International Journal of Cardiology 359 (2022) 61–68

Contents lists available at ScienceDirect

International Journal of Cardiology

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

Blunted coronary flow velocity reserve is associated with impairment in systolic function and functional capacity in hypertrophic cardiomyopathy

Sílvia Aguiar Rosa [a,b,1,*], Luís Rocha Lopes [c,d,e,1], Luísa Branco [a,1], Ana Galrinho [a,1], António Fiarresga [a,1], Boban Thomas [b,1], Pedro Brás [a,1], António Gonçalves [a,1], Isabel Cardoso [a,1], Ana Papoila [f,1], Marta Alves [f,1], Pedro Rio [a,1], Inês Cruz [g,1], Mafalda Selas [a,1], Filipa Silva [a,1], Ana Silva [a,1], Rui Cruz Ferreira [a,1], Miguel Mota Carmo [f,1,†]

[a] Department of Cardiology, Santa Marta Hospital, Lisbon, Portugal
[b] Heart Center, Hospital da Cruz Vermelha Portuguesa, Lisbon, Portugal
[c] Inherited Cardiac Disease Unit, Bart's Heart Centre, St Bartholomew's Hospital, London, United Kingdom
[d] Centre for Heart Muscle Disease, Institute of Cardiovascular Science, University College London, United Kingdom
[e] Cardiovascular Centre, University of Lisbon, Portugal
[f] NOVA Medical School/Faculdade de Ciências Médicas, Lisbon, Portugal
[g] Hospital Garcia de Orta, Almada, Portugal

ARTICLE INFO

Keywords:
Hypertrophic cardiomyopathy
Coronary flow velocity reserve
Ventricular function, functional capacity
Echocardiography
Cardiopulmonary exercise testing

ABSTRACT

Background: Coronary microvascular dysfunction constitutes an important pathophysiological feature in hypertrophic cardiomyopathy (HCM).
We aimed to assess the association between impaired coronary flow velocity reserve (CFVR) and ventricular systolic function and functional capacity.
Methods: Eighty-three patients with HCM were enrolled in this prospective cohort study. Patients underwent echocardiogram to evaluate ventricular performance and CFVR in the left anterior descending artery (LAD) and posterior descending artery (PD). Diastolic coronary flow velocity was measured in basal conditions and in hyperemia. CFVR was calculated as the ratio of hyperemic and basal peak diastolic flow velocities. Functional capacity was evaluated by cardiopulmonary exercise testing (CPET). The link between CFVR and biventricular systolic function and peak VO_2 was studied.
Results: Age was 55.0(14.4)years, 50 patients (60%) were male; 59 patients (71%) had nonobstructive HCM. Mean CFVR LAD was 1.81(0.49) and CFVR PD was 1.73(0.55). Lower CFVR PD was associated with impaired global longitudinal strain (GLS) 2D (β-estimate:-3.240,95%CI:-4.634;-1.846, $p < 0.001$), GLS 3D (β-estimate:-2.559,95%CI:-3.932;-1.186, $p < 0.001$) and area strain (β-estimate:-3.044,95%CI:-5.373;-0.716, $p = 0.011$). Lower values of CFVR PD related to worse global work index (β-estimate:267.824,95%CI:75.964;459.683, $p = 0.007$), global constructive work (β-estimate:217.300,95%CI:38.750;395.850, $p = 0.018$) and global work efficiency (β-estimate:5.656,95%CI:2.229;9.084, $p = 0.002$). Impaired CFVR LAD (β-estimate:2.826, 95% CI:0.913;4.739, $p = 0.004$) and CFVR PD (β-estimate:2.801,95%CI:0.657;4.945, $p = 0.011$) were associated with lower TAPSE. Lower values of CFVR LAD (β-estimate:2.580, 95%CI:0.169;4.991, $p = 0.036$) and CFVR PD (β-estimate:3.163, 95%CI: 0.721;5.606, $p = 0.012$) were associated with worse peak VO_2.
Conclusion: Lower CFVR was associated with impairment in biventricular systolic function parameters and functional capacity assessed by pVO_2.

* Corresponding author at: Rua de Santa Marta, n.50, 1169-024 Lisbon, Portugal.
E-mail address: silvia.rosa@chlc.min-saude.pt (S. Aguiar Rosa).
[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.
[†] Deceased.

https://doi.org/10.1016/j.ijcard.2022.04.032
Received 21 January 2022; Received in revised form 6 April 2022; Accepted 11 April 2022
Available online 12 April 2022

1. Introdution

Hypertrophic cardiomyopathy (HCM) is defined by the presence of unexplained left ventricular (LV) hypertrophy that cannot be solely explained by abnormal loading conditions [1].

Patients with HCM were found to have a reduction in coronary vasodilator reserve in hypertrophied and non-hypertrophied LV segments in the absence of epicardial coronary artery stenosis [2–4]. This microvascular dysfunction is likely multifactorial, including reduced capillary density, vascular remodelling, fibrosis, myocyte disarray, extravascular compression due to ventricular hypertrophy, diastolic dysfunction and left ventricular outflow tract (LVOT) obstruction.

Since the direct visualization of coronary microcirculation *in vivo* is still not possible, multiple invasive and non-invasive techniques have been developed [5]. Non-invasive methods, such as the evaluation of coronary flow velocity reserve (CFVR) by echocardiography [6,7] or detection of ischemia by cardiovascular magnetic resonance (CMR) [8,9] or positron emission tomography (PET) [10,11] have been used in HCM.

Despite the current knowledge on microcirculation abnormalities in HCM, further investigation is needed to delineate more precise interrelationship between microvascular dysfunction and ventricular function and clinical manifestations. Although potentially important from the clinical point of view [12], coronary microvascular dysfunction (CMD) is not a systematic evaluated parameter for clinical decision making in HCM. Furthermore, the identification of patients at risk for progression to heart failure and systolic dysfunction constitutes one of the main clinical concerns in HCM. However, this remains a challenge and more precise criteria are needed to identify at-risk patients and to determine their management.

We hypothesized that CMD is associated with biventricular systolic function and functional capacity in patients with HCM and prospectively investigated CMD by assessing CFVR using echocardiography, during adenosine-induced hyperemia. Firstly we investigated, among our cohort of patients with HCM, clinical and echocardiographic findings linked to impaired CFVR, in order to elucidate which patients are at higher risk of CMD. Secondly, knowing that cardiovascular magnetic resonance (CMR) is a recommended imaging technique to evaluate patients with HCM and consistently validated for the study of ischemia [13], we correlated the CFVR assessed by echocardiography with the extent of ischemic burden evaluated by CMR.

The present research aimed to study the association between blunted CFVR and:

a) impaired biventricular systolic function evaluated by two-dimensional (2D), three-dimensional (3D) and myocardial deformation parameters;
b) functional capacity assessed by peak oxygen uptake (VO_2);
c) ischemic burden assessed by CMR.

2. Material and methods

2.1. Study design and sample

Multicenter prospective cohort study, with recruitment performed at Hospital de Santa Marta, Centro Hospitalar Universitário de Lisboa Central and Hospital Garcia de Orta, Almada, between December 2017 and August 2020. The investigations took place in Hospital de Santa Marta.

The study included adult patients with diagnosis of HCM according to published guidelines [14]. Patients with LV ejection fraction (LVEF) <50%, prior septal reduction therapy and epicardial coronary artery disease were excluded. Obstructive epicardial coronary artery disease was excluded by invasive coronary angiography or coronary computerized tomography in symptomatic patients or asymptomatic patients older than 40 years. In asymptomatic patients younger than 40 years and without cardiovascular risk factors, it was assumed a low likelihood of obstructive coronary artery disease. The investigation followed the principles outlined in the Declaration of Helsinki. The institutional ethics committee of the NOVA Medical School, Lisbon and Centro Hospitalar Universitário de Lisboa Central approved the study protocol. All patients provided written informed consent.

2.2. Echocardiography

Patients underwent a comprehensive Doppler echocardiographic study using a commercially available ultrasound system (Vivid E95; General Electric).

LV myocardial deformation was evaluated by 2D global longitudinal strain (GLS), and by 3D speckle-tracking echocardiography including GLS, global circumferential strain (GCS), global radial strain (GRS), area strain, twist and torsion. Myocardial work and related indices were also analyzed: global constructive work (GCW), global wasted work (GWW), global work efficiency (GWE) and global work index (GWI).

Right ventricular systolic function was assessed by tricuspid annular plane systolic excursion (TAPSE) and tricuspid s' velocity.

The evaluation of coronary flow velocity reserve was performed in apical three chambers view for the LAD and in apical two chambers view for the PD. Blood flow was identified with colour Doppler and blood flow velocity was measured by pulsed-wave Doppler echocardiography. Peak diastolic coronary flow velocity was measured in basal conditions and during hyperemia, induced by adenosine infusion (0.14 mg/kg/min intravenously, for 2 min). In patients with atrial fibrillation, three diastolic flow profiles at rest and during hyperemia were measured, and results were averaged. CFVR was calculated as the ratio of hyperemic and basal peak diastolic flow velocities. CFVR≥2 was considered normal [15].

2.3. Cardiopulmonary exercise testing

Maximal symptom-limited treadmill cardiopulmonary exercise testing (CPET) was performed using a modified Bruce protocol. CPET and recovery period were performed under monitoring with continuous 12-lead electrocardiogram, blood pressure cuff, saturation probe and a face mask to measure respiratory gases. Blood pressure was measured at rest, in each stage, at peak exercise and at the first, third and sixth minute of the recovery phase. Respiratory gases were analyzed using the equipment Ergostik, Geratherm®, Cardio Solutions. $VO_2$was measured on a breath-by-breath basis.

2.4. Stress cardiovascular magnetic resonance

Stress CMR was done on a 1.5T system (Sola, Siemens, Erlangen, Germany), performed 90 s after hyperemia induced by regadenoson. Images were acquired apex to base during breath-hold at the first pass of contrast (60 measurements). A gradient echo sequence was used. Perfusion defects were considered surrogates for ischemia.

More details on echocardiography, CPET and CMR protocols are provided in supplemental material.

2.5. Statistical analysis

An exploratory analysis of the variables under study was carried out with categorical variables being described by frequencies (percentages), and quantitative variables by the mean (standard deviation).

To identify factors contributing to CFVR (dependent variable) and to study the association between CFVR (independent variable) and echocardiographic findings and functional capacity, generalized linear regression models for continuous response were applied. Univariable and multivariable models included patients' characteristics which might potentially influence these outcomes, including age, gender, cardiovascular risk factors, maximum wall thickness (MWT), and LVOT

obstruction.

All variables that in the univariable analysis attained a *p*-value ≤0.25 were selected for the multivariable models. Crude and adjusted regression coefficients (β) were estimated with corresponding 95% confidence intervals (95%CI). Normality assumption of the residuals was verified using Shapiro-Wilk test. To check the assumption of linearity for the continuous independent variables, generalized additive regression models were used.

The level of significance α = 0.05 was considered.

Considering the outcome CFVR as a binary variable (CFVR LAD ≥2.0; CFVR LAD <2.0), a cut-off point was determined for ischemia using the criterion that maximizes sensitivity and specificity.

Data were analyzed using the Statistical Package for the Social Science for Windows, version 25.0 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) and R (R: A Language and Environment for Statistical Computing, R Core Team, R Foundation for Statistical Computing, Vienna, Austria, year = 2021, http://www.R-project.org.).

3. Results

3.1. Clinical and echocardiographic findings

Eighty-three patients were recruited, 50(60%) were male, mean age was 55.0(14.4) years. The pattern of hypertrophy was asymmetric septal in 54(65%), apical in 22(27%) and concentric in 7 (8%). Fifty-nine patients (71%) had non obstructive HCM and mean MWT was 20.4(4.1) mm. Myocardial bridging was noted in 6 patients (supplemental table 1). Baseline characteristics are shown in Table 1.

CFV was successfully measured in the LAD in all patients, and in the PD in 62(75%) patients. In 21 patients the evaluation of CFV PD was not possible due to technical issues related to poor acoustic window and anatomical constraints. At baseline, mean coronary flow velocity in the LAD was 36.28(10.29)cm/s and mean coronary flow velocity in the PD was 36.54(11.15)cm/s; during hyperemia mean coronary flow velocity in the LAD was 63.00(16.70)cm/s and mean coronary flow velocity in the PD was 58.91(13.48)cm/s. Basal coronary flow velocity was higher in patients with higher heart rate and more severe LV hypertrophy (supplemental table 2). CFVR LAD was <2.0 in 49(59%) patients and CFVR PD was <2.0 in 43(52%) patients, denoting CMD (Table 1)(Fig. 1) (Supplemental Fig. 1 and 2).

The potential association between clinical and echocardiographic parameters with CFVR was studied. Supplemental table 3 shows the univariable and multivariable results.

In multivariable analysis, greater LV maximum wall thickness (MWT)(β-estimate:-0.040,95%CI:-0.071;-0.010, p = 0.010) and female gender (β-estimate:-0.379,95%CI:-0.640;-0.118, p = 0.005) were independently associated with impaired CFVR PD. No association was found between LVOT obstruction and CFVR, neither with age or cardiovascular risk factors. No multivariable model was obtained for CFVR LAD.

3.2. Association between coronary flow velocity reserve and other echocardiographic findings

Mean values of all parameters of speckle-tracking echocardiography were impaired with the exception of 3D torsion (Supplemental Fig. 3).

The association between CFVR and parameters of LV myocardial performance was studied; the univariable analysis is detailed in Supplemental Table 4.

No relation was found between CFVR or other echocardiographic findings with LV ejection fraction.

Regarding deformation parameters by 2D echocardiography, the multivariable analysis showed that lower CFVR PD was associated with impaired GLS (β-estimate:-3.240,95%CI:-4.634;-1.846, p < 0.001). Using 3D analysis, decreased CFVR PD was associated with impaired myocardial deformation parameters, namely GLS 3D (β-estimate:-2.559,95%CI:-3.932;-1.186, p < 0.001), GCS (β-estimate:-5.190,95% CI:-7.823;-2.557, p < 0.001) and area strain (β-estimate:-3.044,95%CI:-5.373;-0.716, p = 0.011). No association was found between CFVR LAD and LV myocardial strain parameters (Table 2).

A link between CFVR PD and myocardial work was also demonstrated, with lower values of CFVR PD relating to worse GWI (β-estimate:267.824,95%CI:75.964;459.683, p = 0.007), GCW (β-estimate:217.300,95%CI:38.750;395.850, p = 0.018) and GWE (β-estimate:5.656,95%CI: 2.229;9.084, p = 0.002). No association was found between CFVR LAD and LV myocardial work (Table 2).

Besides CFVR, the other HCM related anatomical and functional

Table 1
Baseline characteristics and echocardiographic findings of the study population.

Baseline characteristics	*n* = 83
Male gender, n(%)	50(60)
Age(years), mean(SD)	55.0(14.4)
Hypertension, n(%)	40(48)
Diabetes, n(%)	14(17)
Dyslipidaemia, n(%)	33(40)
Current smoker, n(%)	13(16)
Beta blocker, n(%)	62(75)
Calcium channel blocker, n(%)	19(23)
Nonobstructive HCM, n(%)	59(71)
NYHA I, n(%)	45(54)
NYHA II-III, n(%)	38(46)
Angina, n(%)	28(34)
Syncope, n(%)	2(2)
Palpitations, n(%)	27(33)
Sinus rhythm, n(%)	66(80)
Atrial fibrillation/atrial flutter, n(%)	17(21)
Atrial fibrillation, n(%)	15
Atrial flutter, n(%)	2
Echocardiographic parameters	n = 83
Maximum wall thickness(mm), mean(SD)	20.4(4.1)
LVOT gradient(mmHg), mean(SD)	36.2(51.3)
LVEDV(mL/m^2), mean(SD)	43.3(11.7)
LVESV(mL/m^2), mean(SD)	15.1(5.9)
LV ejection fraction(%), mean(SD)	67.9(7.2)
Global longitudinal strain(%), mean(SD)	−14.22(3.74)
LVEDV 3D(mL/m^2), mean(SD)	58.1(14.4)
LVESV 3D(mL/m^2), mean(SD)	22.1(7.2)
LVEF 3D(%), mean(SD)	62.7(6.1)
LV mass 3D(g/m^2), mean(SD)	95.6(23.1)
Global longitudinal strain 3D(%), mean(SD)	−9.57(3.68)
Global circumferential strain 3D(%), mean(SD)	−13.16(5.97)
Global radial strain 3D (%), mean(SD)	29.47(11.39)
Area strain 3D(%), mean(SD)	−19.49(5.97)
Twist 3D(deg), mean(SD)	5.19(5.43)
Torsion 3D(deg/cm), mean(SD)	1.10(0.89)
Myocardial global work index(mmHg%), mean(SD)	1326.4(440.4)
Myocardial global constructive work(mmHg%), mean(SD)	1551.8(437.7)
Myocardial global wasted work(mmHg%), mean(SD)	168.2(119.5)
Myocardial global work efficiency(%), mean(SD)	86.9(7.5)
Tricuspid annular plane systolic excursion(mm), mean(SD)	23.5(4.3)
Tricuspid s' velocity(cm/s), mean(SD)	13.9(3.2)
E/e', mean(SD)	12.55(4.71)
Peak tricuspid regurgitation velocity(cm/s), mean(SD)	247.8(37.6)
Left atrial volume(ml/m^2), mean(SD)	46.2(16.6)
Moderate/severe mitral regurgitation, n (%)	4 (5)
Baseline coronary flow velocity(cm/s)	
Left anterior descending artery, mean(SD)	36.28(10.29)
Posterior descending artery, mean(SD)	36.54(11.15)
Hyperemia coronary flow velocity(cm/s)	
Left anterior descending artery, mean(SD)	63.00(16.70)
Posterior descending artery, mean(SD)	58.91(13.48)
Coronary flow velocity reserve LAD, mean(SD)	1.81(0.49)
Coronary flow velocity reserve PD, mean(SD)	1.73(0.55)
Heart rate at rest, mean (SD)	66.1(12.0)
Heart rate during hyperemia, mean (SD)	84.7(17.2)

BSA-body surface area; LVEDV-left ventricular end-diastolic volume; LVEF-left ventricular ejection fraction; LVESV-left ventricular end-systolic volume; LVOT-left ventricular outflow tract; LAD-left anterior descending artery; NYHA-New York Heart Association; PD-posterior descending artery; SD-standard deviation.

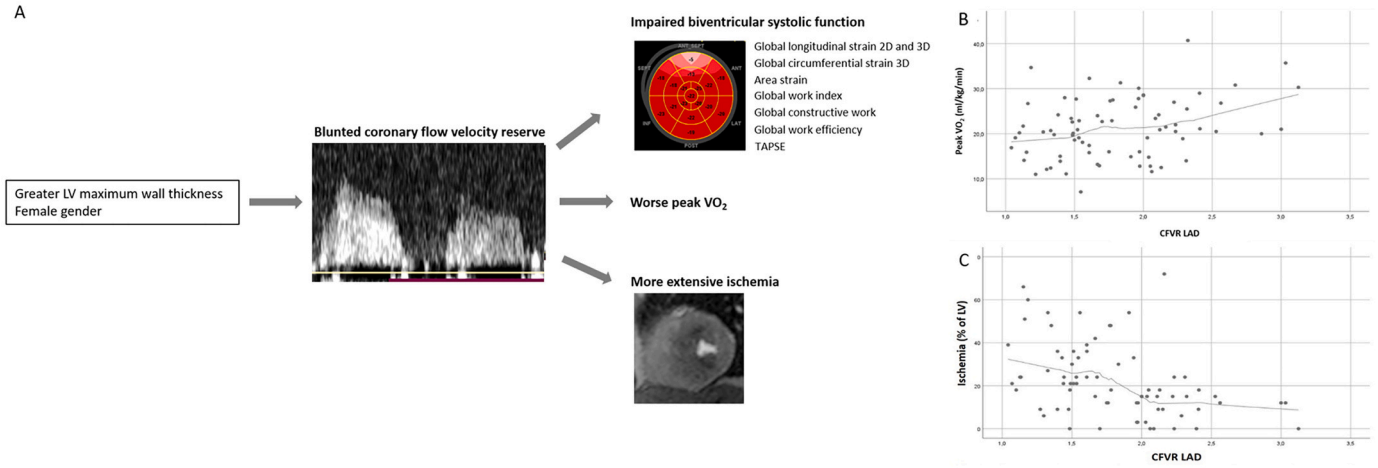

Fig. 1. Blunted coronary flow velocity reserve assessed by echocardiography was associated with worse biventricular function, lower peak VO_2 (B) and more extent ischemia by CMR (C). Patients with greater left ventricular (LV) wall thickness and females had more severe impairment in coronary flow velocity reserve. *In the example, CFRV LAD calculated in 1.5.*

abnormalities associated with impaired myocardial deformation were MWT and LVOT gradient (Table 2).

Regarding the right ventricular systolic function, in univariable analysis (no multivariable model was obtained), lower values of CFVR LAD (β-estimate:2.826,95%CI:0.913;4.739, p = 0.004) and CFVR PD (β-estimate:2.801,95%CI:0.657;4.945, p = 0.011) were found to be associated with lower TAPSE (Supplemental Table 4). Higher MWT and LVOT gradient were related with slight increase in tricuspid s' velocity (Table 2).

3.3. Association between coronary flow velocity reserve and functional capacity

CPET parameters were not available in 7 patients: in two patients it was not possible to interpret CPET parameters due to intolerance to the face mask leading to inaccurate analysis of expired gases; four patients refused to do CPET; one patient died during the study period, of a non-cardiac cause.

The CPET duration was 12.3(4.3) minutes, basal heart rate was 69.8 (13.5) beats per minute, peak heart rate was 135.2(25.4) beats per minute, 45(59%) patients achieved at least 80% of maximum heart rate and in 51(67%) patients VCO_2/VO_2 ratio was ≥1. Peak VO_2 was 21.15 (6.64)ml/kg/min. During CPET, two patients had NSVT and 14 had premature ventricular beats during exercise or recovery phase; four patients presented abnormal blood pressure response (increase systolic pressure < 20 mmHg).

Multivariable analysis results showed that both CFVR LAD and CFVR PD were related to peak VO_2, with lower values of CFVR associated with worse peak VO_2 (Supplemental Fig. 4). For each unit increase in CFVR LAD, there was a mean increase of 2.58 ml/kg/min in the value of peak VO_2, while a mean increase in peak VO_2 of 3.16 ml/kg/min was verified for each unit increase in CFVR PD (Table 2).

Univariable analysis is shown in Supplemental Table 5.

3.4. Relationship between coronary flow velocity reserve by echocardiography and extent of ischemia demonstrated by cardiovascular magnetic resonance

Seventy-five patients underwent CMR, the remaining eight patients did not undergo CMR due to claustrophobia, the existence of previous unknown metal object in the body, one patient was submitted to ICD implantation during the study period and one patient died for a non-cardiac cause as mentioned above.

Perfusion defect in at least one segment was noted in 68(91%) patients and ischemic burden was 22.5(16.9)% of LV.

We investigated the association between CFVR measured by echocardiography and the extent of ischemia assessed by CMR. In univariable analysis (Supplemental Table 6), both CFVR LAD (β-estimate:-15.218,95%CI:-22.951;-7.485, p < 0.001) and CFVR PD (β-estimate:-9.977,95%CI:-18.395;-1.559, p = 0.021) had an inverse relationship with the severity of ischemia: lower values of CFVR LAD and CFVR PD were associated with more extensive ischemia. In multivariable analysis, the association between CFVR LAD and ischemia was more robust (p = 0.001) comparing to the link between CFVR PD and ischemia (p = 0.077)(Table 3). For each 1.0 increase in CFVR LAD, there was a decrease of 12.5% in the extent of LV ischemia. Analyzing CFVR LAD as a binary variable (CFVR LAD ≥2.0; CFVR LAD <2.0), higher ischemia values were obtained for CFVR LAD <2.0, with an area under the ROC curve of 0.768. At the ischemia estimated cut-off point at 18%, a sensitivity of 0.729, and a specificity of 0.769 were achieved.

The analysis was repeated only for the 62 patients with both CFVR LAD and CFVR PD measurements, and similar results were obtained (supplemental tables 7 and 8).

4. Discussion

In this study, we showed that blunted CFVR is associated with LV systolic function assessed by myocardial deformation parameters, RV systolic function and functional capacity assessed by peak VO_2 on CPET.

Published data using imaging methods for the study of CMD highlighted the prevalence and prognostic importance of microcirculation abnormalities in HCM [6–11,16]. Our study adds the detailed association between CFVR and pVO_2 which constitutes a more accurate method to evaluate functional class comparing to clinical assessment using NYHA classification. Furthermore, besides myocardial strains analysis we also analyzed myocardial work, which is a more recent echocardiographic parameters of LV performance that enhances the information provided by GLS, allowing a correct investigation of cardiac contractility in an afterload independent manner [17]. To the best of our knowledge, this is the first study that assesses the relationship between myocardial deformation parameters, particularly myocardial work, and CFVR.

In our cohort, CMD assessed by echocardiography was found in more than half of the patients, and was more severe in patients with higher MWT and females. The extent of hypertrophy and higher regional wall thickness have been related to a decrease in hyperemic perfusion and microvascular dysfunction in HCM [18], likely due to extravascular compression, as a consequence of impaired LV relaxation and increased filling pressure [19]. Additionally, women are more often affected by

Table 2
Multivariable linear regression for factors related with echocardiographic findings and peak VO_2.

	Multivariable		
CFVR LAD			
	β-estimate	95% confidence interval	p-value
LV ejection fraction 2D(%)			
No multivariable model			
Global Longitudinal strain 2D (%)			
CFVR LAD	−0.856	−2.329;0.618	0.251
MWT(mm)	0.376	0.206;0.546	<0.001
Diabetes	3.101	1.218;4.985	0.002
Left ventricular ejection fraction 3D(%)			
No multivariable model			
Global Longitudinal strain 3D (%)			
CFVR LAD	−0.983	−2.543;0.577	0.213
Age(years)	0.068	0.014;0.122	0.014
Diabetes	2.985	0.929;5.041	0.005
Global circumferential strain 3D (%)			
CFVR LAD	−0.956	−3.713;1.801	0.492
Diabetes	4.513	1.112;7.914	0.010
Global radial strain 3D(%)			
CFVR LAD	0.602	−4.434;5.638	0.812
Diabetes	−12.042	−18.254;-5.830	<0.001
Area strain 3D(%)			
CFVR LAD	0.807	−1.731;3.345	0.528
Diabetes	6.681	3.573;9.789	<0.001
Hypertension	2.580	0.218;4.943	0.033
Twist 3D(deg)			
No multivariable model			
Torsion 3D(deg/cm)			
CFVR LAD	0.113	−0.309;0.536	0.594
LVOT gradient (mmHg)	0.004	0.000;0.008	0.047
GWI(mmHg%)			
CFVR LAD	62.002	−127.633;251.636	0.517
MWT(mm)	−40.188	−62.403;-17.973	0.001
GCW(mmHg%)			
CFVR LAD	37.938	−148.539;224.414	0.686
MWT(mm)	−43.309	−65.154;-21.464	<0.001
GWW(mmHg%)			
CFVR LAD	−35.012	−88.061;18.036	0.193
Hypertension	69.772	17.840;121.704	0.009
GWE(%)			
CFVR LAD	1.999	−1.289;5.288	0.230
MWT(mm)	−0.448	−0.828;-0.069	0.021
Diabetes	−4.778	−9.083;-0.474	0.030
TAPSE(mm)			
No multivariable model			
Tricuspid s' velocity(cm/s)			
CFVR LAD	1.253	−0.145;2.651	0.078
MWT(mm)	0.236	0.067;0.405	0.007
LVOT gradient(mmHg)	0.017	0.004;0.030	0.009
CFVR PD			
LV ejection fraction 2D(%)			
No multivariable model			
Global Longitudinal strain 2D (%)			
CFVR PD	−3.240	−4.634;-1.846	<0.001
MWT(mm)	0.282	0.098;0.465	0.003
Left ventricular ejection fraction 3D(%)			
No multivariable model			
Global Longitudinal strain 3D (%)			
CFVR PD	−2.559	−3.932;-1.186	<0.001
Age(years)	0.097	0.046;0.148	<0.001
Global circumferential strain 3D (%)			
No multivariable model			
Global radial strain 3D(%)			
CFVR PD	2.491	−2.384;7.366	0.310
Age(years)	−0.280	−0.461;-0.099	0.003
Area strain 3D(%)			
CFVR PD	−3.044	−5.373;-0.716	0.011
Age(years)	0.133	−0.047;0.220	0.003
Twist 3D(deg)			
No multivariable model			
Torsion 3D(deg/cm)			
No multivariable model			
GWI(mmHg%)			
CFVR PD	267.824	75.964;459.683	0.007
MWT(mm)	−26.115	−51.422;-0.808	0.043
GCW(mmHg%)			
CFVR PD	217.300	38.750;395.850	0.018
MWT (mm)	−31.081	−54.633;-7.530	0.011
GWW(mmHg%)			
CFVR PD	−42.390	−101.832;17.052	0.159
Hypertension	90.439	24.420;156.458	0.008
GWE(%)			
No multivariable model			
TAPSE(mm)			
No multivariable model			
Tricuspid s' velocity(cm/s)			
CFVR PD	−0.078	−1.402;1.246	0.906
LVOT gradient(mmHg)	0.019	0.002;0.035	0.028
Age(years)	−0.054	−0.102;-0.006	0.029

	Multivariable		
CFVR LAD			
	β-estimate	95% confidence interval	p-value
Peak VO_2(ml/kg/min)			
CFVR LAD	2.580	0.169;4.991	0.036
Female	−4.201	−6.784;-1.619	0.002
Age (years)	−0.197	−0.282;-0.112	<0.001
CFVR PD			
	β-estimate	95% confidence interval	p-value
Peak VO_2(ml/kg/min)			
CFVR PD	3.163	0.721;5.606	0.012
Tricuspid s' velocity(cm/s)	0.579	0.134;1.023	0.012
Female	−4.144	−7.033;-1.255	0.006
Age(years)	−0.180	−0.271;-0.088	<0.001

CFVR - Coronary flow velocity reserve; LAD – left anterior descending artery; GCW - global constructive work; GWE - global work efficiency; GWI - global work index; GWW - global wasted work; LVOT – left ventricular outflow tract; MWT – maximum wall thickness; TAPSE - Tricuspid annular plane systolic excursion TR - tricuspid regurgitation; VO_2- Oxygen uptake; 3D - three-dimensional.

Table 3
Multivariable analysis for the association between coronary flow velocity reserve by echocardiography and ischemia by cardiovascular magnetic resonance.

	Multivariable		
	β-estimate	95% confidence interval	p-value
CFVR LAD			
Ischemia(% of LV)			
CFVR LAD	−12.469	−19.640;-5.298	0.001
MWT(mm)	1.584	0.793;2.374	<0.001
CFVR PD			
Ischemia(% of LV)			
CFVR PD	−7.477	−15.787;0.832	0.077
MWT(mm)	1.167	0.210,2.125	0.018

CFVR-coronary flow velocity reserve; LAD-left anterior descending artery; LV-left ventricle; MWT-maximum wall thickness; PD-posterior descending artery.

microcirculation abnormalities than men [20]. The relationship between LVOT gradient and CMD has been described [7,18], although it is not consistently found in all studies [21]. We did not find a relationship between CMD and LVOT gradient, however it should be taken into account that only 29% of patients in our cohort had obstructive HCM.

Comparing to values published for controls [7,22], we found higher values of CFV at baseline in patients with HCM. By Doppler echocardiography and by cardiac catheterization using a Doppler wire, it was previously demonstrated an increase in basal diastolic coronary flow and lower coronary flow reserve in patients with HCM comparing to normal subjects [7,22–24]. At rest conditions, patients with HCM have recruitment of vasodilatory capacity in order to maintain flow per unit mass of myocardium, and so to supply oxygen demand of the hypertrophied myocardium [25,26]. Thus, during pharmacological stress, the autoregulatory mechanisms of the microvessels are exhausted and vascular resistance and extravascular compressive forces became the predominant determinants of perfusion, resulting in blunted coronary flow reserve and ischemia [18].

4.1. Association between coronary flow velocity reserve and biventricular performance

Regarding LV systolic function, no echocardiographic finding was associated with LV ejection fraction, which denotes the modest accuracy of this parameter for detection of impaired LV performance in HCM, since the majority of patients have normal or supranormal LV ejection fraction. Furthermore, LV ejection fraction <50% was an exclusion criterion in the present study. On the other hand, the study of myocardial deformation has been pointed as a tool to early detect deterioration of systolic function, before an overt decrease in ejection fraction [27], and even to differentiate mutation carriers from controls [28].

Blunted CFVR PD was an independent factor associated with impaired 2D and 3D GLS, area strain and myocardial work. We hypothesize that ischemia secondary to CMD damages myocytes energetic metabolism culminating in worse systolic performance. Recurrent episodes of ischemia due to CMD results in myocyte death and fibrotic replacement [29], and attenuated GLS, area strain and myocardial work were shown to be related with more extensive fibrosis in HCM [30–33].

The impact of CFVR in LV performance may lead to worse outcome, including impaired functional capacity and heart failure. GLS > -16% showed to be associated with progression to heart failure and cardiac transplantation [34]. These consecutive associations suggest a link between blunted CFVR, impaired LV myocardial deformation and lower pVO_2 found in our study.

Surprisingly, we found a stronger association between CFVR PD and LV performance parameters compared with CFVR LAD. The LAD territory is affected in the majority of patients with HCM since this is the location most frequently hypertrophied, while the inferior segments of the LV are affected in more extensive disease, and thus may have more discriminative power as surrogate markers of disease severity. Different CFVR between coronary arteries was already described in HCM in relation with the severity of hypertrophy in the respective territory. The inherent morphological heterogeneity within the left ventricle, in a single patient, may be related to the difference found between CFVR LAD and CFVR PD, and may further explain the stronger association between CFVR PD and LV performance parameters.

Although we verified lower feasibility for the evaluation of CFVR PD compared to CFVR LAD, the evaluation of CFVR for both LAD and PD may have an important additive prognostic value, as was also demonstrated previously in patients with known or suspected coronary artery disease and negative stress echocardiography [35].

In our cohort, CFVR was found to be positively related with TAPSE, suggesting that CMD is also related to RV energetic imbalance and systolic function.

4.2. Association between coronary flow velocity reserve and functional capacity

The mechanism of exercise limitation in patients with HCM is multifactorial, encompassing LV systolic and diastolic dysfunction, LVOT obstruction, and myocardial ischemia. The severity of microvascular dysfunction has been reported as possibly relevant in the development of heart failure, and an inverse relationship between myocardial blood flow and functional class was previously documented [11]. Furthermore, CFVR demonstrated to be an independent predictor of heart transplant and hospitalizations for acute heart failure [36,37]. Recently, Tesic and co-workers demonstrated that CFVR LAD was effective in risk stratification of patients with HCM, particularly for the onset of heart failure during a long follow up period, considering the evaluation of CFVR PD redundant to this regard [21].

Both CFVR LAD and CFVR PD were associated with peak VO_2, independently of other markers of disease severity, as MWT, LVOT obstruction or diastolic dysfunction. Peak VO_2 is an important predictor of outcome, including cardiac-related death, heart transplant, and functional deterioration [38–40]. This emphasizes that CMD is not only an important pathophysiological feature in the unfolding of disease natural history, as well as a potential therapeutic target in order to improve outcome.

No relationship was noted between LV ejection fraction and functional capacity. On the other hand, tricuspid s' velocity showed to be associated with peak VO_2. It has been demonstrated that RV function is a key determinant of exercise capacity in heart failure with reduced systolic function [41], however its role in the context of HCM is less studied.

4.3. Multimodality approach in the study of coronary microvascular dysfunction in hypertrophic cardiomyopathy – comparison between echocardiography and CMR

CMR has been pointed as a valuable tool to assess LV ischemia in different conditions [8,9,13], however it is not available at all centers. On the other hand, transthoracic echocardiography is extensively available and constitutes the first-line imaging technique to evaluate patients with HCM [42]. The approach of CMD study by echocardiography has the potential to make this evaluation more widespread among patients with HCM, despite the longer time needed per study and the difficulty of CFVR PD evaluation in a significant proportion of patients.

Using a multimodality approach including echocardiography and CMR, this study showed that CMD is a frequent finding in HCM. With CMR, microvascular dysfunction was detected in a bigger proportion of patients. Whether all the spectrum of ischemia values has clinical relevance needs further investigation. In fact, we found that the cut-off point of 18% of LV ischemia was associated with CFVR <2.0. Consistently lower values of CFVR LAD by echocardiography were associated with higher ischemic burden by CMR.

4.4. Study limitations

Our cohort is relatively small which may limit the generalisation of these findings. The small sample size also limited the achievement of statistical significance in some associations. Only 29% of patients had obstructive HCM and this may explain the absence of association between CFVR and LVOT obstruction, found in previous studies. LVOT obstruction was studied at rest and after Valsalva maneuver; an exercise echocardiogram was performed in some patients according to physicians' judgment. Doppler echocardiography does not provide absolute measures of volumetric flow, but rather provides measures of coronary flow velocity. CFVR were considered as surrogates for CMD, similarly to several other studies in multiple conditions. Due to poor acoustic window, CFVR in the PD was not assessed in 25% of the patients. The evaluation of coronary flow velocities is not widely used at all centers which may limit the clinically applicability and reproducibility of our

findings.

Adenosine was used for echocardiography and regadenoson for CMR; hyperemia may vary for different vasodilators [43].

The absence of control group does not allow the direct comparison of parameters and associations between HCM and normal population.

5. Conclusion

Blunted CFVR is a frequent finding in patients with HCM without epicardial coronary artery disease. In our cohort, lower CFVR evaluated by echocardiography was associated with impaired biventricular systolic function, particularly with LV myocardial deformation parameters and including with the novel parameters of myocardial work. Furthermore, this study emphasizes the link between CFVR and functional capacity objectively assessed by pVO2. When compared with stress CMR, the severity of CMD was concordant between the two imaging techniques.

The routine assessment of CFVR may be potentially incorporated in clinical practice, as more accurate predictive factors for evolution to heart failure are still needed.

Conflicts of interest

Nothing to Disclose.

Acknowledgements

This article is dedicated to the memory of Prof. Miguel Mota Carmo.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2022.04.032.

References

[1] S.R. Ommen, S. Mital, M.A. Burke, S.M. Day, A. Deswal, P. Elliott, et al., 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines, J. Am. Coll. Cardiol. 142 (25) (2020 Nov) e533–e557.
[2] C. Basso, G. Thiene, D. Corrado, G. Buja, P. Melacini, A. Nava, Hypertrophic cardiomyopathy and sudden death in the young: pathologic evidence of myocardial ischemia, Hum. Pathol. 31 (8) (2000) 988–998.
[3] B.J. Maron, J.K. Wolfson, S.E. Epstein, W.C. Roberts, Intramural ("small vessel") coronary artery disease in hypertrophic cardiomyopathy, J. Am. Coll. Cardiol. 8 (3) (1986) 545–557.
[4] B. Schwartzkopff, M. Mundhenke, B.E. Strauer, Alterations of the architecture of subendocardial arterioles in patients with hypertrophic cardiomyopathy and impaired coronary vasodilator reserve: a possible cause for myocardial ischemia, J. Am. Coll. Cardiol. 31 (5) (1998) 1089–1096.
[5] S. Aguiar Rosa, L. Rocha Lopes, A. Fiarresga, R.C. Ferreira, Carmo M. Mota, Coronary microvascular dysfunction in hypertrophic cardiomyopathy: pathophysiology, assessment, and clinical impact, Microcirculation (2020) 1–17 (June).
[6] L. Cortigiani, F. Rigo, S. Gherardi, M. Galderisi, R. Sicari, E. Picano, Prognostic implications of coronary flow reserve on left anterior descending coronary artery in hypertrophic cardiomyopathy, Am. J. Cardiol. 102 (12) (2008) 1718–1723.
[7] M. Tesic, A. Djordjevic-Dikic, B. Beleslin, D. Trifunovic, V. Giga, J. Marinkovic, et al., Regional difference of microcirculation in patients with asymmetric hypertrophic cardiomyopathy: transthoracic Doppler coronary flow velocity reserve analysis, J. Am. Soc. Echocardiogr. 26 (7) (2013) 775–782.
[8] A.D.M. Villa, E. Sammut, N. Zarinabad, G. Carr-White, J. Lee, N. Bettencourt, et al., Microvascular ischemia in hypertrophic cardiomyopathy: new insights from high-resolution combined quantification of perfusion and late gadolinium enhancement, J. Cardiovasc. Magn. Reson. 18 (2016) 4.
[9] C. Camaioni, K.D. Knott, J.B. Augusto, A. Seraphim, S. Rosmini, F. Ricci, et al., Inline perfusion mapping provides insights into the disease mechanism in hypertrophic cardiomyopathy, Heart (2019) 1–6.
[10] P. Camici, G. Chiriatti, R. Lorenzoni, R.C. Bellina, R. Gistri, G. Italiani, et al., Coronary vasodilation is impaired in both hypertrophied and nonhypertrophied myocardium of patients with hypertrophic cardiomyopathy: a study with nitrogen-13 ammonia and positron emission tomography, J. Am. Coll. Cardiol. 17 (4) (1991) 879–886.
[11] R. Lorenzoni, R. Gistri, F. Cecchi, I. Olivotto, G. Chiriatti, P. Elliott, et al., Coronary vasodilator reserve is impaired in patients with hypertrophic cardiomyopathy and left ventricular dysfunction, Am. Heart J. 136 (6) (1998) 972–981.
[12] I. Olivotto, F. Cecchi, P.G. Camici, Coronary microvascular dysfunction and ischemia in hypertrophic cardiomyopathy. Mechanisms and clinical consequences, Ital. Hear J. 5 (8) (2004) 572–580.
[13] E. Nagel, J.P. Greenwood, G.P. McCann, N. Bettencourt, A.M. Shah, S.T. Hussain, et al., Magnetic resonance perfusion or fractional flow reserve in coronary disease, N. Engl. J. Med. 380 (25) (2019) 2418–2428.
[14] P.M. Elliott, A. Anastasakis, M.A. Borger, M. Borggrefe, F. Cecchi, P. Charron, A. A. Hagege, A. Lafont, G. Limongelli, H. Mahrholdt, W.J. McKenna, J. Mogensen, P. Nihoyannopoulos, S. Nistri, P.G. Pieper, B. Pieske, C. Rapezzi, F.H. Rutten, C.W. H. Tillmanns, 2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy: the task force for the diagnosis and management of hypertrophic cardiomyopathy of the European Society of Cardiology (ESC), Eur. Heart J. 35 (39) (2014) 2733–2779.
[15] I. Simova, Coronary flow velocity reserve assessment with transthoracic doppler echocardiography, Eur. Cardiol. Rev. 10 (1) (2015) 12–18.
[16] I. Olivotto, F. Cecchi, R. Gistri, R. Lorenzoni, G. Chiriatti, F. Girolami, et al., Relevance of coronary microvascular flow impairment to long-term remodeling and systolic dysfunction in hypertrophic cardiomyopathy, J. Am. Coll. Cardiol. 47 (5) (2006) 1043–1048.
[17] K. Russell, M. Eriksen, L. Aaberge, N. Wilhelmsen, H. Skulstad, E.W. Remme, et al., A novel clinical method for quantification of regional left ventricular pressurestrain loop area: a non-invasive index of myocardial work, Eur. Heart J. 33 (6) (2012) 724–733.
[18] P. Knaapen, T. Germans, P.G. Camici, O.E. Rimoldi, F.J. Ten Cate, J.M. Ten Berg, et al., Determinants of coronary microvascular dysfunction in symptomatic hypertrophic cardiomyopathy, Am. J. Physiol. Heart Circ. Physiol. 294 (2) (2008) 986–993.
[19] O.I.I. Soliman, P. Knaapen, M.L. Geleijnse, P.A. Dijkmans, A.M. Anwar, A. Nemes, et al., Assessment of intravascular and extravascular mechanisms of myocardial perfusion abnormalities in obstructive hypertrophic cardiomyopathy by myocardial contrast echocardiography, Heart 93 (10) (2007) 1204–1212.
[20] V.R. Taqueti, L.J. Shaw, N.R. Cook, V.L. Murthy, N.R. Shah, C.R. Foster, et al., Excess cardiovascular risk in women relative to men referred for coronary angiography is associated with severely impaired coronary flow reserve, not obstructive disease, Circulation 135 (6) (2017) 566–577.
[21] M. Tesic, B. Beleslin, V. Giga, I. Jovanovic, J. Marinkovic, D. Trifunovic, et al., Prognostic value of transthoracic doppler echocardiography coronary flow velocity reserve in patients with asymmetric hypertrophic cardiomyopathy, J. Am. Heart Assoc. 10 (20) (2021) 1–12.
[22] D.E. Ferreiro, T.F. Cianciulli, M.C. Saccheri, J.A. Lax, L. Celano, M.A. Beck, et al., Assessment of coronary flow with transthoracic color doppler echocardiography in patients with hypertrophic cardiomyopathy, Echocardiography 30 (10) (2013 Nov) 1156–1163.
[23] H.J. Youn, J.M. Lee, C.S. Park, S.H. Ihm, E.J. Cho, H.O. Jung, et al., The impaired flow reserve capacity of penetrating intramyocardial coronary arteries in apical hypertrophic cardiomyopathy, J. Am. Soc. Echocardiogr. 18 (2) (2005) 128–132.
[24] H.S. Ahn, H.K. Kim, E.A. Park, W. Lee, Y.J. Kim, G.Y. Cho, et al., Coronary flow reserve impairment in apical vs asymmetrical septal hypertrophic cardiomyopathy, Clin. Cardiol. 36 (4) (2013) 207–216.
[25] M.K. Kyriakidis, J.M. Dernellis, A.E. Androulakis, G.A. Kelepeshis, J. Barbetseas, A. N. Anastasakis, A.G. Trikas, C.A. Tentolouris, J.E.T.P. Gialafos, Changes in phasic coronary blood flow velocity profile and relative coronary flow reserve in patients with hypertrophic obstructive cardiomyopathy, Circulation 96 (3) (1997) 834–841.
[26] H.K. Kim, Y.J. Kim, D.W. Sohn, Y.B. Park, Y.S. Choi, Transthoracic echocardiographic evaluation of coronary flow reserve in patients with hypertrophic cardiomyopathy, Int. J. Cardiol. 94 (2–3) (2004) 167–171.
[27] Z. Chen, C. Li, Y. Li, L. Rao, X. Zhang, D. Long, et al., Layer-specific strain echocardiography may reflect regional myocardial impairment in patients with hypertrophic cardiomyopathy, Cardiovasc. Ultrasound 19 (1) (2021) 1–12.
[28] G. Baudry, N. Mansencal, A. Reynaud, P. Richard, O. Dubourg, M. Komajda, et al., Global and regional echocardiographic strain to assess the early phase of hypertrophic cardiomyopathy due to sarcomeric mutations, Eur. Heart J. Cardiovasc. Imaging 21 (3) (2020) 291–298.
[29] M.S. Maron, I. Olivotto, B.J. Maron, S.K. Prasad, F. Cecchi, J.E. Udelson, et al., The case for myocardial ischemia in hypertrophic cardiomyopathy, J. Am. Coll. Cardiol. 54 (9) (2009) 866–875.
[30] A.V. Gonçalves, S.A. Rosa, L. Branco, A. Galrinho, A. Fiarresga, L.R. Lopes, et al., Myocardial work is associated with significant left ventricular myocardial fibrosis in patients with hypertrophic cardiomyopathy, Int. J. Card. Imaging (2021) 17. ; Feb.
[31] T.F. Haland, V.M. Almaas, N.E. Hasselberg, J. Saberniak, I.S. Leren, E. Hopp, et al., Strain echocardiography is related to fibrosis and ventricular arrhythmias in hypertrophic cardiomyopathy, Eur. Heart J. Cardiovasc. Imaging 17 (6) (2016) 613–621.
[32] J.A. Urbano-Moral, E.J. Rowin, M.S. Maron, A. Crean, N.G. Pandian, Investigation of global and regional myocardial mechanics with 3-dimensional speckle tracking echocardiography and relations to hypertrophy and fibrosis in hypertrophic cardiomyopathy, Circ. Cardiovasc. Imaging 7 (1) (2014) 11–19.
[33] E. Wabich, K. Dorniak, A. Zienciuk-Krajka, R. Nowak, G. Raczak, L. Daniłowicz-Szymanowicz, Segmental longitudinal strain as the most accurate predictor of the patchy pattern late gadolinium enhancement in hypertrophic cardiomyopathy, J. Cardiol. 77 (5) (2021) 475–481.

[34] H. Liu, I. Pozios, B. Haileselassie, A. Nowbar, L.L. Sorensen, S. Phillip, et al., Role of global longitudinal strain in predicting outcomes in hypertrophic cardiomyopathy, Am. J. Cardiol. 120 (4) (2017) 670–675.
[35] L. Cortigiani, F. Rigo, F. Bovenzi, R. Sicari, E. Picano, The prognostic value of coronary flow velocity reserve in two coronary arteries during vasodilator stress echocardiography, J. Am. Soc. Echocardiogr. 32 (1) (2019) 81–91.
[36] Q. Ciampi, I. Olivotto, C. Gardini, F. Mori, J. Peteiro, L. Monserrat, et al., Prognostic role of stress echocardiography in hypertrophic cardiomyopathy: the international stress Echo registry, Int. J. Cardiol. 219 (2016) 331–338.
[37] A. Nemes, E. Balázs, O.I.I. Soliman, R. Sepp, M. Csanády, T. Forster, Long-term prognostic value of coronary flow velocity reserve in patients with hypertrophic cardiomyopathy: 9-year follow-up results from SZEGED study, Heart Vessel. 24 (5) (2009) 352–356.
[38] G. Finocchiaro, F. Haddad, J.W. Knowles, C. Caleshu, A. Pavlovic, J. Homburger, et al., Cardiopulmonary responses and prognosis in hypertrophic cardiomyopathy. A potential role for comprehensive noninvasive hemodynamic assessment, JACC Hear Fail. 3 (5) (2015) 408–418.
[39] P. Sorajja, T. Allison, C. Hayes, R.A. Nishimura, C.S.P. Lam, S.R. Ommen, Prognostic utility of metabolic exercise testing in minimally symptomatic patients with obstructive hypertrophic cardiomyopathy, Am. J. Cardiol. 109 (10) (2012) 1494–1498.
[40] C.J. Coats, K. Rantell, A. Bartnik, A. Patel, B. Mist, W.J. McKenna, et al., Cardiopulmonary exercise testing and prognosis in hypertrophic cardiomyopathy, Circ. Heart Fail. 8 (6) (2015) 1022–1031.
[41] G. Salerno, A. D'Andrea, E. Bossone, R. Scarafile, L. Riegler, G. Di Salvo, et al., Association between right ventricular two-dimensional strain and exercise capacity in patients with either idiopathic or ischemic dilated cardiomyopathy, J. Cardiovasc. Med. 12 (9) (2011) 625–634.
[42] S.F. Nagueh, S.M. Bierig, M.J. Budoff, M. Desai, V. Dilsizian, B. Eidem, et al., American society of echocardiography clinical recommendations for multimodality cardiovascular imaging of patients with hypertrophic cardiomyopathy: endorsed by the American society of nuclear cardiology, society for cardiovascular magnetic resonance, and, J. Am. Soc. Echocardiogr. 24 (5) (2011) 473–498.
[43] N.P. Johnson, K.L. Gould, Regadenoson versus dipyridamole hyperemia for cardiac PET imaging, JACC Cardiovasc. Imaging 8 (4) (2015) 438–447.