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# Myocardial Contraction Fraction is Superior to Ejection Fraction in Predicting Functional Capacity in Patients with Heart Failure with Reduced Ejection Fraction

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## Abstract

**Objectives:** In this study, we aimed to evaluate the relationship between three-dimensional echocardiography (3DE)-determined myocardial contraction fraction (MCF) and functional capacity in heart failure with reduced ejection fraction (HFrEF) patients. The MCF is a volumetric index of myocardial function, defined as stroke volume ratio to myocardial volume (MV). Functional capacity was evaluated by a 6-min walk test (6MWT), and health-related quality of life (HRQOL) was assessed by the Minnesota Living with Heart Failure Questionnaire (MLHFQ). In view of cardiac remodeling, we hypothesized that MCF would be superior to left ventricular ejection fraction (LVEF) in predicting functional capacity in HFrEF patients.

**Methods:** The study was conducted on thirty HFrEF patients with an LVEF of no more than 40% with NYHA functional class I-III. Each patient performed, on the same day, the MLHFQ, 6MWT (to calculate the 6-min walk distance “6MWD”), and an ECG gated echocardiographic study including 3DE-determined MCF. MV was calculated as 3DE determined LV mass divided by the specific gravity of the myocardium.

**Results:** Our results showed that MCF is inversely correlated with the Minnesota score ( $r = -0.6$ ,  $p < 0.001$ ) and positively correlated with 6MWD ( $r = 0.65$ ,  $p < 0.001$ ). However, no significant relationship existed between LVEF and MLHFQ score or 6MWD. In a multivariate model, MCF was shown to be an independent echocardiographic predictor (besides pulmonary artery systolic pressure) of 6MWD; however, LVEF failed to offer such potential.

**Conclusion:** Among various echocardiographic parameters, MCF can be considered a volumetric index superior to LVEF in predicting functional capacity in HFrEF patients.

**Keywords:** Myocardial contraction fraction, Heart failure, HFrEF, Functional capacity, MLHFQ, Six-minute walk test

## 1. Introduction

Heart failure (HF) is a significant global health burden affecting 1–2% of the population and more than an estimated 64 million people worldwide and resulting in more than one million hospitalizations annually [1]. Adults with HF have a lower health-related quality of life (HRQOL) and more inferior functional capacity than those without HF. Both HRQOL and functional capacity are

predictors of HF outcomes (hospitalization and mortality). Because of such association, these variables have become important endpoints of HF care. Numerous investigators have tested and subsequently approved interventions to improve HRQOL, functional status, and survival. Functional status was shown to be a mediator between HRQOL and cardiac event-free survival [2].

Pathologic left ventricular remodeling is the final common pathway to HF, whether the initial

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stimulus is chronic pressure or chronic volume overload, genetically determined cardiomyopathy, or myocardial infarction. Cardiac remodeling is a major determinant of the clinical course of HF [3]. As cardiac remodeling of the left ventricle results in alteration of intracardiac geometry and hemodynamics, echocardiography represents a cornerstone imaging investigation tool that is crucial in the diagnosis and management of HF patients. Assessment of left ventricular systolic function by left ventricular ejection fraction (LVEF) has been traditionally utilized as an index of myocardial performance and a crucial metric in assessing HF patients' progression. However, cardiologists have tried to solve the long-standing dilemma of discrepant functional capacity in patients with HFrEF and numerically similar LVEF [4].

Myocardial contraction fraction (MCF), defined as the ratio of stroke volume (SV) to end-diastolic myocardial volume “MV” ( $MCF = SV/MV$ ), has been suggested as an easily determined volumetric LV index. In this ratio, the SV is a measure of the amount of shortening and thickening that has occurred. Its ratio to MV is an index of the fractional shortening of the myocardium in volumetric terms and hence a measure of ventricular function [5]. It has been shown that decreased cardiac magnetic resonance imaging (CMR)–derived MCF is an independent predictor of future hard cardiovascular disease events in initially healthy adults [6].

In reference to CMR, LV volumes and mass calculated from three-dimensional (3D) echocardiography showed significantly better agreement and lower intra- and inter-observer variability than two-dimensional (2D) echocardiography [7–9]. Whether 3D-echocardiography-derived MCF is associated with functional capacity in patients with HFrEF and hence a useful prognostic metric in this patient population has not been studied yet.

## 2. Materials and methods

### 2.1. Patient selection

The study included 30 patients with chronic stable heart failure, aged 18–65 years with a left ventricular ejection fraction (LVEF)  $\leq 40\%$  and NYHA class I–III, receiving the standard treatment for HF at the cardiac rehabilitation outpatient clinic of the University Hospital. Patients with acute decompensated HFrEF, hospitalization within the past six months, atrial fibrillation or frequent extrasystoles, recent acute coronary syndrome, acute myocarditis, or heart failure due to valvular heart disease were excluded from the study group. Patients were also

### Abbreviations

2D	two-dimensional
3D	three-dimensional
3DE	three-dimensional echocardiography
6MWD	6-minute walk distance
6MWT	6-minute walk test
BMI	body mass index
BSA	body surface area
CMR	cardiac magnetic resonance imaging
FC	functional capacity
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
HRQOL	Health-related quality of life
LAD	left atrial diameter
LAV	left atrial volume
LV	left ventricle
LVEDD	left ventricular end-diastolic diameter
LVEDV	left ventricular end-diastolic volume
LVEF	left ventricular ejection fraction
LVEDS	left ventricular end-systolic diameter
LVESV	left ventricular end-systolic volume
LVM	left ventricular mass
LVMI	left ventricular mass index
MCF	Myocardial contraction fraction
MLHFQ	Minnesota Living with Heart Failure Questionnaire
MV	Myocardial volume
PWT	posterior wall thickness
ROC	Receiver-Operating Characteristic
SPAP	Systolic pulmonary artery pressure
SV	Stroke volume
SWT	septal wall thickness
TAPSE	Tricuspid Annular Plane Systolic Excursion

excluded if they had poor epicardial or endocardial visualization on 2D echocardiography of  $\geq 3$  contiguous segments using a 17-segment model or complex congenital heart disease.

MCF from the HFrEF patients was compared with that obtained from 30 healthy subjects with no history of cardiovascular disease or systemic illness, with a normal physical examination, electrocardiogram, and echocardiographic examination (control group).

This study was approved by our institutional review board and local ethical committee. Informed consent was obtained from all enrolled individuals. The procedures followed during the study were in accordance with the ethical standards of the Helsinki Declaration of the World Medical Association.

### 2.2. Study group

#### 2.2.1. Clinical data collection

Patient characteristics were obtained, including cardiac risk factors (hypertension, diabetes mellitus, smoking) and etiology of heart failure (ischemic or

non-ischemic). Ischemic etiology was determined by either angiographic evidence of  $\geq 70\%$  lesion in one or more of the three major coronary vessels, history of previous myocardial infarction or revascularization procedure, or evident significant perfusion defect concomitant with ischemic symptoms.

### 2.2.2. Assessment of functional capacity

Functional capacity was objectively assessed by a 6-min walk test (6MWT) performed on the same day of clinical and echocardiographic assessment. The test was conducted along a long, flat, straight, enclosed corridor with a hard surface. We used a 30-m walking corridor with marks on the wall every 3 m. The patient had to turn around at the end of each 30 m to complete one lap at 60 m.

### 2.2.3. Assessment of health-related quality of life

Health-related Quality of life (HRQoL) was assessed on the same day of clinical and echocardiographic assessment with the “Minnesota living with heart failure questionnaire” (MLHFQ). The MLHFQ is a self-administered disease-specific questionnaire for patients with HF, comprising 21 items rated on six-point Likert scales, from 0 (none) to 5 (very much), representing physical (8 items, range 0–40), emotional (5 items, range 0–25) and socioeconomic (8 items, range 0–40) degrees of impact of HF on HRQoL, thus provides a total score (range 0–105, from best to worst HRQoL) [10,11].

### 2.2.4. Echocardiographic assessment

All echocardiographic measurements were obtained on the same day of the 6MWT by an observer blinded to the test result data. Transthoracic echocardiographic examination with machine-integrated ECG recording was performed, mainly with the patients lying in the left lateral decubitus position. The study was conducted using a commercially available echocardiography system (Vivid E9, GE Vingmed, Horten, Norway) equipped with a 2.5-MHz multifrequency phased array transducer and a 3V cardiac vector array probe with a frequency range of 1.5–3.6 MHz. All echocardiographic measurements in this study were done in concordance with the recommendations for performance and reporting of the American Society of Echocardiography (ASE) [12].

**2.2.4.1. Two dimensional (2D) echocardiographic parameters.** Digital routine grayscale two dimensional (2D) and tissue Doppler cine loops including mid-left ventricular short-axis views at the papillary muscle level and standard apical views (4-chamber,

2-chamber, and long axis) were obtained at end-expiratory apnea from standard apical views at a depth of 12–20 cm. Gain settings were adjusted for routine grayscale 2D imaging to optimize endocardial definitions. All parameters were averaged over three heart cycles. The following parameters were obtained: Left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), interventricular septal wall thickness (SWT), posterior wall thickness (PWT), and anteroposterior left atrial diameter (LAD). 2D-derived left ventricular mass was calculated based on the following formula:

2D-derived LV mass (cube formula):  $0.8 (1.04 ([LVEDD + PWT + SWT]^3 - [LVEDD]^3)) + 0.6 \text{ g}$  [12].

Using modified biplane Simpson's, left ventricular end-diastolic volume (LVEDV2D), left ventricular systolic end-systolic volume (LVESV2D), left atrial volume (LAV), and left ventricular ejection fraction (LVEF2D) were calculated. Tricuspid Annular Plane Systolic Excursion (TAPSE) and E/E' (peak transmitral flow velocity in early diastole (E)/average of lateral and septal early mitral annular tissue velocity) were calculated.

**2.2.4.2. Three-Dimensional (3D) Echocardiographic parameters.** Real-time 3D echocardiography LV full volume acquisition was performed from the apical window during held end-expiration. To ensure the inclusion of the entire left ventricle within the pyramidal scan volume, data sets were acquired using the wide-angle mode, wherein four-beat ECG-gated sub-volumes were obtained from the apical view, during an end-expiratory apnea to generate the full-volume data set using the wide-angle default during a single 5- to 7-sec breath-hold.

The acquired loops included end-diastole and end-systole and spanned the ventricle from the inferior surface of the aortic valve to the epicardial apex about one centimeter apart. The acquired full volume cine loops were digitally stored and transmitted to the attached workstation for offline analysis using the 4DAutoLVQ package (Echo PAC v110.1.3, GE-Healthcare, Horten, Norway) [12,13].

Data sets acquired with Vivid E9 were analyzed offline. The end-diastolic frames needed for contour detection were automatically displayed in a quad view (Fig. 1). Manual alignment by pivoting and translating the four-chamber plane was performed to align the three apical views. The corresponding intersection line of all planes was placed in the middle of the LV cavity, crossing the LV apex and the center of the mitral valve in each view. We used

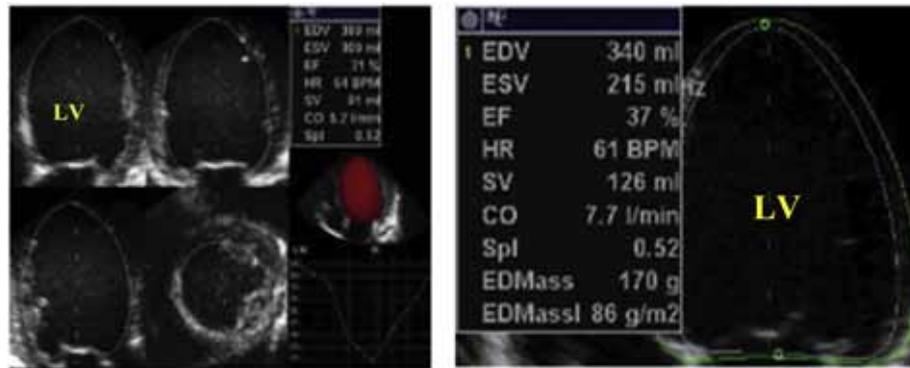


Fig. 1. Displays 3D acquisition from two different patients of LV volumes (LVEDV3D and LVESV3D), LVEF3D, SV, and LVM parameters (LVM3D and LVMI3D).

the semi-automated option to identify a fitting geometric model subsequently. The software required the manual input of only two points (one point at the apex and another at the tip of the mitral leaflet) on the end-diastolic and end-systolic frames of the four-chamber view slice.

End-diastole was identified automatically by the software as the time point in which the LV cavity is the largest and end-systole as the time point at which the cavity was smallest. The LV outflow tract, papillary muscles, and trabeculae were included within the LV cavity. Finally, the program generated an endocardial surface shell from which LV volumes (LVEDV3D and LVESV3D) and LV ejection fraction (LVEF3D) were calculated. After LV volumes and ejection fraction measurements, an automatic trace of the epicardial border at end-diastole was displayed to identify the region of interest required for LV mass. Epicardial trace could be manually adjusted with the same point-click method, and LV mass parameters were derived (LVM3D and LVMI3D).

Myocardial contraction fraction (MCF) was calculated as the ratio of SV to end-diastolic myocardial volume “MV” ( $MCF = SV/MV$ ), where  $MV = LVM3D/1.05$  (the specific gravity of the myocardium) [14].

### 2.3. Statistical analysis

Categorical variables were expressed as numbers (%), and continuous variables were represented as mean  $\pm$  SD. Qualitative variables were compared using the Chi-squared test. The independent sample t-test and ANOVA were used to compare the quantitative variables of different groups. Linear regression was used for correlation analyses, expressed as Pearson correlation coefficients. For an analysis of the independent determinants,

multivariate linear and logistic regression analysis models based on stepwise selection were generated for variables that showed linear correlations. Receiver operating characteristic curve analysis was used to determine the best cutoff values. For all tests, a p-value  $< 0.05$  was considered statistically significant. All the analyses were performed using the commercially available statistical software (SPSS, Inc., Chicago, IL, USA).

### 3. Results

Due to poor epicardial or endocardial definition, two patients from the screened control group and three patients from the screened study group were excluded. Although there was no difference between the HF and control groups regarding age and gender ( $P > 0.05$ ), there were significant differences in all echocardiographic parameters denoting the occurrence of remodeling in the HF group. HF group had significantly greater LV internal dimensions, wall thickness, LV volumes (2D and 3D), LV mass index (2D and 3D), LA anteroposterior diameter & volumes. Besides, the HF group had significantly lower LVEF (either by 2D or 3D measurements) and RV function (TAPSE), besides higher E/e' and SPAP as shown in table 1. Regarding MCF, there was a highly significant difference between the HF group and controls, where the mean MCF of HF patients was lower than that of control ( $0.28 \pm 0.5\%$  vs.  $0.56 \pm 0.09\%$ ,  $P < 0.001$ ) as shown in table 1.

#### 3.1. Association of echocardiographic parameters with HRQOL and functional capacity

##### 3.1.1. Quality of life (QOL)

Although there was a lack of significant correlation between LVEF2D and MLHFQ, there was a significant negative correlation between LVEF3D

Table 1. Demographic and echocardiographic characteristics of heart failure and control groups.

Variables	Heart failure group	Control group	X <sup>2</sup> or t	P-value
<b>Demographic data</b>				
Age	59.6 ± 6.5	58.9 ± 6	0.454	0.651
Gender (Males)	25 (83.3%)	24 (80%)	0.111	0.739
<b>2D- echocardiographic parameters</b>				
LVEDD (mm)	59.63 ± 10.66	47.33 ± 4.2	5.883	<0.001
LVESD (mm)	49.10 ± 10.97	31.87 ± 3.80	8.129	<0.001
SWT (mm)	10.17 ± 0.99	9.23 ± 0.94	3.763	<0.001
PWT (mm)	10.30 ± 1.32	9.20 ± 1.13	3.477	0.001
LVEDV2D (ml)	178.83 ± 64.86	92.93 ± 10.30	7.164	<0.001
LVESV2D (ml)	128.40 ± 58.59	34.87 ± 4.94	8.713	<0.001
LVEF2D (%)	30.00 ± 7.38	62.80 ± 3.69	-20.835	<0.001
LVMi2D (g/m <sup>2</sup> )	143.34 ± 52.75	89.35 ± 15.37	5.382	<0.001
LAD (mm)	41.50 ± 6.86	31.60 ± 5.15	6.323	<0.001
LAV (ml)	65.93 ± 30.63	29.80 ± 6.18	6.334	<0.001
E/E'	8.86 ± 2.92	5.14 ± 0.89	6.690	<0.001
TAPSE (mm)	18.40 ± 3.91	20.17 ± 1.76	-2.256	0.028
SPAP (mmHg)	42.32 ± 11.08	22.77 ± 3.03	6.191	<0.001
<b>3D-echocardiographic parameters</b>				
LVEDV3D (ml)	191.57 ± 75.59	98.20 ± 13.21	6.665	<0.001
LVESV3D (ml)	137.63 ± 66.72	38.57 ± 7.36	8.084	<0.001
LVEF3D (%)	31.03 ± 7.27	62.83 ± 3.04	-22.101	<0.001
LVMi3D (g/m <sup>2</sup> )	110.6 ± 38.31	66.16 ± 5.46	6.290	<0.001
MV (ml)	196.95 ± 61.8	107.81 ± 3.85	7.884	<0.001
MCF	0.28 ± 0.05	0.56 ± 0.09	-14.022	<0.001

and MLFHQ ( $r = -0.39$ ,  $P = 0.031$ ) as well as between MCF and MLHFQ ( $r = -0.6$ ,  $P < 0.001$ ), as shown in figure 2. Also, a significant positive correlation was witnessed between SPAP and MLHFQ ( $r = 0.69$ ,  $P < 0.001$ ), as shown in table 2.

3.1.2. Functional capacity (FC)

It has been demonstrated that MCF is positively correlated with 6MWD ( $r = 0.65$ ,  $P < 0.001$ ), as shown in figure 1. However, no significant relationship existed between LVEF (whether 2D or 3D) and functional capacity assessed by 6MWD. Multivariate analysis revealed that besides age, SPAP and MCF were the only independent echocardiographic predictors of 6MWD; however, E/e' and LVEF

(whether 2D or 3D-measured) did not show statistical significance, as shown in table 3.

It is worth mentioning that regarding MCF; there was a moderately significant correlation between MCF and LVEF2D ( $r = 0.48$ ,  $P = 0.008$ ) and between MCF and LVEF3D ( $r = 0.6$ ,  $P < 0.001$ ).

Table 2. Correlation between some echocardiographic parameters and MLHFQ.

	r	P-value
LVEF2D	-0.297	0.111
LVEF3D	-0.394	0.031*
SPAP	0.693	<0.001*
MCF	-0.603	<0.001*

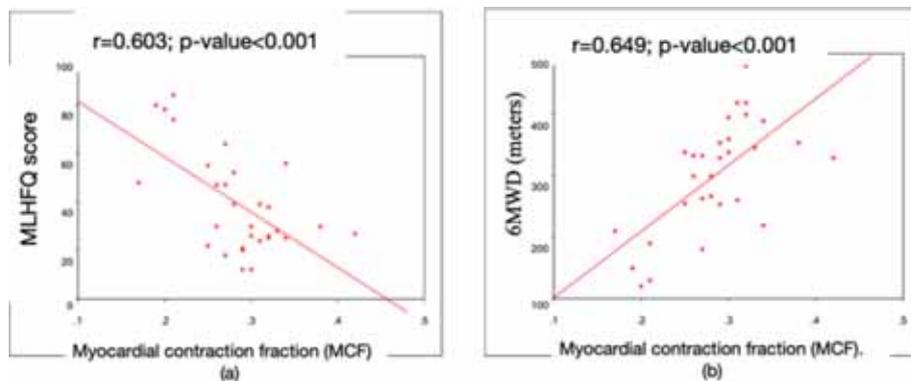


Fig. 2. Shows plot charts showing a significant inverse correlation between myocardial contraction fraction (MCF) and MLHFQ score (a) and a significant positive correlation between MCF and 6MWD.

Table 3. Linear regression analysis for 6MWD.

	Unstandardized Coefficients		Standardized Coefficients Beta	t	P-value	95% Confidence Interval for B	
	B	Standard Error				Lower Bound	Upper Bound
(Constant)	494.177	125.872		3.926	0.001*	225.887	762.467
Age	-1.687	1.553	-0.127	-1.086	0.295	-4.997	1.623
SPAP	-4.582	0.908	-0.599	-5.046	<0.001*	-6.518	-2.646
MCF	644.343	256.450	0.370	2.513	0.024*	97.734	1190.953
LVEF2D	-0.360	2.940	-0.032	-0.122	0.904	-6.627	5.906
LVEF3D	-1.527	3.134	-0.135	-0.487	0.633	-8.206	5.153
E/e'	-4.596	3.409	-0.162	-1.348	0.198	-11.861	2.669

Dependent Variable: 6MWD

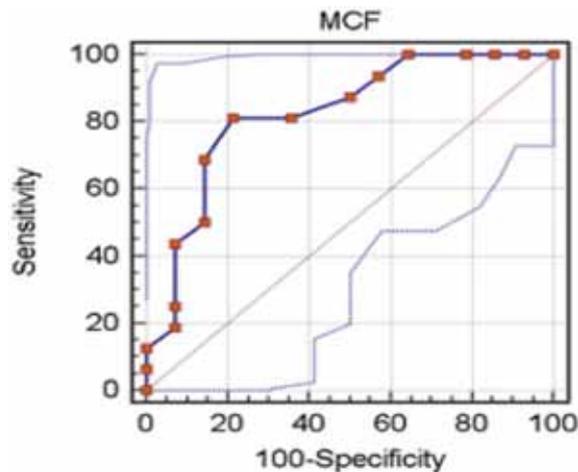


Fig. 3. Shows ROC curve to determine the cutoff value of Myocardial contraction Fractional (MCF) to discriminate between good and poor functional capacity HF subgroups.

As most previous studies utilizing the 6MWT classified the HF patients using a cutoff of 300 m for its prognostic implications, we dichotomized the 30 patients in our study into two groups according to the 6MWD, a poor FC subgroup (14 patients, 46.7%) with 6MWD below 300 m and a good FC subgroup (16

patients, 53.3%) with 6MWD exceeding 300 m. Both groups were subsequently compared regarding demographic data, risk factors, and echocardiographic parameters, as shown in table 4. Patients with poor FC were significantly older with higher BMI and worse HRQOL (higher MLHFQ score). Concerning echocardiographic parameters, although they lacked a significant difference in LVEF (2D or 3D), LAV or LVMI, the poor FC subgroup had a significantly lower MCF, higher E/E', and SPAP.

### 3.2. Cutoff Value of Myocardial contraction Fractional (MCF) to predict good and poor functional capacity

Receiver Operating Characteristic (ROC) curve was done to determine the best MCF cutoff value between both subgroups. The best cutoff value of MCF was 0.28 (28%) with a sensitivity of 81.25% and specificity of 78.57% (Fig. 3).

## 4. Discussion

Several studies have attempted to stratify HF patients according to their functional status to follow their clinical status over time and assess the effects

Table 4. Comparison between poor and good functional capacity subgroups regarding age, BMI, and echocardiographic parameters.

	Poor FC subgroup (46.7%)	Good FC subgroup (53.3%)	t	P-value
Age	63.36 ± 4.77	56.38 ± 6.15	3.43	0.002*
BMI	28.71 ± 3.79	25.94 ± 3.51	2.08	0.047*
MLHFQ score	56.00 ± 18.14	24.56 ± 6.72	6.46	<0.01*
LVEF2D	29.07 ± 6.85	30.81 ± 7.94	-0.64	0.528
LAV	68.79 ± 34.04	63.44 ± 28.20	0.47	0.641
E/e'	10.23 ± 3.14	7.67 ± 2.16	2.64	0.014*
TAPSE	17.21 ± 3.22	19.44 ± 4.26	-1.60	0.122
SPAP	47.86 ± 9.63	32.63 ± 5.23	4.11	0.001*
LVEDV3D	212.79 ± 85.72	173.00 ± 62.37	1.47	0.154
LVESV3D	157.50 ± 75.85	120.25 ± 54.11	1.56	0.129
LVEF3D	29.07 ± 7.48	32.75 ± 6.86	-1.41	0.171
LVMI2D	154.35 ± 58.78	133.70 ± 46.60	1.07	0.292
LVMI3D	124.74 ± 43.16	98.226 ± 29.56	1.98	0.057
MCF	0.25 ± 0.05	0.313 ± 0.04	-3.60	0.001*

of therapeutic interventions and rehabilitation programs. Besides being considered salient endpoints in HF studies, both quality of life and functional capacity are essential clinical and prognostic measures in HF patients. [15] As a validated prognostic tool, the Minnesota Living with Heart Failure Questionnaire (MLHFQ) was used to evaluate HRQOL. We used the 6-min walk test (6MWT) to assess exercise capacity at submaximal exercise levels with high test-retest reliability and a proven sensitive index to assess response to therapeutic interventions in HF. It has been shown to be an independent predictor of mortality and mortality or hospitalization for cardiovascular reasons in patients with stable systolic HF. [16–18]

Lower levels of functional capacity (a distance <300 m during 6MWT) have proven to be predictive of both mortality (total or cardiovascular) and morbidity (hospitalization for worsening heart failure) in HFrEF patients. [19,20] Therefore, we used 300 m in the 6MWT as an arbitrary cutoff value to stratify the HF study group according to their walking capability.

Assessment of left ventricular systolic function by LVEF has been traditionally utilized as an indispensable metric of myocardial performance and progression in patients with HFrEF [21,22]. For years, cardiologists have tried to solve the long-standing challenging dilemma of discrepant functional capacity in patients with HFrEF and similar chronic ventricular dysfunction. Several explanations have been suggested that attributed this discrepancy to the fact that LVEF is influenced by loading conditions and does not account for myocardial volume. Failure of LVEF to accurately predict patient functional capacity and hence prognosis has stimulated researchers to search for other alternative echocardiographic indices that can possess the potential to predict LV myocardial performance, integrating structure and function.

Recent theories in the pathophysiology of HF have posed intense emphasis upon cardiac remodeling. Several therapeutic interventions have been devised to reverse this adverse remodeling and hence prognosis. Therefore, we opted for an echocardiographic dimensionless index that encompasses myocardial volume instead of chamber size to be more representative of the remodeling process. This index was first coined by King et al. called myocardial contraction fraction (MCF) is defined as  $MCF = SV/MV$  [5].

As myocardial volume is constant from end-diastole to end-systole, indexing SV to myocardial volume represents a volumetric index of myocardial function (shortening) independent of the geometric

influence of chamber volume. It could be intuitively viewed as a hybrid measure of an LV functional index (SV) and a structural measure (LV mass), which could be potentially sensitive to varying physiologic and pathologic conditions [6]. Thus, it represents a metric of LV myocardial performance per volume of myocardial fiber. Consequently, a decrease in MCF, which is positively correlated with global longitudinal strain on echocardiography [23], indicates abnormal myocardial shortening and reflects abnormalities in myocardial properties induced by hypertrophy, inflammation, microvascular dysfunction, and alterations of the interstitium.

MCF thus seems to offer a clear, simple definition with a relatively easily acquired echocardiographic parameter. Being a dimensionless index analogous to LVEF, MCF easily permits comparing myocardial shortening between subjects. Owing to its inclusion of myocardial volume in its calculation, MCF has been recently studied in cardiomyopathy, namely hypertrophic cardiomyopathy by Shimada et al., AL cardiac amyloidosis by Tendler et al., transthyretin amyloidosis by Rubin et al., diabetic cardiomyopathy by Bertoni et al. and non-ischemic dilated cardiomyopathy by Arenja [6,24–28]. Arenja et al. demonstrated that a depressed MCF level was associated with a higher risk of the combined outcome of cardiac death, heart transplantation, sudden cardiac death aborted by appropriate implantable cardioverter-defibrillator discharge due to ventricular tachycardia or fibrillation, and hospitalization due to congestive heart failure among individuals with non-ischemic dilated cardiomyopathy (LVEF<55%) [28].

In our study, we aimed to assess the relationship between 3D-echocardiographically derived MCF and functional capacity in patients with HFrEF, assessed by 6MWT and HRQOL assessed by MLHFQ. To our knowledge, there were no previously published studies performed to interrogate such a relationship in patients with HFrEF.

MCF requires accurate measurement of both SV and MV. 3D echocardiography has been resorted to in our study, as 3D echocardiography and cardiac myocardial resonance (CMR) have been shown to yield equivalent results in assessing chamber volume and myocardial volume that are superior to M-mode and 2D echocardiographic techniques. This may be accounted for by the fact that 3D echocardiography avoids geometric assumptions and errors in image plane position and reduces sampling errors.

In our study, the calculated MCF of the control group was  $0.56 \pm 0.09$ , which is comparable to that

achieved by Chuang et al., who estimated MCF in healthy men and women using CMR (males  $0.52 \pm 0.11$  and females  $0.58 \pm 0.13$ ). King et al. study yielded 3D echo-derived MCF of  $0.44 \pm 0.07$  in normal sedentary individuals and  $0.50 \pm 0.05$  in adult athletes [5]. It has been demonstrated that MCF, like LVEF, could discriminate the HF group from the healthy group, which was shown to be of highly significant difference statistically ( $0.28 \pm 0.05$  in the HF group versus  $0.56 \pm 0.09$  in the control group,  $P < 0.001$ ). This can be explained by remodeling in the HF group with significantly higher LV volumes and mass with lower SV than the control group [6].

In the HF study group, the calculated MCF was associated with quality of life and functional capacity. It has been shown that MCF is inversely correlated with the MLHFQ score ( $r = -0.6$ ,  $p < 0.001$ ) and positively correlated with 6MWD ( $r = 0.65$ ,  $p < 0.001$ ). However, no significant relationship existed between LVEF2D by biplane Simpson's and either MLHFQ or 6MWT. Indeed, MCF was shown to be an independent predictor—besides SPAP—of 6MWT; however, LVEF failed to offer such potential.

In our study, to further distinguish HF patients with good functional capacity from those with poor functional capacity according to arbitrary walking distance of 300 m in the 6MWT, an MCF of 28% as a cutoff value showed a sensitivity of 81% and a specificity of 79%. This further strengthens the hypothesis that MCF may be a superior metric—better than LVEF—in predicting the functional capacity of the HFrEF population. These results are commensurate with the conclusion achieved by Shimada et al. and Maurer et al. that showed that MCF is associated with subjective functional capacity in hypertrophic cardiomyopathy much more strongly than LVEF [26,29].

## 5. Limitations of the study

The conducted study has some limitations, as it is a single-center study that comprised a relatively small sample size. Poor endocardial or epicardial visualization precluded involving a minority of patients. It also did not interrogate the long-term prognostic utility of this echocardiographic index. Further larger multicenter studies are warranted to further elaborate the capability of MCF as a promising echocardiographic index in the prediction of functional capacity as well as overall survival and prognosis in patients with HFrEF.

## 6. Conclusion

MCF can be considered a volumetric echocardiographic index superior to LVEF in predicting functional capacity in HFrEF patients.

## Author contribution

Conception and design of Study: YAA Literature review: YAA, HAA Acquisition of data: YAA, HAA Analysis and interpretation of data: YAA, HAA, RRE Research investigation and analysis: YAA, HAA Data collection: YAA, HAA Drafting of manuscript: YAA Revising and editing the manuscript critically for important intellectual contents: YAA, HAA, RRE Data preparation and presentation: YAA Supervision of the research: YAA, RRE Research coordination and management: YAA, RRE.

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## Conflict of interest

None declared.

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