52)*	P-*value*
Age (yr)	58.19 ± 7.70	59.62 ± 6.51	0.266
Male gender (*n*, %)	32/88 (36.4%)	26/52 (50.0%)	0.114
BMI (kg m^{-2})	25.16 ± 3.58	25.22 ± 3.36	0.920
Smoker (*n*, %)	22/88 (25.0%)	23/52(44.2%)	0.019
Manual labour (*n*, %)	56/88 (63.6%)	34/52(67.3%)	0.835
*Education (*n*, %)*			0.357
Primary school and below (*n*, %)	7/88(8.0%)	5/52 (9.6%)	
Middle school (*n*, %)	29/88 (33.0%)	17/52 (32.7%)	
High school (*n*, %)	36/88 (40.9%)	26/52 (50.0%)	
University and above (*n*, %)	16/88 (18.2%)	4/52 (7.7%)	
CAD (*n*, %)	28/88 (31.8%)	17/52 (32.3%)	0.915
DM (*n*, %)	16/88 (18.2%)	11/52 (21.2%)	0.667
Dyslipidemia (*n*, %)	72/88 (81.8%)	44/52 (84.6%)	0.671
Creatinine (μM)	66.27 ± 14.68	66.03 ± 14.90	0.927
CHOL(mM)	4.73 ± 1.14	4.77 ± 0.95	0.850
TG (mM)	2.10 ± 1.69	2.22 ± 1.77	0.677
LDL-c (mM)	2.82 ± 1.06	2.87 ± 0.83	0.758
HDL-c (mM)	1.10 ± 0.33	1.02 ± 0.29	0.170
HR before Ex (b.p.m.)	79.82 ± 12.13	82.77 ± 12.24	0.168
Peak HR (b.p.m.)	140.84 ± 7.40	139.81 ± 6.78	0.412
HR1 (b.p.m.)	113.71 ± 10.44	115.92 ± 9.46	0.213
HRR1 (b.p.m.)	27.13 ± 7.59	23.88 ± 7.96	0.018
HRR1 ⩽24 b.p.m. (%)	33/88(37.5%)	32/52(61.5%)	0.006
HR2 (b.p.m.)	95.18 ± 12.27	97.88 ± 14.90	0.247
HRR2 (b.p.m.)	45.66 ± 9.42	41.92 ± 14.12	0.093
HRR2 ⩽42 b.p.m. (%)	37/88 (42.05%)	26/52 (50.00%)	0.361
HR3 (b.p.m.)	88.86 ± 12.03	92.60 ± 13.23	0.090
HRR3 (b.p.m.)	51.98 ± 9.76	47.21 ± 12.84	0.014
HR4 (b.p.m.)	86.51 ± 10.97	89.52 ± 13.09	0.147
HRR4 (b.p.m.)	54.33 ± 9.10	50.29 ± 12.89	0.050
HR5 (b.p.m.)	85.30 ± 11.31	88.21 ± 12.91	0.164
HRR5 (b.p.m.)	55.55 ± 9.41	51.60 ± 12.51	0.036
SBP before Ex (mm Hg)	121.80 ± 8.60	145.21 ± 9.09	0.000
DBP before Ex (mm Hg)	77.02 ± 6.28	87.10 ± 9.22	0.000
SBP peak (mm Hg)	164.55 ± 16.22	181.26 ± 20.07	0.026
DBP peak (mm Hg)	70.82 ± 8.40	85.63 ± 9.09	0.000
SBP at 1 min post Ex (mm Hg)	144.07 ± 19.70	166.31 ± 19.62	0.001
DBP at 1 min post Ex (mm Hg)	77.93 ± 9.40	85.62 ± 12.08	0.018
SBP at 5 min post Ex (mm Hg)	132.42 ± 17.22	138.60 ± 32.99	0.249
DBP at 5 min post Ex (mm Hg)	77.68 ± 7.62	80.96 ± 20.24	0.311
Time for Ex (minute)	4.30 ± 1.69	4.14 ± 1.77	0.598
Exercise tolerance (Mets)	6.49 ± 1.76	6.16 ± 1.78	0.286
Ejection fraction	0.63 ± 0.07	0.62 ± 0.07	0.279
Medication			
Aspirin use (*n*, %)	53/88 (60.2%)	37/52 (71.1%)	0.192
Statin use (*n*, %)	59/88 (67.0%)	39/52 (75.0%)	0.321
Bata-blockers use (*n*, %)	46/88 (52.3%)	24/52 (46.2%)	0.484
ACEI use (*n*, %)	23/88 (26.1%)	16/52 (30.8%)	0.555
ARBs use (*n*, %)	23/88 (26.1%)	18/52 (34.6%)	0.287
CCB use (*n*, %)	53/88 (60.2%)	40/52 (76.9%)	0.043
Diuretics use (*n*, %)	7/88 (8.0%)	5/52 (9.6%)	0.979
categories of drugs			0.039
Monotherapy (*n*, %)	35/88 (39.8%)	12/52 (23.1%)	
Two drug therapy (*n*, %)	43/88 (48.9%)	27/52 (51.9%)	
⩾Three drug therapy (*n*, %)	10/88 (11.4%)	13/52 (25.0%)	

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blocker; BP, blood pressure; BMI, body mass index; CAD, coronary artery disease; CCB, calcium channel blocker; CHOL, cholesterol; DBP, diastolic blood pressure; DM, diabetes mellitus; Ex, treadmill exercise; HDL-c, high density lipoprotein cholesterol; HP, hypertensive; HR, heart rate; HRn, heart rate at n minute post exercise; HRR, heart rate recovery; HRRn, heart rate recovery at n minute post exercise; LDL-c, low density lipoprotein cholesterol; Mets, metabolic equivalents (1MET = 3.5 ml kg^{-1} per minute of oxygen consumption); SBP, systolic blood pressure; TG, triglyceride; yr, year.

Table 5. Clinical characteristic of HP patients with and without beta-blockers

	Without beta-blockers (n = 70)	*With beta-blockers (n = 70)*	P-*value*
Age (yr)	58.29 ± 7.41	59.16 ± 7.20	0.482
Male gender (*n*, %)	28/70 (40.0%)	30/70 (42.9%)	0.731
BMI (kg m^{-2})	25.85 ± 3.25	24.51 ± 3.61	0.022
Smoker (*n*, %)	21/70 (30.0%)	24/70 (34.3%)	0.587
Manual labour (*n*, %)	46/70 (65.7%)	44/70 (62.9%)	0.724
*Education (*n*, %)*			0.316
Primary school and below (*n*, %)	7/70 (10.0%)	5/70 (7.1%)	
Middle school (*n*, %)	18/70 (25.7%)	28/70 (40.0%)	
High school (*n*, %)	35/70 (50.0%)	27/70 (38.6%)	
University and above (*n*, %)	10/70 (14.3%)	10/70 (14.3%)	
CAD (*n*, %)	12/70 (18.6%)	33/70 (47.1%)	0.000
DM (*n*, %)	17/70 (24.3%)	10/70 (14.3%)	0.134
Dyslipidemia (*n*, %)	60/70 (85.7%)	56/70 (80.0%)	0.370
Creatinine (μM)	66.73 ± 13.83	65.63 ± 15.61	0.659
CHOL (mM)	4.78 ± 0.94	4.71 ± 1.19	0.706
TG (mM)	2.11 ± 1.50	2.18 ± 1.92	0.822
LDL-c (mM)	2.88 ± 0.77	2.80 ± 1.15	0.637
HDL-c (mM)	1.06 ± 0.28	1.09 ± 0.35	0.514
HR before Ex (b.p.m.)	81.41 ± 11.92	80.41 ± 12.57	0.630
Peak HR (b.p.m.)	140.91 ± 6.84	140.00 ± 7.50	0.452
HR1(b.p.m.)	114.59 ± 9.68	114.49 ± 10.59	0.954
HRR1 (b.p.m.)	26.33 ± 7.06	25.51 ± 8.62	0.542
HRR1 ⩽24 b.p.m. (%)	31/70 (44.3%)	34/70 (48.6%)	0.611
HR2 (b.p.m.)	97.06 ± 12.49	95.31 ± 14.14	0.441
HRR2 (b.p.m.)	43.86 ± 11.11	44.69 ± 11.92	0.671
HRR2 ⩽42 b.p.m. (%)	31/70 (44.3%)	22/70 (31.4%)	0.865
HR3 (b.p.m.)	90.73 ± 12.35	89.77 ± 12.86	0.654
HRR3 (b.p.m.)	50.19 ± 11.18	50.23 ± 11.31	0.982
HR4 (b.p.m.)	87.77 ± 11.53	87.49 ± 12.24	0.887
HRR4 (b.p.m.)	53.14 ± 10.44	52.51 ± 11.21	0.732
HR5 (b.p.m.)	85.99 ± 11.43	86.77 ± 12.55	0.699
HRR5 (b.p.m.)	54.93 ± 10.51	53.23 ± 11.08	0.353
SBP before Ex (mm Hg)	131.36 ± 15.16	129.63 ± 13.52	0.478
DBP before Ex (mm Hg)	81.37 ± 8.93	80.16 ± 8.95	0.423
SBP peak (mm Hg)	181.36 ± 19.98	168.00 ± 18.62	0.069
DBP peak (mm Hg)	82.06 ± 11.75	78.07 ± 10.86	0.345
SBP at 1 min post Ex (mm Hg)	154.71 ± 22.54	144.90 ± 19.05	0.062
DBP at 1 min post Ex (mm Hg)	80.17 ± 9.80	78.52 ± 10.50	0.510
SBP at 5 min post Ex (mm Hg)	136.20 ± 27.88	134.58 ± 24.35	0.736
DBP at 5 min post Ex (mm Hg)	81.50 ± 15.95	78.08 ± 14.14	0.433
Time for Ex (minute)	4.14 ± 1.61	4.35 ± 1.83	0.478
Exercise tolerance (Mets)	6.16 ± 1.56	6.57 ± 1.94	0.177
Ejection fraction	0.63 ± 0.06	0.62 ± 0.07	0.325
Medication			
Aspirin use (*n*, %)	39/70 (55.7%)	51/70 (72.9%)	0.034
Statin use (*n*, %)	47/70 (67.1%)	51/70 (72.9%)	0.461
ACEI use (*n*, %)	20/70 (28.6%)	19/70 (27.1%)	0.850
ARBs use (*n*, %)	27/70 (38.6%)	14/70 (20.0%)	0.016
CCB use (*n*, %)	57/70 (81.4%)	36/70 (51.4%)	0.000
Diuretics use (*n*, %)	9/70 (12.9%)	3/70 (4.3%)	0.070

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blocker; BP, blood pressure; BMI, body mass index; CAD, coronary artery disease; CCB, calcium channel blocker; CHOL, cholesterol; DBP, diastolic blood pressure; DM, diabetes mellitus; Ex, treadmill exercise; HDL-c, high density lipoprotein cholesterol; HP, hypertensive; HR, heart rate; HRn, heart rate at n minute post exercise; HRR, heart rate recovery; HRRn, heart rate recovery at n minute post exercise; LDL-c, low density lipoprotein cholesterol; Mets, metabolic equivalents (1MET = 3.5 ml kg^{-1} per minute of oxygen consumption); SBP, systolic blood pressure; TG, triglyceride; yr, year.

prospective study is needed to explore the impact of intensive BP control on HRR and outcome in hypertensive patients. Notably, HRR could be affected by aerobic fitness, and the lower HRR in hypertensive patients with uncontrolled BP compared to hypertensive patients with controlled BP might reflect differences in aerobic fitness. The present study could not clarify this issue because of the lack of some data, such as VO_2 peak derived from

Table 6. Multivariate logistic regression results for risk of uncontrolled BP

	B	*s.e.*	*Wald*	P-*value*	*Exp*	*95% CI lower limit*	*95% CI upper limit*
HRR1 (b.p.m.)	0.040	0.027	2.157	0.142	1.041	0.987	1.096
HRR1 ⩽24 (%)	0.801	0.388	4.250	0.039	2.227	1.040	4.768
HRR3 (b.p.m.)	0.032	0.020	2.713	0.100	1.033	0.994	1.074
HRR4 (b.p.m.)	0.028	0.021	1.816	0.178	1.028	0.987	1.071
HRR5 (b.p.m.)	0.026	0.021	1.529	0.216	1.026	0.985	1.068

Abbreviations: BP, blood pressure; CI, confidence interval; HRR, heart rate recovery; HRRn, heart rate recovery at n minute post exercise.

cardiopulmonary exercise tests. Future studies are warranted to clarify this issue using cardiopulmonary exercise tests. The resting HR was relatively high (~80 per minute) in the N-HP and HP groups, although beta-blockers were prescribed to approximately 30% of the patients without hypertension and 50% of the hypertensive patients. Mental stress before the treadmill exercise test might play a minor role in these subjects, but this factor could not be confirmed in this study. Medication compliance might be another difficult-to-confirm issue for the relatively high resting HR in the study subjects. Although all patients confirmed their prescribed medications by answering the questionnaire sheets, we could not confirm whether individual patients actually took their prescribed medication.

CONCLUSIONS

The present results show that uncontrolled BP post antihypertensive medication is associated with lower HRR in hypertensive patients. Monitoring HRR might be an important strategy to optimize therapeutic efficacy by focusing on improving autonomous balance and outcome for hypertensive patients.

What is known about the topic?

- Reduced heart rate recovery (HRR) post-treadmill exercise testing reflects autonomic dysfunction.
- Reduced HRR is related to worse cardiovascular outcome.

What this study adds?

- HRR was significantly lower in the HP group than the N-HP group.
- HRR was also significantly lower in hypertensive patients with uncontrolled BP than hypertensive patients with controlled BP post antihypertensive medication.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

1 Chobanian AV. Time to reassess blood-pressure goals. *N Engl J Med* 2015; **373**: 2093–2095.
2 Ramos RP, Arakaki JS, Barbosa P, Treptow E, Valois FM, Ferreira EV *et al.* Heart rate recovery in pulmonary arterial hypertension: relationship with exercise capacity and prognosis. *Am Heart J* 2012; **163**: 580–588.
3 Erdogan D, Gonul E, Icli A, Yucel H, Arslan A, Akcay S *et al.* Effects of normal blood pressure, prehypertension, and hypertension on autonomic nervous system function. *Int J Cardiol* 2011; **151**: 50–53.
4 Best SA, Bivens TB, Dean Palmer M, Boyd KN, Melyn Galbreath M, Okada Y *et al.* Heart rate recovery after maximal exercise is blunted in hypertensive seniors. *J Appl Physiol (1985)* 2014; **117**: 1302–1307.
5 Arena R, Myers J, Abella J, Peberdy MA, Bensimhon D, Chase P *et al.* The prognostic value of the heart rate response during exercise and recovery in patients with heart failure: influence of beta-blockade. *Int J Cardiol* 2010; **138**: 166–173.
6 Karnik RS, Lewis W, Miles P, Baker L. The effect of beta-blockade on heart rate recovery following exercise stress echocardiography. *Prev Cardiol* 2008; **11**: 26–28.
7 Gibbons RJ, Balady GJ, Bricker JT, Chaitman BR, Fletcher GF, Froelicher VF *et al.* ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). *Circulation* 2002; **106**: 1883–1892.
8 Yu Y, Peng D, Liu T, Bai Y, Zou W, Gao B *et al.* Diagnostic value of combined exercise-induced ST segment changes and heart rate recovery post treadmill exercise for the detection of coronary artery disease in the real world: a single center experience. *IRJPEH* 2015; **2**: 232–237.
9 Ghaffari S, Kazemi B, Aliakbarzadeh P. Abnormal heart rate recovery after exercise predicts coronary artery disease severity. *Cardiol J* 2011; **18**: 47–54.
10 Perloff D, Grim C, Flack J, Frohlich ED, Hill M, McDonald M *et al.* Human blood pressure determination by sphygmomanometry. *Circulation* 1993; **88**: 2460–2470.
11 Gharacholou SM, Scott CG, Borlaug BA, Kane GC, McCully RB, Oh JK *et al.* Relationship between diastolic function and heart rate recovery after symptom-limited exercise. *J Card Fail* 2012; **18**: 34–40.
12 Jaques H. NICE guideline on hypertension. *Eur Heart J* 2013; **34**: 406–408.
13 Bilsel T, Terzi S, Akbulut T, Sayar N, Hobikoglu G, Yesilcimen K. Abnormal heart rate recovery immediately after cardiopulmonary exercise testing in heart failure patients. *Int Heart J* 2006; **47**: 431–440.
14 Yilmaz A, Erdem A, Kucukdurmaz Z, Karapinar H, Gul I, Sarikaya S *et al.* Abnormal heart rate recovery in stable heart failure patients. *Pacing Clin Electrophysiol* 2013; **36**: 591–595.