

Left ventricular diastolic function assessed with cardiovascular magnetic resonance imaging and exercise capacity in patients with non-obstructive hypertrophic cardiomyopathy

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Abstract

Background: In patients with non-obstructive hypertrophic cardiomyopathy (HCM) and preserved left ventricular (LV) systolic function, diastolic dysfunction is one of the major factors contributing to limited exercise capacity. Cardiovascular magnetic resonance (CMR) imaging has become a useful tool in diagnosis, risk stratification and treatment monitoring in patients with HCM.

Aim: To assess the relationship between simple CMR parameters of LV diastolic function at rest and exercise capacity measured by means of cardiopulmonary exercise testing on a treadmill in patients with non-obstructive HCM and preserved LV systolic function.

Methods: The study included 13 patients with non-obstructive HCM and preserved LV systolic function who underwent cardiopulmonary exercise testing on a treadmill and CMR within 1 month. Analysed parameters of diastolic function included: LV mass index (LVMI), peak filling rate normalised to LV stroke volume index (PFR/LVSVI) and time from the end-systole to PFR normalised to heart rhythm (TPFR).

Results: There was a significant correlation between PFR/LVSVI at rest and peak oxygen uptake (VO_{2peak}) ($r=0.64$, $p=0.02$). Patients with VO_{2peak} below median (<30 ml/kg/min) had a significantly lower PFR/LVSVI than patients with higher VO_{2peak} [5.12 m²/s, interquartile range (IQR) 4.16-6.82 vs. 7.93 m²/s, IQR 7.49-8.21 respectively, $p=0.035$]. LVMI, TPFR were not related to exercise capacity. There was also no correlation between VO_{2peak} and age ($r=-0.38$, $p=0.19$), LV ejection fraction ($r=-0.36$, $p=0.22$) or normalised LV volume indices: LVEDVI ($r=0.09$, $p=0.76$), LVESVI ($r=0.34$, $p=0.26$).

Conclusions: Assessment of LV diastolic function by peak filling rate normalised to stroke volume index by means of CMR at rest in patients with non-obstructive HCM and preserved LV systolic function is a useful marker of exercise capacity.

Key words: hypertrophic cardiomyopathy, diastolic function, cardiovascular magnetic resonance, exercise capacity

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Introduction

Hypertrophic cardiomyopathy (HCM) is characterised by left ventricular (LV) hypertrophy leading to its abnormal relaxation and sudden cardiac death [1]. In patients without obstruction of the LV outflow tract and preserved systolic function, diastolic dysfunction is one of the major factors contributing to limited exercise capacity and symptoms of heart failure [1, 2]. It has been previously demonstrated that parameters of left heart catheterisation or tissue Doppler echocardiography at rest or during exercise correlate with peak oxygen uptake during cardiopulmonary

exercise testing [3-6]. Recently it has been shown that cardiovascular magnetic resonance (CMR) imaging can improve the management of patients with HCM [7-14]. However, there are no reports on the relationship between LV diastolic dysfunction assessed by means of CMR and exercise capacity in this group of patients, which can provide additional and important clinical information.

The aim of the study was to assess the relationship between simple CMR parameters of LV diastolic function at rest and exercise capacity measured by means of cardiopulmonary exercise testing on a treadmill in patients with non-obstructive HCM and preserved LV systolic function.

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Methods

The study included 13 patients with non-obstructive HCM and preserved LV systolic function. The diagnosis of HCM was defined by the presence of hypertrophied ventricle on 2-dimensional echocardiography and eventually CMR (maximal wall thickness >15 mm) in the absence of other disease that would account for the hypertrophy [2]. Data were collected on baseline clinical parameters. All patients underwent cardiopulmonary exercise testing on a treadmill and CMR imaging at rest within 1 month. The criteria for CMR assessment of LV diastolic function were based on a recent study in normal subjects and other studies on LV diastolic function using CMR [15-17]. Exclusion criteria consisted of: atrial fibrillation, arrhythmias limiting CMR data acquisition, unstable angina pectoris or NYHA class IV heart failure, moderate or severe mitral regurgitation, respiratory diseases, claustrophobia and implanted cardioverter-defibrillator or pacemaker. Preserved systolic function was defined as LV ejection fraction (LVEF) >50% and LV end-diastolic volume index (LVEDVI) <97 ml/m² according to recent echocardiographic guidelines on the diagnosis of diastolic function [18].

The CMR protocol

Steady-state cinematic magnetic resonance images were obtained with a 1.5 Tesla CMR imager (Magnetom Avanto, Siemens, Erlangen, Germany). Coronal, transaxial and single-oblique long-axis images of the LV were obtained using a breath-hold sequence with a steady state free precession (SSFP) to register the final short axis imaging planes. Short-axis images were obtained from the mitral valve insertion to apex with 8 to 10 slices to encompass the entire LV. The imaging parameters were as follows: repetition time of 30 ms, echo time of 1.15 ms, flip angle of 80°, matrix of 156 x 192, field of view 276 x 340 mm, slice thickness of 8 mm with slice gap of 1.6 mm and temporal resolution <30 ms.

Image analysis

Images were analysed using dedicated software (MASS, Medis, Leiden, Netherlands). The investigator (L.A.M.) assessing the CMR images was blinded to the results of the cardiopulmonary exercise testing. Initially, short axis images were previewed from base to apex in a cinematic mode, then endocardial and epicardial contours for end-diastole and end-systole were manually traced and semi-automatically propagated to other frames with subsequent manual adjustments. Delineated contours were used for the quantification of LV systolic parameters – LVEF, stroke volume index (LVSVI), end-systolic (LVESVI), end-diastolic volume indices (LVEDVI) and mass index (LVMI). Short-axis views were used to calculate maximal interventricular septal dimension (IVSD) and to assess the type of HCM according to the Maron classification (type I-IV

[19]. Parameters of LV diastolic function included: LVMI, peak filling rate (PFR) normalised to LVSVI and time from the end-systole to peak filling rate (TPFR) normalised to heart rhythm. Peak filling rate was calculated from the first derivative of the LV time-volume curve.

Cardiopulmonary exercise testing protocol

Symptom-limited cardiopulmonary exercise testing was performed according to the modified Bruce protocol using a Vmax 29c Series Spectrometer (Sensor Medics, California, U.S.A.). Metabolic gas exchange was measured every 10s to register the peak oxygen uptake (VO₂peak). All patients were exercised to maximum with respiratory quotient (RQ) >1.02. Cardioactive medications were discontinued at each cardiopulmonary test.

Statistical analysis

All results for categorical variables are expressed as numbers and percentages and for continuous variables as median and interquartile range (IQR). Correlations between LV diastolic function parameters and peak oxygen uptake were evaluated using Pearson's correlation coefficient. Wilcoxon rank sum test for independent samples was applied to compare LV diastolic function parameters between groups with peak oxygen uptake below and above median. All tests were two-sided with the significance level of $p < 0.05$. All statistical analyses were performed with SAS software version 8e (SAS Institute Inc., Cary, NY).

Results

Baseline clinical and CMR characteristics of the studied population are presented in Table I.

There was no significant correlation between VO₂peak and: age ($r = -0.38$, $p = 0.19$), LVEF ($r = -0.36$, $p = 0.22$), LVEDVI ($r = 0.09$, $p = 0.76$), LVESVI ($r = 0.34$, $p = 0.26$), IVSD ($r = 0.22$, $p = 0.46$) or LVSVI ($r = -0.23$, $p = 0.44$).

Correlations between cinematic CMR parameters of LV diastolic function at rest and exercise capacity assessed by means of VO₂peak are presented in Table II. A significant correlation was found for PFR and PFR/LVSVI, but not for other studied parameters. A scatter diagram comparing PFR/LVSVI and VO₂peak for each patient with a regression line demonstrating a positive correlation between those parameters is presented in Figure 1.

Two groups of patients were distinguished based on the median peak oxygen uptake: those with VO₂peak <30 ml/kg/min and those with VO₂peak ≥30 ml/kg/min. Patients with lower VO₂peak had a significantly lower PFR/LVSVI in comparison to patients with higher VO₂peak (5.12 m²/s, IQR 4.16-6.82 and 7.93 m²/s, IQR 7.49-8.21, $p = 0.035$, Figure 2).

Two examples of volume-time curves of the LV filling in patients with high and low PFR/LVSVI and VO₂peak are presented in Figure 3.

Table I. Baseline characteristics of the studied patients

Parameter	Studied group n=13
Clinical	
Age [years] (IQR)	38 (30.49)
Male gender [%]	10 (77)
NYHA class	
I [%]	10 (77)
II [%]	2 (15)
III [%]	1 (8)
CCS class	
I [%]	11 (84)
II [%]	1 (8)
III [%]	1 (8)
Syncope	1 (8)
Antiarrhythmic drugs	
Beta-blocker [%]	10 (77)
Verapamil [%]	2 (15)
CMR parameters	
Type of HCM	
I or II [%]	10 (77)
III [%]	3 (23)
IV [%]	0 (0)
IVSD [mm] (IQR)	25 (16.30)
LVEF [%] (IQR)	72 (66.75)
LVSVI [ml/m ²] (IQR)	54 (50.61)
LVEDVI [ml/m ²] (IQR)	81 (66.96)
LVESVI [ml/m ²] (IQR)	23 (16.32)

Abbreviations: CCS – Canadian Cardiovascular Society, HCM – hypertrophic cardiomyopathy, IQR – interquartile range, IVSD – interventricular septal diameter, LVEF – left ventricular ejection fraction, LVSVI – left ventricular stroke volume index, LVEDVI – left ventricular end-diastolic volume index, LVESVI – left ventricular end-systolic volume index, NYHA – New York Heart Association

Discussion

To our knowledge this is the first study which demonstrates that a simple cinematic CMR parameter, such as LV peak filling rate at rest normalised to stroke volume index, predicts objectively assessed exercise capacity in patients with non-obstructive HCM and preserved LV systolic function. At the same time we showed that neither age nor parameters of LV systolic function correlate with exercise capacity.

Cardiovascular magnetic resonance is becoming one of the most important elements in the management of patients with HCM. Recent studies demonstrated that CMR changes the paradigms of HCM diagnosis, risk stratification and management strategies [12]. Magnetic resonance along with genetic studies has been used to differentiate between primary and secondary causes of LV hypertrophy and may also be useful in the diagnosis of HCM at the early stages of the disease [8, 13]. Recently, it has been

Table II. Correlation between CMR parameters of LV diastolic function at rest and exercise capacity measured with peak oxygen uptake (VO₂peak)

	VO ₂ peak [ml/min/kg]	
	r	p
LVMI [ml/m ²]	0.37	0.22
PFR [ml/s]	0.63	0.02
PFR/LVSVI [m ² /s]	0.64	0.02
TPFR	-0.04	0.90

Abbreviations: LVMI – left ventricular mass index, PFR – peak filling rate, LVSVI – left ventricular stroke volume index, TPFR – time from end-systole to peak filling rate

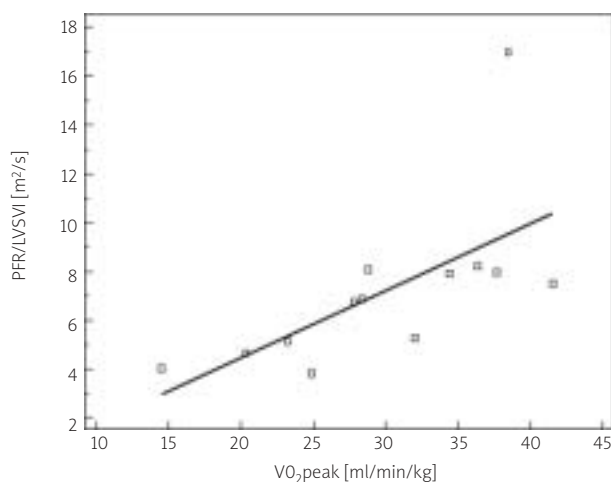


Figure 1. Correlation between peak filling rate normalised to stroke volume index (PFR/LVSVI) at rest and peak oxygen uptake (VO₂peak) during cardiopulmonary exercise testing on a treadmill

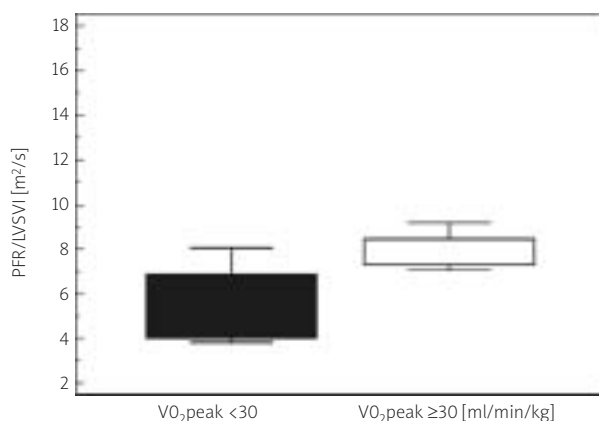


Figure 2. Box plots of PFR/LVSVI in patients with peak oxygen uptake (VO₂peak) below and above the median. Boxes indicate 25th and 75th percentiles (IQR); whiskers denote 10th and 90th percentiles. See Figure 1 for abbreviations

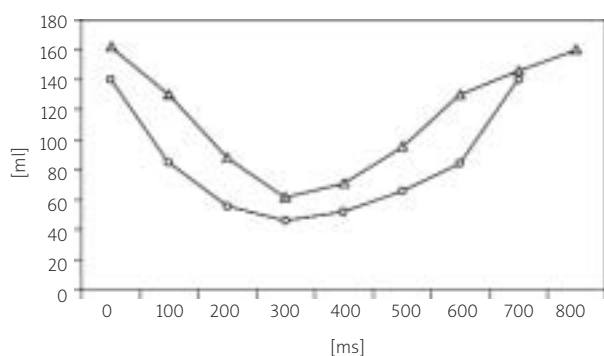


Figure 3. Two volume-time curves of LV filling in patients with high (curve with triangles) and low (curve with circles) PFR/LVSVI. The PFR/LVSVI and VO_2 peak in those patients were respectively: 8.21 m^2/s and 36.4 ml/min/kg, 3.81 m^2/s and 24.9 ml/min/kg

proved that in patients without or only with mild symptoms myocardial fibrosis detected by means of late enhancement is related to higher risk of ventricular tachyarrhythmias [7, 10]. Magnetic resonance may also be used to assess the LV outflow tract gradients as well as a tool for the monitoring of the results of percutaneous transluminal septal myocardial ablation or septal myectomy [9, 14].

We demonstrated that simple, routinely acquired cinematic views can be predictive of limited exercise capacity. Left ventricular peak filling rate can be easily obtained as an addition to the assessment of LV systolic function with semi-automatic contour detection. Therefore, it may become a valuable asset to the evaluation of late enhancement, perfusion defects, LV outflow tract gradient or other parameters in patients with HCM referred for CMR.

Previously published studies confirmed the fact that impairment of echocardiographically or invasively determined LV diastolic function at rest or during exercise is one of the most important factors limiting exercise capacity in patients with HCM [1, 3-6, 20]. In one of the first studies on this subject, Chikamori et al. found that maximal oxygen consumption was related to the ratio of peak ejection to peak filling rate [3]. In another study changes in peak filling rate and time from end-systole to peak filling rate after administration of verapamil in patients with HCM were predictive of changes in exercise duration [21]. Interestingly, Lele et al. showed that maximal oxygen uptake was significantly inversely related to time to peak filling rate at peak exercise but did not correlate with time to peak filling rate at rest, resting ejection fraction, peak filling rate, or peak exercise peak filling rate assessed invasively [5]. The results are in contrast with the findings of the current study. However, there is a limitation in that the patients in the Lele et al. study were not classified according to the presence or absence of LV outflow obstruction.

We did not find a significant correlation between peak oxygen uptake and LVMI. This may suggest that dynamic parameters such as volume/time curve better reflect the global, three-dimensional changes in LV function in comparison to the static parameters such as LV mass index.

A limitation of our study is the relatively small number of patients. We also did not analyse other CMR parameters of LV diastolic function such as flow mapping of the mitral valve or pulmonary veins by means of CMR phase contrast imaging, myocardial velocities also measured with phase contrast imaging, three-dimensional strain obtained by means of CMR tagging or myocardial metabolism assessed by means of CMR spectroscopy [17]. However, all those techniques require additional acquisitions and work-up which prolongs the study time and analysis of the results.

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Funkcja rozkurczowa lewej komory serca oceniana metodą rezonansu magnetycznego a wydolność fizyczna chorych z kardiomiopatią przerostową niezawężającą

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Streszczenie

Wstęp: U chorych z kardiomiopatią przerostową (KP) niezawężającą i zachowaną funkcją skurczową lewej komory serca dysfunkcja rozkurczowa stanowi jeden z głównych czynników ograniczających wydolność fizyczną. Rezonans magnetyczny serca staje się użytecznym narzędziem diagnostyki, stratyfikacji ryzyka oraz oceny efektów leczenia chorych z KP.

Cel: Ocena zależności między prostymi parametrami funkcji rozkurczowej lewej komory uzyskanymi metodą rezonansu magnetycznego serca w spoczynku a wydolnością fizyczną mierzoną w badaniu ergospirometrycznym na bieżni u chorych z KP niezawężającą i zachowaną funkcją skurczową lewej komory.

Metody: Do badania włączono 13 osób z KP niezawężającą oraz zachowaną funkcją skurczową lewej komory, u których wykonano badanie ergospirometryczne na bieżni oraz rezonans magnetyczny serca w odstępie maksymalnie miesiąca. Analizowano następujące parametry funkcji rozkurczowej serca: indeks masy lewej komory (LVMI), szczytowe napętnianie lewej komory uśrednione dla indeksu objętości wyrzutowej lewej komory (PFR/LVSVI) oraz czas między końcem skurczu a PFR uśredniony dla częstotliwości rytmu serca (TPFR).

Wyniki: W badanej grupie stwierdzono istotną korelację między PFR/LVSVI a szczytowym pochłanianiem tlenu (VO_2 peak) ($r=0,64$, $p=0,02$). Chorzy z VO_2 peak poniżej mediany (<30 ml/kg/min) cechowali się istotnie niższym PFR/LVSVI w porównaniu z pacjentami z wyższym VO_2 peak [5,12 m²/s, przedział między kwartylami (IQR) 4,16–6,82 vs 7,93 m²/s, IQR 7,49–8,21, $p=0,035$]. Zarówno LVMI oraz TPFR nie były związane z wydolnością fizyczną osób badanych. Jednocześnie nie stwierdzono korelacji między VO_2 peak a wiekiem pacjentów ($r=-0,38$, $p=0,19$), frakcją wyrzutową LV ($r=-0,36$, $p=0,22$) oraz uśrednionymi parametrami objętościowymi LV: LVEDVI ($r=0,09$, $p=0,76$), LVESVI ($r=0,34$, $p=0,26$).

Wnioski: Analiza funkcji rozkurczowej na podstawie szczytowego napętniania lewej komory serca uśrednionego dla indeksu objętości wyrzutowej lewej komory podczas badania rezonansu magnetycznego serca w spoczynku jest przydatnym parametrem oceny wydolności fizycznej u chorych z KP niezawężającą i zachowaną funkcją skurczową.

Słowa kluczowe: kardiomiopatia przerostowa, funkcja rozkurczowa, rezonans magnetyczny serca, wydolność fizyczna

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