Clinical Investigation

Myocardial Contraction Fraction Predicts Cardiovascular Events in Patients With Hypertrophic Cardiomyopathy and Normal Ejection Fraction

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ABSTRACT

Background: Myocardial contraction fraction (MCF), the ratio of left ventricular stroke volume to myocardial volume, is a novel parameter that can distinguish between pathologic and physiologic hypertrophy. However, its prognostic value in hypertrophic cardiomyopathy (HCM) has never been examined. The objective was to determine if MCF is associated with functional capacity and predicts adverse cardiovascular outcomes in patients with HCM and normal left ventricular ejection fraction (LVEF).

Methods and Results: We conducted a prospective cohort study of 137 patients with HCM and LVEF ≥55%. Patients were followed for 2.7 ± 2.5 years. We examined association of MCF with New York Heart Association (NYHA) functional class and a composite outcome of embolic stroke, heart transplantation, and cardiac death. We performed time-to-event analysis with the use of Cox proportional hazards modeling and stepwise elimination. The average age was 52 ± 18 years. The average MCF was 26 ± 11%. MCF was inversely correlated with NYHA functional class ($P = .001$). A total of 20 subjects experienced an outcome event with an event rate of 5.6% per patient-year. MCF independently predicted the outcome (adjusted hazard ratio 0.50 per 10% increase, 95% confidence interval 0.28−0.90, adjusted $P = .02$).

Conclusions: In patients with HCM and normal LVEF, MCF is associated with functional capacity and independently predicts adverse cardiovascular outcomes. (*J Cardiac Fail 2019;25:450−456*)

Key Words: Hypertrophic cardiomyopathy, left ventricular ejection fraction, myocardial contraction fraction, prognosis.

Left ventricular ejection fraction (LVEF) is a commonly used index of systolic function. However, the LVEF often remains normal in patients with hypertrophic cardiomyopathy (HCM) despite disease progression until the end-stage of the disease. This is because myocardial hypertrophy results in progressive declines in ventricular capacitance and end-diastolic volume, which are accompanied by reduction in stroke volume.[1−5] Accordingly, the LVEF does not correlate with functional capacity in HCM[6] and is not predictive of adverse events including worsening heart failure, arrhythmias, sudden death, or appropriate implantable cardioverter-defibrillator (ICD) firing.[3,7,8] Myocardial contraction fraction (MCF), defined as the ratio of the LV stroke volume to the LV myocardial volume, is a novel measure of LV myocardial shortening that may be more predictive of such adverse events than LVEF.[9] Our previous study demonstrated that MCF, unlike LVEF, can distinguish between normal subjects, patients with pathologic LV hypertrophy due to hypertension (MCF is decreased), and

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athletes with physiologic hypertrophy (MCF is increased).[9] Regarding the predictive value of MCF, in healthy adults MCF was an independent predictor of cardiovascular death, myocardial infarction, stroke, and new heart failure after controlling for standard cardiovascular risk factors.[10] Indeed, MCF was a stronger predictor of cardiovascular morbidity and mortality than LVEF.[10] Similarly, among adults aged ≥65 years MCF was independently associated with incident heart failure, atherosclerotic cardiovascular disease, and mortality.[11] The prognostic capacity of MCF has also been demonstrated in patients with nonischemic cardiomyopathy and cardiac amyloidosis.[12–14] Nevertheless, no studies have determined the association of MCF with functional capacity or the prognostic value of MCF in the HCM population. To address these knowledge gaps in the literature, we designed the present study to investigate whether MCF (1) correlates with subjective New York Heart Association (NYHA) functional class at baseline and (2) predicts adverse cardiovascular events in patients with HCM and normal LVEF.

Methods

Patient Population

Patients ≥18 years of age with a clinical diagnosis of HCM and normal LVEF who were seen at the Center for Advanced Cardiac Care (heart failure and transplant program) at Columbia University Medical Center (New York) were enrolled. Baseline characteristics of the population, LVEF, and MCF were assessed at the time of initial echocardiographic study. Demographic, clinical, echocardiographic, and outcome data were entered prospectively into a database. The Columbia University Institutional Review Board approved this study.

Echocardiographic Measurements

Echocardiographic images were obtained with the use of commercially available ultrasound systems. The images were acquired with the patient in the left lateral decubitus position. Two-dimensional echocardiography-guided M-mode data were acquired in the parasternal long-axis view. The presence of an LV outflow tract gradient was defined as a gradient >30 mm Hg seen at rest, with Valsalva maneuver, or with exercise. LV end-diastolic (LVEDV) and end-systolic (LVESV) volumes were calculated based on LV end-diastolic (LVEDD) and LV end-systolic (LVESD) diameters with the use of the following formulas[15]: LVEDV $(mL) = 4.5(LVEDD)^2$ and LVESV $(mL) = 3.72(LVESD)^2$. LV myocardial volume (LVMV) was calculated from 1-dimensional measurements of the maximum thickness of the septal wall in end-diastole (intraventricular septal thickness; IVST) and the thickness of the posterior wall of the LV in end-diastole (posterior wall thickness; PWT) with the use of the formula[16]: $LVMV\ (mL) = 0.8 \times ([LVEDD + IVST + PWT]^3 - LVEDD^3) + 0.6$. LVEF (%) was calculated as (LVEDV − LVESV)/LVEDV * 100. MCF (%) was calculated as (LVEDV-LVESV)/LVMV × 100. A normal LVEF was defined as ≥55%. In patients with atrial fibrillation, the measurements were obtained from a representative beat.

Outcome Measures

The primary outcome was a composite of embolic stroke with underlying atrial fibrillation, sudden cardiac death (SCD) with or without successful resuscitation, heart transplantation, death due to heart failure, or procedure-related death. The total event rate of the population was expressed as % per patient-year and calculated as the number of events divided by the product of the average follow-up time in years and the total number of study subjects.

Statistical Analysis

Continuous variables are expressed as mean ± SD or median (interquartile range) as appropriate. Categoric variables are expressed as frequency and percentage. Hazards are expressed as ratios and 95% confidence intervals (CIs). Two-sided P values were considered to be statistically significant when <.05. With the use of the Spearman rank correlation test, MCF was tested for correlation with NYHA functional class, LV outflow tract gradient, degree of mitral regurgitation, and echocardiography-derived parameters of diastolic dysfunction—ie, diastolic dysfunction grade, E/e′, and lateral e′. Kaplan-Meier survival curves were generated by separating subjects into groups with MCF above and below the median MCF of the study sample, and statistical significance was determined with the use of the log-rank test. Time-to-event analysis was performed by means of univariable Cox proportional hazards modeling. The start time of the observation period was the time of initial echocardiographic study. All univariable predictors with P values <.05 were included in the multivariable Cox proportional hazards model and analyzed with the use of a backward stepwise elimination method with removal from the model if $P > .02$. This stringent significance level for removal was selected to limit the number of parameters in the final model to address the possibility of overfitting. To test the robustness of the findings, a sensitivity analysis was performed by including all univariable predictors of the outcome and all parameters with significant correlation with MCF at baseline. Statistical analysis was performed with the use of Stata software (version 14.2; Statacorp).

Results

A total of 137 patients with HCM and normal LVEF were included in the analysis (Table 1). The average age was 52 ± 18 years and the sample had a slight predominance of men (53%). The average LVEF was 70 ± 8%, and the average MCF was 26 ± 11%. Six patients (4%) had a history of ventricular fibrillation or sustained ventricular tachycardia before the initial evaluation. Amiodarone therapy was prescribed in 10% of the subjects at the start of the study, and 10% received disopyramide to manage LV outflow tract

Table 1. Baseline Characteristics of Patients With Hypertrophic Cardiomyopathy and Normal Ejection Fraction

Characteristic	(n = 137)
Age (y)	52 ± 18
Female sex	64 (46.7%)
Race	
White	96 (70.1%)
Black	9 (6.6%)
Asian	11 (8.0%)
Native American	1 (0.7)
Other	20 (14.6%)
Body mass index (kg/m^2)	29.4 ± 6.6
Systolic blood pressure (mm Hg)	122 ± 20
Diastolic blood pressure (mm Hg)	72 ± 11
Persistent atrial fibrillation	9 (6.6%)
Ventricular fibrillation or sustained ventricular tachycardia	6 (4.4%)
Family history of HCM in first-degree relative	26 (19.0%)
Medication	
Beta-blocker	101 (73.7%)
Calcium channel blocker	44 (32.1%)
Angiotensin-converting enzyme inhibitor	11 (8.0%)
Angiotensin II receptor blocker	16 (11.7%)
Diuretic	53 (38.7%)
Loop diuretic	28 (20.4%)
Thiazide	11 (8.0%)
Potassium-sparing	6 (4.4%)
Clonidine	3 (2.2%)
Digoxin	3 (2.2%)
Aspirin	38 (27.7%)
Anticoagulant	26 (19.0%)
Statin	40 (29.2%)
Amiodarone	13 (9.5%)
Disopyramide	14 (10.2%)
New York Heart Association functional class (n = 113)	
1	25 (22.1%)
2	48 (42.5%)
3	34 (30.1%)
4	6 (5.3%)
Genetic testing (n = 57)	
Positive	27 (47.4%)
Negative	24 (42.1%)
Variant of unknown significance	6 (10.5%)
Echocardiography-derived parameters	
Left ventricular end-diastolic diameter (mm)	43.0 ± 6.6
Left ventricular end-systolic diameter (mm)	25.6 ± 5.7
Interventricular septal thickness (mm)	17.4 ± 5.0
Left ventricular posterior wall thickness (mm)	12.6 ± 3.8
Stroke volume (mL)	60 ± 18
Diastolic dysfunction grade (n = 45)	
Normal	2 (4.4%)
1	28 (62.2%)
2	10 (22.2%)
3	5 (11.1%)
E/e′	13.8 ± 6.3
Lateral e′ (cm/s)	7.8 ± 3.0
Obstructive HCM	39 (28.5%)
Distribution of hypertrophy (n = 103)	
Asymmetric septal hypertrophy	71 (68.9%)
Diffuse hypertrophy	22 (21.4%)
Localized hypertrophy	6 (5.8%)
Apical hypertrophy	4 (3.8%)
Predictor of sudden cardiac death*	
Maximum wall thickness (mm)	17 ± 5.0
Left atrial diameter (mm)	43 (35–48)
Maximum LVOT gradient (mm Hg)	28 (1–74)
Family history of sudden cardiac death	8 (5.8%)
Nonsustained ventricular tachycardia	12 (8.8%)
History of unexplained syncope	19 (13.9%)

Data are presented as n (%), mean ± SD, or median (interquartile range). HCM, hypertrophic cardiomyopathy; LVOT, left ventricular outflow tract

*Predictors are defined according to the 2014 European Society of Cardiology guidelines on diagnosis and management of hypertrophic cardiomyopathy.[8]

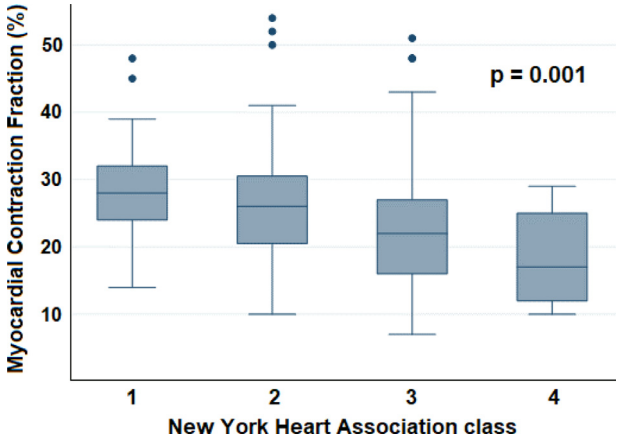

Fig. 1. Association between New York Heart Association (NYHA) functional class and myocardial contraction fraction (MCF). Each box plot represents distribution of MCF (%) in patients that fall within each NYHA functional class. *P* value was calculated with the use of Spearman rank correlation test.

obstruction during the study period. In this cohort, 35% demonstrated symptoms compatible with NYHA functional class 3 or 4 at baseline.

MCF was inversely associated with NYHA functional class in the study sample (Fig. 1; $P = .001$) whereas LVEF was not ($P = .10$). Subjects in NYHA functional class 1 had an average MCF of 27%, and those who in class 4 had an average MCF of 16%. MCF did not have a significant correlation with LV outflow tract gradient ($P = .45$), degree of mitral regurgitation ($P = .62$), or E/e′ ($P = .10$), but had a significant correlation with diastolic dysfunction grade ($P = .04$) and lateral e′ ($P = .001$).

Table 2 lists the HCM-related procedures and cardiovascular events experienced by the sample during the study period.

Table 2. Procedures and Events Observed During the Study Period

Procedure or Event	(n = 137)
Procedures	
Myectomy	41 (29.9%)
Alcohol septal ablation	1 (0.7%)
ICD implantation	34 (24.8%)
Primary Prevention	30 (21.9%)
Secondary Prevention	4 (2.9%)
Pacemaker implantation	5 (3.7%)
Implantation for sinoatrial disease	3 (2.2%)
Implantation for atrioventricular nodal disease	2 (1.5%)
Events	
Embolic stroke	2 (1.5%)
SCD with appropriate ICD shock	2 (1.5%)
SCD without ICD	0
Heart transplant	14 (10.2%)
Death due to heart failure	1 (0.7)
Procedure-related death	1 (0.7)
Other	1 (0.7)
Total events	21 (15.3%)
Follow up time (y)	2.7 ± 2.5
Event rate per patient-year (%)	5.6
SCD event rate per patient-year (%)	0.53

Data are presented as n (%) or mean ± SD, unless otherwise indicated. ICD, implantable cardioverter-defibrillator; SCD, sudden cardiac death.

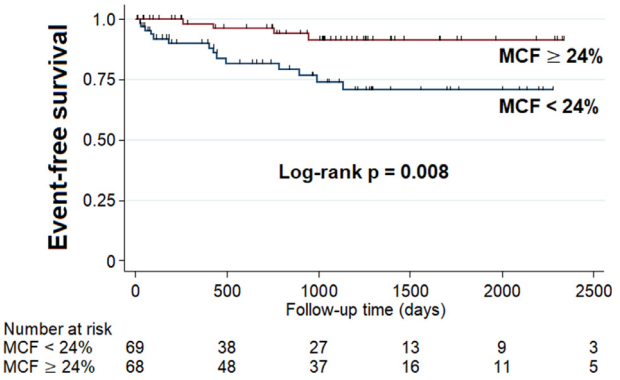

Fig. 2. Event-free survival of patients with myocardial contraction fraction (MCF) above and below the median of the study population. *P* value was determined with the use of the log-rank test.

The most common event experienced in the population was heart transplantation (14 patients). Two patients experienced SCD and both received successful ICD shock. The total event rate of the composite outcome was 5.6% per patient-year and the SCD event rate was 0.5% per patient-year.

With the use of the median MCF for this population of 24%, subjects with MCF ≥24% had a lower rate of the outcome events throughout the study period (log-rank $P = .008$; Fig. 2).

Increase in MCF (hazard ratio [HR] 0.45 per 10% increase, 95% CI 0.26−0.79; $P = .005$), higher systolic blood pressure, and higher LV outflow tract gradient were protective factors in the univariable Cox proportional hazards model (Table 3). Persistent atrial fibrillation, history of ventricular fibrillation or sustained ventricular tachycardia, NYHA functional class 3 or 4, relative wall thickness, and history of unexplained syncope were significantly associated with the outcome events. In the multivariable Cox proportional hazards model with stepwise elimination method, MCF remained as an independent predictor of the primary outcome (adjusted HR 0.50 per 10% increase, 95% CI 0.28−0.90; adjusted $P = .02$; Table 3). The sensitivity analysis including all parameters in the main analysis and those with significant correlation with MCF showed similar findings (adjusted HR 0.12 per 10% increase, 95% CI 0.04−0.33; adjusted $P < .001$; Supplemental Table 1).

Table 3. Univariable and Multivariable Predictors of the Outcome Events

Parameter	Univariable Analysis			Multivariable Analysis (Full Model)			Multivariable Analysis (After Stepwise Elimination)		
	HR	95% CI	*P* Value	Adjusted HR	95% CI	Adjusted *P* Value	Adjusted HR	95% CI	Adjusted *P* Value
Myocardial contraction fraction (per 10% increase)	0.45	0.26–0.79	.005	0.47	0.18–1.24	.13	0.50	0.28–0.90	.02
Systolic blood pressure (per 10 mm Hg increase)	0.61	0.44–0.86	.004	0.69	0.44–1.06	.09	*		
Persistent atrial fibrillation	11.9	4.6–31.0	<.001	1.80	0.39–8.4	.45	*		
Ventricular fibrillation or sustained ventricular tachycardia	6.8	2.2–20.7	<.001	4.7	1.17–18.9	.03	*		
New York Heart Association functional class ≥3	6.9	2.4–19.3	<.001	4.8	1.25–18.4	.02	7.7	2.3–26.0	.001
Relative wall thickness (per 0.1 increase)	1.18	1.03–1.36	.02	1.002	0.70–1.43	.99	*		
Maximum LVOT gradient (per 10 mm Hg increase)	0.79	0.66–0.96	.02	0.80	0.65–0.99	.04	0.78	0.66–0.93	.005
History of unexplained syncope	3.7	1.46–9.4	.006	1.86	0.49–7.0	.36	*		

Only variables with significant association with the outcome events in the univariable analysis are shown. CI, confidence interval; HR, hazard ratio; LVOT, left ventricular outflow tract.
*Eliminated through the stepwise elimination method.

Discussion

The principal findings of this study were that in patients with HCM and normal LVEF, MCF correlates with subjective functional capacity and is an independent predictor of a composite outcome of embolic stroke, heart transplantation, and cardiac death. The present study is the first to elucidate the association of MCF with functional capacity and its prognostic value in patients with HCM.

Relation of MCF to Subjective Functional Capacity

One common feature of heart failure in HCM is reduced functional capacity. In previous reports, LVEF failed to correlate with functional capacity in HCM.[6] This is consistent

with the findings in the present study showing the lack of association between LVEF and NYHA functional class. In contrast, our previous study reported that MCF is lower in patients with pathologic LV hypertrophy due to hypertension and higher in athletes with physiologic LV hypertrophy, compared with normal subjects.[9] Furthermore, a recent report showed that MCF performs better than LVEF in distinguishing between healthy control subjects and patients with heart failure and LV hypertrophy due to various causes (eg, hypertension, amyloidosis, and HCM) and that MCF correlates with NYHA functional class among these patients.[14,17] The present study demonstrated, for the first time in the HCM population, that MCF is inversely associated with subjective functional capacity measured as NYHA functional class. Our observations are in agreement with the previous studies and together support the notion that MCF can serve as a marker of disease progression while LVEF remains normal across a wide spectrum of HCM phenotypes.

Association of MCF With Adverse Cardiovascular Events

The capacity of MCF to predict adverse cardiovascular events has been previously investigated in healthy subjects and in patients with various cardiac diseases other than HCM. Among initially healthy volunteers enrolled in the Framingham Heart Study, in which 99% of participants had normal LVEF, MCF predicted development of cardiovascular events consisting of cardiovascular death, myocardial infarction, stroke, and heart failure.[10] This association remained significant after adjustment for traditional cardiovascular risk factors and LV mass. Moreover, the Cardiovascular Health Study revealed that, in subjects ≥65 years of age with normal LVEF and without apparent cardiovascular disease, MCF was independently associated with incident heart failure, atherosclerotic cardiovascular disease, and death after controlling for clinical and echocardiographic variables.[11] In patients with cardiomyopathy, recent reports have demonstrated the prognostic value of MCF in nonischemic cardiomyopathy and in cardiac amyloidosis.[12,13] Observations in the present study corroborate with those previous reports and expand them by exhibiting for the first time that MCF is an independent predictor of major adverse cardiovascular events in the HCM population with normal LVEF. This indicates that MCF offers incremental value in addition to the conventional predictors of adverse outcomes. In addition, the only known predictor of end-stage disease in HCM is family history of end-stage HCM.[3] Because the majority of adverse cardiovascular events in the present study were heart transplantation or heart failure death, MCF may serve as an additional marker to specify patients who are more likely to progress to end-stage HCM.

Physiologic Basis of MCF and Relevance to Heart Failure in HCM

MCF can be intuitively understood as the LV stroke volume that 1 mL of myocardium can generate, which is an index that represents the overall efficiency of myocardium. Recently, a subset of functionally incapacitated patients with a nonobstructive HCM phenotype has been described.[18,19] These patients typically have a normal LVEF, but they are symptomatic chiefly owing to diastolic dysfunction. In this setting, MCF is decreased because of decreased LV stroke volume and pathologically increased LV mass, ie, reduced myocardial efficiency. This would explain the associations of MCF with the subjective measure of functional capacity and markers of diastolic dysfunction seen in the present study. These observations further support the concept that MCF is a simple and clinically useful index to assess the overall efficiency of the heart and can function as a marker of disease progression in HCM while LVEF remains normal. In this context, inferences from the present study—ie, that MCF predicts adverse cardiovascular events in HCM cases with normal LVEF—build on previous reports and extend them by indicating that MCF may be a more useful noninvasive clinical parameter than LVEF to identify patients with HCM who are more likely to develop adverse cardiovascular events in the future.

Association Between LV Outflow Tract Obstruction and Adverse Events

Recent studies have shown inverse relationship between degree of LV outflow tract obstruction and risk to require heart transplantation.[18,20] Findings from the present study are consistent with these reports in that higher LV outflow tract gradient was associated with a lower risk of adverse cardiovascular events, which mainly consisted of heart transplantation in the present study, in both univariable and multivariable analyses. A possible explanation would be that LV contractility and degree of LV outflow tract obstruction become diminished as patients develop end-stage HCM.

Study Limitations

First, the present study was performed at a tertiary referral center for HCM with a large-scale heart failure program, so the patient population was likely sicker than the general population with HCM, as reflected by a high rate of heart transplantation and lower MCF than in other studies.[17] Therefore, the generalizability of this study to patients with more benign HCM may be limited. Our event rate of ~6% per patient-year corresponds to early reports from similar HCM centers (>5%). However, when heart transplantation was excluded, the event rate was ~1%, which is similar to more recent reports.[21–25] Second, the measurement of MCF relied on 2-dimensionally guided M-mode measurements of LV dimensions and wall thickness that were used to estimate LV volumes and mass. These measures, though accurate in symmetrically contracting ventricles,[15,16] may have measurement errors due to the asymmetric nature of LV hypertrophy in HCM. Although other modalities to assess LV volume and mass are available, eg, cardiac

magnetic resonance imaging, computed tomography, these are more time- and resource-intensive and may involve radiation.[17] The main objective of the present study was to demonstrate that MCF, even if measured with the simplest method, can predict adverse cardiovascular events. Our approach is clinically relevant because these parameters are easily obtainable from routine transthoracic echocardiography in a noninvasive and timely manner. Third, parameters of diastolic dysfunction could not be added to the multivariable model because of missing values due to mitral valve calcification, status after mitral valve repair/replacement, atrial fibrillation, poor imaging quality, and other technical reasons. Finally, this study was not powered to examine the risk of SCD, owing to a small number of events, and does not address whether MCF-guided therapy would improve the prognosis in patients with HCM.

Conclusion

This prospective cohort study in patients with HCM and normal LVEF shows that MCF is associated with functional capacity and development of adverse cardiovascular events defined as a composite of embolic stroke, heart transplantation, and cardiac death. This study builds on previous studies in other cardiac conditions and serves as the first to elucidate the prognostic value of MCF in HCM.

Disclosures

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2019.03.016.

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