International Journal of Cardiology 228 (2017) 588–593

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Heart rate response to exercise in heart failure patients: The prognostic role of metabolic–chronotropic relation and heart rate recovery

Pavel Hajdusek [a,1], Martin Kotrc [a,1], Josef Kautzner [a,1], Vojtech Melenovsky [a,1], Eva Benesova [b,2], Petr Jarolim [c,3], Jan Benes [a,*,1]

[a] Department of Cardiology, Institute for Clinical and Experimental Medicine-IKEM, Prague, Czech Republic
[b] Institute for History of Medicine, Charles University, Prague, Czech Republic
[c] Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

ARTICLE INFO

Article history:
Received 28 July 2016
Accepted 5 November 2016
Available online 09 November 2016

Keywords:
Metabolic–chronotropic relation
Heart rate recovery
Heart failure
Prognosis
Cardiopulmonary exercise testing

ABSTRACT

Background: The dynamics of the sinus node response to exercise is linked to functional capacity and outcome in heart failure (HF). The goal of the work was to analyze determinants and impacts of cardio-acceleration, described by the concept of metabolic-chronotropic relation (MCR) and of cardio-deceleration, described by heart rate recovery (HRR).
Methods: A cohort of 25 healthy controls and 78 patients with advanced systolic HF and optimized medical and/or device therapy (97% receiving beta-blockers, 54% ICD) underwent maximal cardiopulmonary exercise test and were prospectively followed.
Results: HF patients had impaired exercise performance compared with controls (pVO_2 15 ± 4 vs. 29 ± 7 $ml.kg^{-1}.min^{-1}$, $p < 0.0001$) and lower both MCR slope (0.54 ± 0.24 vs. 0.90 ± 0.15, $p < 0.0001$) and HRR (14.7 ± 7.9 vs. 18.3 ± 4.2 min^{-1}, $p = 0.03$). In HF patients, MCR slope was inversely associated with beta-blocker dose ($r = -0.24$), NYHA class ($r = -0.28$) and HF duration ($r = -0.25$), whereas HRR with estimated glomerular filtration rate (eGFR, $r = 0.39$), age ($r = -0.28$) and BMI ($r = -0.31$, all $p < 0.05$). During a follow-up of 1269 ± 933 days, 64% patients experienced an adverse outcome (death, urgent transplantation, left ventricular assist device implantation). Those patients had higher NT-proBNP ($p = 0.02$), worse left ventricular systolic function (LVEF, $p = 0.03$) and lower MCR slope ($p = 0.02$) but not HRR ($p = 0.19$). MCR slope (but not HRR) was a significant outcome predictor ($p = 0.02$ for Cox unadjusted model) even after adjustment for LVEF, serum natrium, systolic blood pressure, eGFR and NT-proBNP ($p = 0.04$).
Conclusion: MCR slope is associated with different clinical variables than HRR. Compared to HRR, MCR slope provides significant prognostic information in HF patients.

1. Introduction

The dynamics of heart rate (HR) response during exercise affects not only functional capacity but also confers important prognostic information. Cardiac acceleration can be most precisely quantified by metabolic chronotropic relation (MCR) slope which describes the relationship between HR and oxygen consumption during exercise [1]. This model assumes that the percentage of HR reserve during exercise (i.e. HR change normalized to baseline HR) is linearly proportional to the percentage of metabolic reserve achieved. When percentage of HR reserve is plotted against percentage of metabolic reserve, a subject with an adequate chronotropic response has a linear relationship with a MCR slope of close to 1.0; patients with impaired chronotropic response have MCR slope lower than 1. The advantage of MCR approach is that it partly normalizes sinus node chronotropic response to differences in age, physical fitness, functional capacity and exercise testing protocol and therefore, better reflects intrinsic properties of the sinus node and its autonomic modulation [2]. In addition, the calculation of MCR slope can be successfully performed even in subjects who are not able to achieve maximal effort (peak respiratory exchange ratio <1).

Cardiac deceleration can be assessed by the post-exercise recovery of HR. HR recovery (HRR) immediately after exercise is a function of vagal reactivation and has been proved to be a predictor of mortality both in the general population [3] as well as in heart failure (HF)

* Corresponding author at: Department of Cardiology, Institute for Clinical and Experimental Medicine-IKEM, Videnska 1958/9, 140 21 Praha 4 Krc, Czech Republic.
E-mail address: jan.benes@ikem.cz (J. Benes).
[1] This author takes responsibility for all aspects and the reliability and freedom from bias of the data presented and their discussed interpretation.
[2] This author was involved in statistical analysis and manuscript preparation.
[3] This author was responsible for a substantial part of laboratory analysis and manuscript preparation.

http://dx.doi.org/10.1016/j.ijcard.2016.11.083
0167-5273/

patients [4,5]. The relationship between MCR and HRR, their determinants and prognostic influence has never been compared in HF patients so far. The goal of the work was to analyze cardiac acceleration using MCR slope and cardiac deceleration using HRR in the cohort of controls and adequately treated HF patients, and to address the impact of these variables on prognosis.

2. Methods

2.1. Study subjects

The study enrolled patients with chronic (>6 months) stable advanced HF with reduced ejection fraction of the left ventricle (LVEF <40%) in sinus rhythm, on stable optimized medical therapy, who were electively hospitalized at our institution for assessment of transplant eligibility or device implantation. Patients with recent decompensation of HF and/or reversible LV dysfunction (planned valve surgery, revascularization, or tachycardia induced cardiomyopathy) were excluded. Healthy controls (hospital employees) free of medication or cardiovascular disease were recruited by advertisement to match age, gender and body composition of the HF cohort. The protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the ethics committee. Prior to enrollment all subjects signed an informed consent. From the initial cohort of 81 patients, 2 patients were further excluded due to missing deceleration part of the CPX (technical reasons) and 1 patient had such a low exercise tolerance that made it impossible to calculate MCR slope. Finally, 78 patients were analyzed.

2.2. Protocol

Prior to exercise, patients completed anthropometric tests and echocardiography (Vivid-7; General Electric, Milwaukee, Wisconsin) was performed. LV function and dimensions were measured according to published recommendations [6]. Subjects then underwent symptom-limited upright bicycle ergometry (VmaxEncore29S; SensorMedics, Palo Alto, California) starting at 25 W, followed by 25-W stepwise 3-min increments until exhaustion. Heart rhythm was monitored by continuous 12-lead electrocardiography. Expired gas analysis was used to measure minute ventilation (VE), oxygen consumption (VO_2), carbon dioxide production (VCO_2) and peak respiratory exchange ratio (RER). Peak VO_2 was determined as the highest VO_2 achieved. Blood samples were taken prior to exercise by peripheral venous cannula (after >20 min in supine rest).

Metabolic chronotropic relation (MCR) slope was evaluated as a ratio between metabolic reserve (plotted on x-axis) and HR reserve (plotted on y-axis). Metabolic reserve was calculated as follows:

$$Metabolic\ \ reserve = \frac{METS_{stage} - METS_{rest}}{METS_{peak} - METS_{rest}}$$

Resting METS were equal to 1, thus

$$Metabolic\ \ reserve = \frac{METS_{stage} - 1}{METS_{peak} - 1}$$

Table 1
Baseline characteristics.

Characteristic	Controls (n = 25)	HF (n = 78)	p-Value
Age (yrs)	50.3 ± 7.8	52.4 ± 8.1	0.26
Male gender *(%)*	88.0%	85.9%	0.78
Body mass index *(kg. m^{-2})*	28.4 ± 2.5	27.5 ± 4.0	0.27
Heart failure and comorbidities			
Ischemic HF cause *(%)*	–	47.4%	<**0.0001**
HF duration *(yrs)*	–	5.7 ± 6.6	<**0.0001**
NYHA class	1.0 ± 0.0	2.7 ± 0.6	<**0.0001**
Diabetes mellitus *(%)*	0	28%	<**0.0001**
eGFR *(ml/s/1.73 m^2)*	1.52 ± 0.25	1.18 ± 0.33	<**0.0001**
Cardiac function			
Resting heart rate *(min^{-1})*	74.3 ± 9.3	78.7 ± 11.7	0.09
Systolic/diastolic BP *(mmHg)*	120 ± 16/84 ± 12	110 ± 17 / 71 ± 11	**0.02**/<**0.0001**
LV ejection fraction *(%)*	60 ± 0	23.5 ± 6.3	<**0.0001**
LV end-diastolic dimension *(mm)*	50.3 ± 5.2	70.8 ± 8.8	<**0.0001**
Therapy			
Beta-blocker therapy and dose *(0–3)*	0, 0	97.4%, 1.4 ± 0.7	<**0.0001**
ACEi/ARB therapy	0	92%	<**0.0001**
Furosemide therapy and daily dose *(mg)*	0	95%, 89.3 ± 67.3	<**0.0001**
Mineralocorticoid receptor antagonist	0	83.3%	<**0.0001**
Laboratory parameters			
NT-proBNP *(pg. ml^{-1})*	36.4 ± 25.0	1910.8 ± 1854. 9	<**0.0001**
Hb1Ac *($mmol.mol^{-1}$)*	37.7 ± 3.4	53.0 ± 23.6	**0.002**
Leukocyte count *(10^9 $.l^{-1}$)*	5.9 ± 0.9	7.3 ± 2.0	**0.002**
Cardiopulmonary exercise			
Systolic/diastolic BP at peak exercise *(mmHg)*	194 ± 27/92 ± 14	124 ± 24/75 ± 13	<**0.0001**
Heart rate at peak exercise *(min^{-1})*	161 ± 16	125 ± 20	<**0.0001**
Peak VO_2 *(ml $.kg^{-1}$ $.min^{-1}$)*	29 ± 7	15 ± 4	<**0.0001**
VE/VCO_2 slope	24 ± 3	35 ± 10	<**0.0001**
Peak respiratory quotient	1.13 ± 0.08	1.12 ± 0.10	0.62
Peak workload *(W)*	172 ± 50	76 ± 28	<**0.0001**
Exercise duration *(min)*	20.6 ± 6.0	9.1 ± 3.4	<**0.0001**
Devices			
BiV-pacemaker	0	2.6%	<**0.0001**
ICD	0	30.8%	<**0.0001**
BiV-ICD	0	23.1%	<**0.0001**
Follow-up			
Follow-up length *(days)*	–	1269 ± 933	–
Event-free survival	–	23 (29.5%)	–
Death without transplantation	–	21 (26.9%)	–
Urgent transplantation	–	18 (23.1%)	–
Non-urgent transplantation	–	5 (6.4%)	–
LVAD implantation	–	11 (14.1%)	

Data are shown as means ± SD. Abbreviations: BP—blood pressure, LVAD—left-ventricle assist device, ICD—implantable cardioverter–defibrillator, BiV—biventricular, VO_2—oxygen consumption, VCO_2—carbon dioxide production, eGFR—estimated glomerular filtration rate.

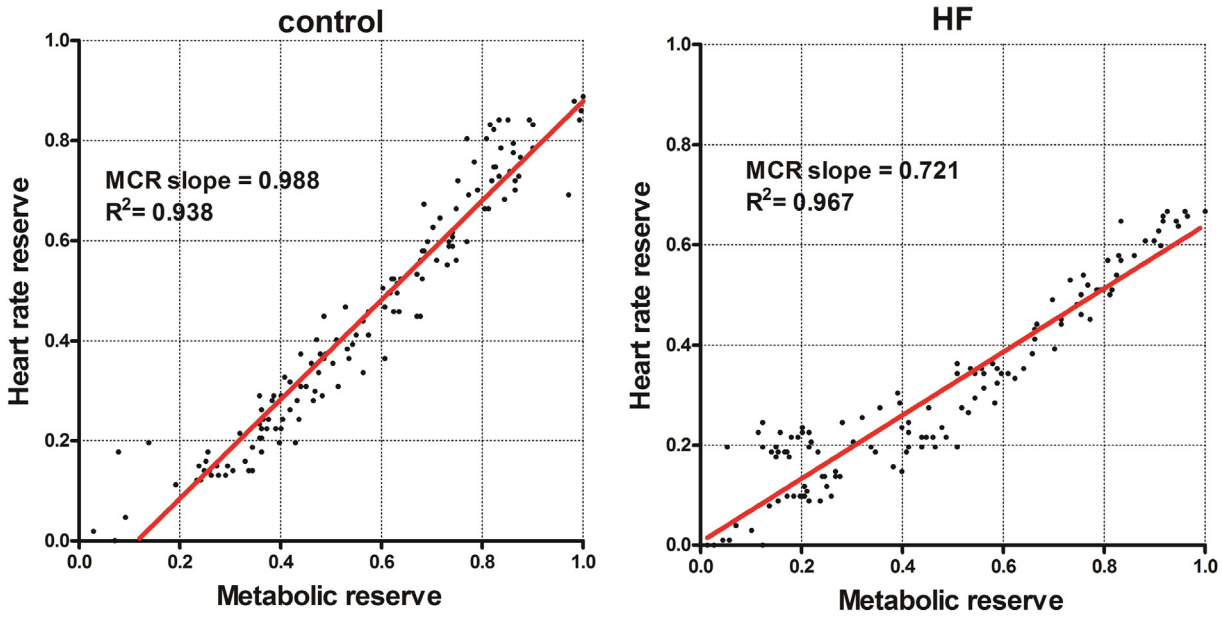

Fig. 1. MCR slope in a representative control subject (left) and HF patient (right). The relation between heart rate reserve and metabolic reserve (MCR slope) was linear both in controls and HF patients.

HR reserve was calculated as follows:

$$Heart\ \ rate\ \ reserve = \frac{HR_{stage} - HR_{rest}}{HR_{\max\_predicted} - HR_{rest}}$$

Age-predicted maximal HR was calculated as (220 − age) [2], thus

$$Heart\ \ rate\ \ reserve = \frac{HR_{stage} - HR_{rest}}{220 - age - HR_{rest}}$$

During exercise, $METS_{stage}$ and HR_{stage} was obtained every 10 s. $METS_{stage}$ was calculated as VO_2 (stage, ml $kg^{-1}.min^{-1}$) divided by 3.5. MCR slope was thus calculated as a slope between metabolic reserve and HR reserve from the whole period of the exercise test (recovery part of the test was not included in the analysis). For each subject, the value of slope between 0 and 1 was obtained. Resting HR was derived from the supine resting recording prior to exercise. HR recovery was calculated as a slope obtained from the first 150 s (2.5 min) after exercise termination where a decrease in HR was linear both in controls and HF patients. The result is given as a decrease in HR per minute.

Cutoff values for partitioning beta-blocker daily doses into low/middle/high (1–3) categories were <12.5/—/≥50 mg/day for carvedilol, <25/—/≥200 mg/day for metoprolol and <2.5/—/≥10 mg/day for bisoprolol; other beta-blockers were not used in our patients. Estimated glomerular filtration rate (eGFR) was calculated based on serum creatinine level, age, ethnicity, and gender [7].

NT-proBNP was measured on the cobas 6000 analyzer (Roche Diagnostics, Indianapolis, IN, USA) using an electrochemiluminescent immunoassay with a limit of detection 5 pg/mL and reportable range 5–35,000 pg/mL. Total imprecision of the assay was 2.5% at both 138 pg/mL and 4578 pg/mL.

2.3. Statistical analysis

Patients were prospectively followed, and the adverse outcome was defined by the combined endpoint of death without transplantation, urgent heart transplantation or ventricular assist device insertion (whatever occurred as the first). Because time to non-urgent transplant reflects donor availability rather than recipient's condition, those patients were censored as having no outcome at the day of transplantation [8].

Data were analyzed using JMP11 (SAS Institute Inc., Cary, NC, USA). To determine whether baseline clinical and biochemical parameters differed between two groups (e.g. cases and controls), an unpaired t-test or chi-square test (when appropriate) were used. Correlations between clinical and biochemical variables were assessed using the Pearson test. The influences of MCR slope and HRR on prognosis were tested using logistic regression and univariate and multivariate Cox model. Kaplan–Meier analysis was used to compare mortality between two groups.

3. Results

3.1. Patient characteristics

Patients suffering with chronic systolic HF were predominantly of a male sex; coronary artery disease was responsible for HF in 47.4%. They were receiving both optimized medical therapy including beta-blockers (97%), ACEi/ARBs (92%) and mineralocorticoid receptor antagonists (83.3%) as well as device therapy (30.8% had an implanted ICD, 23.1% BiV-ICD). Controls were of similar age, sex, and body composition

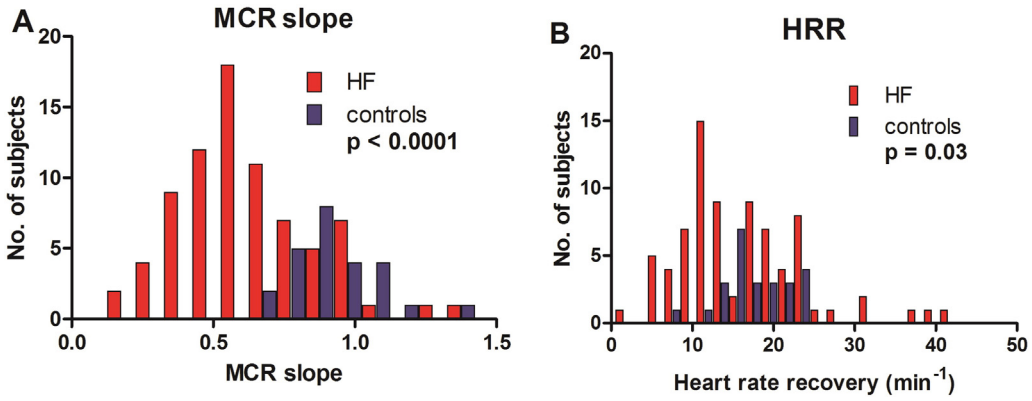

Fig. 2. The distribution of MCR slope (A) and HRR (B) in controls and HF patients. Compared to controls, HF patients had markedly attenuated MCR slope but only marginally attenuated HRR.

Table 2
Correlations between MCR slope, HRR and selected clinical variables.

	Heart failure				Controls			
	MCR slope		HRR		MCR slope		HRR	
	r	p	r	p	r	p	r	p
Peak VO_2	+0.50	<**0.0001**	+0.47	<**0.0001**	+0.47	**0.017**	+0.46	**0.02**
VE/VCO_2 slope	−0.29	**0.009**	−0.31	**0.006**	+0.10	0.64	+0.31	0.14
Exercise duration	+0.43	<**0.0001**	+0.28	**0.01**	+0.50	**0.01**	+0.55	**0.005**
Furosemide daily dose	−0.28	**0.01**	−0.31	**0.007**	–	–	–	–
Beta-blocker dose	−0.24	**0.036**	+0.01	0.92	–	–	–	–
NYHA	−0.28	**0.01**	−0.19	0.09	–	–	–	–
HF duration	−0.25	**0.03**	−0.03	0.78	–	–	–	–
eGFR	+0.17	0.13	+0.39	**0.0005**	−0.29	0.16	+0.08	0.72
Age	+0.06	0.59	−0.28	**0.01**	−0.39	**0.05**	−0.52	**0.008**
Body mass index	−0.16	0.16	−0.31	**0.007**	−0.16	0.43	−0.15	0.47

Data are shown as means ± SD. Abbreviations: MCR—metabolic–chronotropic relation, HRR—heart rate recovery, VO_2—oxygen consumption, VCO_2—carbon dioxide production, eGFR—estimated glomerular filtration rate.

and were free of medical therapy and comorbidities. Patients with HF displayed markedly impaired exercise performance compared with controls. They had lower peak workload, peak VO_2 and higher VE/VCO_2 slope (Table 1). During the follow up, 50 patients (64.1%) experienced an adverse outcome.

3.2. Cardiac acceleration and cardiac deceleration in controls and HF patients

The relation between HRR and metabolic reserve (MCR slope) was linear ($R^2 = 0.84 \pm 0.12$ for HF patients and $R^2 = 0.94 \pm 0.04$ for controls). The representative MCR slopes for a control subject and HF patient are given in Fig. 1. MCR slope was successfully calculated in 98.8% of patients and in all controls.

MCR slope was independent of the maximal respiratory exchange ratio (RER) achieved ($p = 0.50$ for HF and 0.19 for controls). Also in patients with maximal RER < 1 ($n = 10$) there was no relationship between MCR slope and RER ($p = 0.21$). There was no difference in MCR slope in HF patients with maximal RER below and above 1 (0.45 ± 0.15 vs. 0.57 ± 0.24, $p = 0.16$).

HF patients had markedly attenuated MCR slope but only marginally attenuated HRR (Fig. 2). There was significant relationship between MCR slope and HRR ($r^2 = 0.25$ for HF a 0.26 for controls, $p < 0.0001$ for HF and $p = 0.009$ for controls, Suppl. Fig. 1) and the slope of this relation was overlapping in control and HF group.

In controls, MCR slope and HRR were positively associated with peak VO_2 and exercise duration and negatively associated with age (Table 2). In HF patients, MCR slope and HRR were associated with distinct set of clinical correlates. Both variables were positively associated with peak VO_2, exercise duration and negatively with VE/VCO_2 slope and furosemide daily dose. A negative association between MCR slope and beta-blocker dose, NYHA functional class and HF duration was observed. On the contrary, HRR associated significantly with age, BMI and eGFR. No significant association between resting HR, systolic blood pressure, LVEF, NT-proBNP and either MCR slope or HRR was observed. Similarly, neither MCR slope nor HRR was associated with ACEi or ARB dose.

3.3. Prognostic role of cardiac acceleration and cardiac deceleration

Patients who have experienced an adverse outcome were of similar age and BMI, had similar resting HR and were treated with similar dose of beta-blockers as those not experiencing an adverse outcome. On the contrary, they had higher NT-proBNP and significantly worse LV systolic function. Finally, they had markedly lower MCR slope but no difference in HRR was seen (Table 3).

Logistic regression identified MCR slope as a significant predictor of an adverse outcome ($p = 0.015$). On the contrary, the prediction power of HRR was not significant ($p = 0.19$). ROC analysis identified the best cut-off value for MCR slope to be 0.66 (AUC 0.652). When HF patients were dichotomized with respect to this cut-off, those with MCR > 0.66 had borderline lower BMI, better peak VO_2 and borderline lower VE/VCO_2 slope. No difference in LVEF, resting HR, NT-proBNP and NYHA functional class was observed (Table 4). Patients with MCR slope > 0.66 had significantly better survival (Fig. 3).

Univariate Cox proportional hazard model showed significant predictive power for MCR slope ($p = 0.02$) but not HRR ($p = 0.14$), Model 1, Table 5. In the multivariate Cox prognostic model adjusted for other clinical variables (Model 2, Table 5) and NT-proBNP (Model 3, Table 5) MCR slope remained significant predictor of an adverse outcome.

Table 3
The differences between patients with favorable and adverse outcome.

	Adverse outcome	Favorable outcome	p
Age *(yrs)*	53.1 ± 8.2	51.0 ± 7.7	0.28
Body mass index *(kg .m^{-2})*	27.6 ± 3.9	27.2 ± 4.2	0.67
Hb1Ac *(mmol .mol^{-1})*	57.3 ± 27.1	44.4 ± 10.4	**0.045**
NT-proBNP *(pg.ml^{-1})*	2244 ± 2119	1230 ± 820	**0.02**
LV ejection fraction *(%)*	22.4 ± 5.6	25.60 ± 7.1	**0.03**
Beta-blocker dose *(0–3)*	1.5 ± 0.7	1.3 ± 0.7	0.36
Resting heart rate *(min^{-1})*	78.7 ± 12.3	78.6 ± 10.7	0.97
Metabolic–chronotropic relation slope	0.5 ± 0.2	0.6 ± 0.2	**0.02**
Heart rate recovery *(min^{-1})*	13.8 ± 8.4	16.3 ± 6.6	0.19
NYHA	2.8 ± 0.6	2.4 ± 0.6	**0.01**
Peak VO_2 *(ml kg^{-1} min^{-1})*	14.2 ± 3.1	17.0 ± 4.9	**0.002**
VE/VCO_2 slope	36.4 ± 9.9	33.1 ± 10.5	0.17

Data are shown as means ± SD. Notes: Adverse outcome was defined as death without heart transplantation, urgent transplantation or LVAD implantation. Abbreviations: VO_2—oxygen consumption, VCO_2—carbon dioxide production, eGFR—estimated glomerular filtration rate.

Table 4
Differences in patients with MCR slope below and above 0.66.

	MCR slope < 0.66	MCR slope ≥ 0.66	p
Age *(yrs)*	51.9 ± 7.9	53.7 ± 8.5	0.39
Body mass index *(kg m^{-2})*	28.0 ± 4.2	26.1 ± 2.9	0.056
NT-proBNP *(pg ml^{-1})*	1841 ± 1911	2107 ± 1719	0.59
LV ejection fraction *(%)*	23.1 ± 5.2	24.6 ± 8.7	0.36
Resting heart rate *(min^{-1})*	78.3 ± 11.5	79.7 ± 12.6	0.65
NYHA	2.7 ± 0.6	2.5 ± 0.5	0.10
Peak VO_2 *(ml kg^{-1} min^{-1})*	13.9 ± 3.0	18.6 ± 4.3	<**0.0001**
VE/VCO_2 slope	36.6 ± 10.3	31.6 ± 8.8	0.055

Data are shown as means ± SD. Abbreviations: VO_2—oxygen consumption, VCO_2—carbon dioxide production, eGFR—estimated glomerular filtration rate.

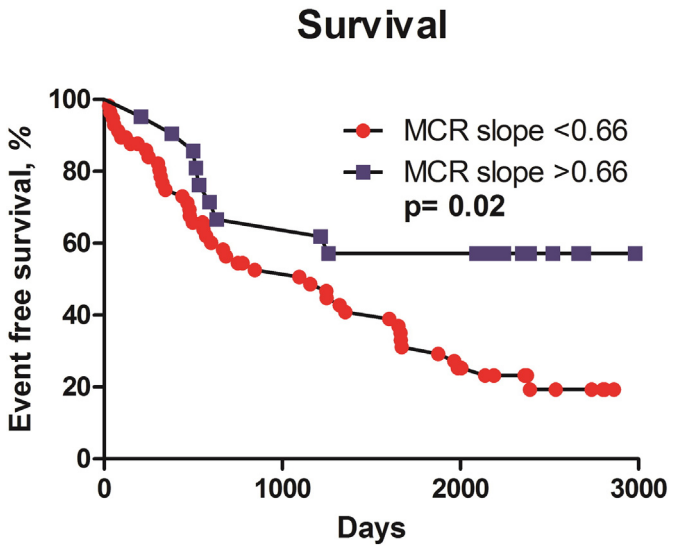

Fig. 3. Survival of HF patients with MCR slope below and above 0.66. Patients with MCR slope >0.66 had significantly better survival.

4. Discussion

In the present study we have examined the role of MCR slope and HRR in adequately treated HF patients. MCR slope and HRR were associated with different variables. MCR slope but not HRR was identified as a significant predictor of an adverse outcome.

4.1. MCR slope and HRR in HF patients

The concept of metabolic-chronotropic relation introduced by Wilkoff [1] describes HR response to exercise as a function of metabolic reserve. An advantage of this approach is that it is less affected by exercise conditions and can be calculated even in patients who achieve only submaximal load. In our study we were able to successfully measure MCR slope in 98.8% of HF patients and in all controls. Consistently with previous work, the relationship between HR reserve and metabolic reserve among individual patients was linear both in healthy controls and HF patients. The data about using this concept in HF patients are scarce. Martins [9] measured MCR slope in 25 patients in HF NYHA II-III and identified an abnormal response (MCR slope <2 SD below mean of healthy controls, i.e. MCR slope <0.84) in 60% of patients. In our HF cohort, MCR slope <0.84 was present in 87.2% of patients, but our cohort included considerably older patients with more advanced HF. MCR slope was significantly lower in HF patients which corresponds to the high prevalence of chronotropic incompetence in these patients [10]. HRR is an established marker of autonomic imbalance (absolute or relative decrease in vagal activity or an increase in sympathetic activity), which is present in HF [11] leading to lower HRR [12,13], which is in agreement with our observation as well.

Table 5
Predictive power of MCR slope, Cox proportional hazard model.

	Hazard ratio	95% confidence interval	p
Model 1	0.25	0.075–0.82	**0.02**
Model 2	0.19	0.036–0.95	**0.04**
Model 3	0.23	0.054–0.93	**0.04**

Explanation:
Model 1. MCR slope alone
Model 2: MCR slope adjusted to left ventricle ejection fraction, serum natrium, systolic blood pressure, estimated glomerular filtration rate
Model 3: Model 2 + NT-proBNP.

4.2. Association of MCR slope and HRR with clinical variables

In controls, both HRR and MCR slope were positively associated with peak VO_2 and exercise duration and negatively with age. The increase in oxygen consumption during aerobic activity is mediated substantially by an increase of HR [2], therefore the association between MCR slope (marker of chronotropic competence) and maximal oxygen consumption is physiological. The parasympathetic activity progressively decreases with aging [2,14], which is ultimately reflected by decreased HRR.

In HF patients, MCR slope was physiologically associated with peak VO_2 and exercise duration, but also a negative association with VE/VCO_2, beta-blocker dose, NYHA functional class, HF duration and furosemide daily dose was seen. The association between MCR slope, NYHA, HF duration and furosemide daily dose reflects the more advanced stage of a disease that is expressed in more advanced chronotropic incompetence and thus lower MCR slope. Flat HR response to exercise in more advanced HF patients reflects not only impaired autonomic balance [11] but also more pronounced beta-receptor downregulation [15] and structural remodeling of the sinus node [16]. The relationship between chronotropic competence and beta-blocker use in HF is controversial. Previous studies reported negative [10], neutral [17] or even positive association between beta-blocker treatment and chronotropic competence [18]. Our findings support negative association between beta-blocker use and chronotropic competence.

In controls, HRR correlated with peak VO_2, exercise duration and age, reflecting physical fitness that is associated with increased vagal tone [19]. In HF patients, HRR associated with age, BMI and eGFR. Renal dysfunction [20] and obesity [21] are both associated with altered autonomic balance and blunted vagal activity. In contrast to MCR slope, HRR was unrelated to beta-blocker dose, suggesting that HRR reflects mostly vagal tone.

4.3. Prognostic role of MCR slope and HRR in HF patients

To our best knowledge, this is the first study that demonstrates significant prognostic role of MCR slope in HF patients. The prognostic power of MCR slope remained significant even after adjustment to number of clinical variables and NT-proBNP. In previously published study, Khan et al. [22] found that chronotropic incompetence is a significant predictor in patients taking beta-blockers. Our results derived from the cohort of 97% beta-blocked HF patients are in agreement with this observation.

HRR was described to be a significant predictor of prognosis in HF patients [4,5,23]. However, we have failed to demonstrate the significant impact of HRR on prognosis in our study. Different properties of analyzed cohorts provide the most plausible explanation for this discrepancy. In previous studies, prevalence of beta-blocker use or ICD implants [4,5] was much lower (around 20–25% patients taking beta-blockers), indicating higher propensity to cardiac arrhythmias. Impaired vagal reactivation (reflected by depressed HRR) is a significant marker of arrhythmic cardiac death [24], which can be successfully prevented by an ICD implantation. This could explain why no predictive power of HRR was found in our cohort where more than 50% of patients had an implanted ICD. This finding raises a question whether vagal tone restoration using device therapy will be able to improve outcome in HF patients on optimized medical therapy and ICDs. In contrast, MCR slope was more predictive of adverse outcome, reflecting perhaps more structural remodeling of the heart and risk of pump failure death, rather than purely arrhythmic death.

4.4. Study limitation

The presented study is limited by its observational character and relatively small sample size. Patients enrolled in the study were treated not only conservatively but also scheduled for heart transplantation and

mechanical circulatory support implantation, which may introduce bias to the analysis of prognosis. Urgent heart transplantation and left ventricle assist device implantation were thus considered an adverse outcome while the patients receiving non-urgent heart transplant were censored as having no outcome on the day of transplantation [8]. Data about HF re-hospitalization were not available from all patients so this endpoint could have not been included in the analysis.

5. Conclusion

MCR slope can be calculated in the vast majority of stable HF patients undergoing cardiopulmonary exercise testing. It is associated with distinct clinical variables than HRR and compared to HRR it provides significant information about prognosis.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2016.11.083.

Conflict of interest

Josef Kautzner is a member of Advisory Board for Bayer, Boehringer Ingelheim, Daiichi Sankyo, Biosense Webster, Boston Scientific, Medtronic, Liva Nova, and St. Jude Medical. He received speaker also honoraria from all of the above companies and from Biotronik.

Petr Jarolim received research support from Abbott Laboratories, Amgen Inc., AstraZeneca LP, Beckman Coulter, Daiichi Sankyo, Inc., GlaxoSmithKline, Merck & Co., Inc., Roche Diagnostics Corporation, Takeda Global Research and Development Center, Waters Technologies Corporation.

Acknowledgments

This work was supported by project of Ministry of Health for development of research organization 00023001 (Institutional support IKEM); by the Grants GACR 15-14200S, AZV 15-27682A and AZV 16-27496A.

References

[1] B.L. Wilkoff, R.E. Miller, Exercise testing for chronotropic assessment, Cardiol. Clin. 10 (1992) 705–717.
[2] P.H. Brubaker, D.W. Kitzman, Chronotropic incompetence: causes, consequences, and management, Circulation 123 (2011) 1010–1020.
[3] X. Jouven, J.P. Empana, P.J. Schwartz, M. Desnos, D. Courbon, P. Ducimetiere, Heart-rate profile during exercise as a predictor of sudden death, N. Engl. J. Med. 352 (2005) 1951–1958.
[4] S. Nanas, M. Anastasiou-Nana, S. Dimopoulos, et al., Early heart rate recovery after exercise predicts mortality in patients with chronic heart failure, Int. J. Cardiol. 110 (2006) 393–400.
[5] V. Kubrychtova, T.P. Olson, K.R. Bailey, P. Thapa, T.G. Allison, B.D. Johnson, Heart rate recovery and prognosis in heart failure patients, Eur. J. Appl. Physiol. 105 (2009) 37–45.
[6] R.M. Lang, M. Bierig, R.B. Devereux, et al., Recommendations for chamber quantification, Eur. J. Echocardiogr. 7 (2006) 79–108.
[7] K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratificationAm. J. Kidney Dis. 39 (2002) S1–266.
[8] K.D. Aaronson, J.S. Schwartz, T.M. Chen, K.L. Wong, J.E. Goin, D.M. Mancini, Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation, Circulation 95 (1997) 2660–2667.
[9] S. Martins, R.M. Soares, C. Cotrim, et al., [The metabolic–chronotropic relation in patients with heart failure—a correlation with functional capacity]. Revista Portuguesa de cardiologia: orgao oficial da Sociedade Portuguesa de Cardiologia = Portuguese journal of cardiology: an official journal of the Portuguese Society of Cardiology, 18 (1999) 887–894.
[10] K.K. Witte, J.G. Cleland, A.L. Clark, Chronic heart failure, chronotropic incompetence, and the effects of beta blockade, Heart 92 (2006) 481–486.
[11] J.S. Floras, P. Ponikowski, The sympathetic/parasympathetic imbalance in heart failure with reduced ejection fraction, Eur. Heart J. 36 (2015) (1974-82b).
[12] S. Lindemberg, S. Chermont, M. Quintao, et al., Heart rate recovery in the first minute at the six-minute walk test in patients with heart failure, Arq. Bras. Cardiol. 102 (2014) 279–287.
[13] B. Krakowiak, W. Banasiak, P. Ponikowski, E.A. Jankowska, Chronotropic response during exercise and recovery in men with mild systolic chronic heart failure, Kardiol. Pol. 68 (2010) 1323–1330.
[14] D.M. Kaye, M.D. Esler, Autonomic control of the aging heart, Neuromolecular Med. 10 (2008) 179–186.
[15] W.S. Colucci, J.P. Ribeiro, M.B. Rocco, et al., Impaired chronotropic response to exercise in patients with congestive heart failure. Role of postsynaptic beta-adrenergic desensitization, Circulation 80 (1989) 314–323.
[16] P. Sanders, P.M. Kistler, J.B. Morton, S.J. Spence, J.M. Kalman, Remodeling of sinus node function in patients with congestive heart failure: reduction in sinus node reserve, Circulation 110 (2004) 897–903.
[17] D. Magri, P. Palermo, F.M. Cauti, et al., Chronotropic incompentence and functional capacity in chronic heart failure: no role of beta-blockers and beta-blocker dose, Cardiovasc. Ther. 30 (2012) 100–108.
[18] T.J. Vittorio, G. Lanier, R. Zolty, et al., Association between endothelial function and chronotropic incompetence in subjects with chronic heart failure receiving optimal medical therapy, Echocardiography 27 (2010) 294–299.
[19] G.A. Trevizani, P.R. Benchimol-Barbosa, J. Nadal, Effects of age and aerobic fitness on heart rate recovery in adult men, Arq. Bras. Cardiol. 99 (2012) 802–810.
[20] I.M. Salman, C.M. Hildreth, O.Z. Ameer, J.K. Phillips, Differential contribution of afferent and central pathways to the development of baroreflex dysfunction in chronic kidney disease, Hypertension 63 (2014) 804–810.
[21] G.E. Alvarez, S.D. Beske, T.P. Ballard, K.P. Davy, Sympathetic neural activation in visceral obesity, Circulation 106 (2002) 2533–2536.
[22] M.N. Khan, C.E. Pothier, M.S. Lauer, Chronotropic incompetence as a predictor of death among patients with normal electrograms taking beta blockers (metoprolol or atenolol), Am. J. Cardiol. 96 (2005) 1328–1333.
[23] L.P. Cahalin, R. Arena, V. Labate, F. Bandera, C.J. Lavie, M. Guazzi, Heart rate recovery after the 6 min walk test rather than distance ambulated is a powerful prognostic indicator in heart failure with reduced and preserved ejection fraction: a comparison with cardiopulmonary exercise testing, Eur. J. Heart Fail. 15 (2013) 519–527.
[24] M.T. La Rovere, G.D. Pinna, S.H. Hohnloser, et al., Baroreflex sensitivity and heart rate variability in the identification of patients at risk for life-threatening arrhythmias: implications for clinical trials, Circulation 103 (2001) 2072–2077.