International Journal of Cardiology 399 (2024) 131772

Contents lists available at ScienceDirect

International Journal of Cardiology

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

Myocardial work and left heart deformation parameters across primary mitral regurgitation severity

Maria Concetta Pastore [a,*,1], Francesca Vannuccini [a,1], Giulia Elena Mandoli [a,1], Matteo Lisi [a,1], Maria Alma Iuliano [a,1], Alfonso Santoro [a,1], Francesco Paolo Niglio [a,1], Enrico Emilio Diviggiano [a,1], Veronica Lorenz [b,1], Gianfranco Montesi [b,1], Luna Cavigli [a,1], Marta Focardi [a,1], Flavio D'Ascenzi [a,1], Matteo Cameli [a,1]

[a] Department of Medical Biotechnologies, Division of Cardiology, University of Siena, Siena, Italy
[b] Division of Cardio-Thoracic Surgery, Department of Medical Biotechnologies, Azienda Ospedaliera Universitaria Senese, Siena, Italy

ARTICLE INFO

Keywords:
Mitral regurgitation
Symptoms
Speckle tracking echocardiography
Myocardial work
Strain

ABSTRACT

Aims: Myocardial work (MW) estimation by pressure-strain loops using speckle tracking echocardiography (STE) has shown to evaluate left ventricular (LV) contraction overcoming the load-dependency limit of LV global longitudinal strain (GLS). This has proved useful in hemodynamic variation settings e.g. heart failure and valvular heart disease. However, the variation of MW and strain parameters across different stages of primary mitral regurgitation (MR) and its impact on symptoms, which was the aim of our study, has never been investigated.

Methods and results: Consecutive patients with mild, moderate and severe MR were prospectively enrolled. Exclusion criteria were: chronic atrial fibrillation, valvular heart prosthesis, previous cardiac surgery.

Clinical evaluation, blood sample tests, ECG and echocardiography with STE and MW measurement were performed. Patients were then divided into groups according to MR severity. Differences among the groups and predictors of symptoms (as NYHA class≥2) were explored as study endpoints.

Overall, 180 patients were enrolled (60 mild,60 moderate,60 severe MR). LV GLS and global peak atrial longitudinal strain (PALS) reduced according to MR severity. Global constructive work (GCW) and global wasted work (GWW) significantly improved, while global work efficiency (GWE) reduced, in patients with moderate and severe MR. Among echocardiographic parameters, global PALS emerged as the best predictor of NYHA class ($p <$ 0.001;area under curve,AUC = 0.7).

Conclusions: MW parameters accurately describe the pathophysiology of MR, with initial attempt of LV increased contractility to compensate volume overload parallel to the disease progress, although with low efficacy, while global PALS is the most associated with the burden of MR symptoms.

1. Introduction

Primary mitral regurgitation (MR) is a degenerative disease involving the mitral valve (MV) characterized by gradually increasing severity and high morbidity and mortality if left untreated [1]. The main cause of primary MR is a myxomatous disease (e.g. MV prolapse) with intrinsic progression and possible complications such as chordal rupture or flail leaflet. Disease progression to severe MR results in cardiac maladaptive remodeling due to volume overload of both the left ventricle (LV) and left atrium (LA) and increased burden of heart failure (HF), atrial fibrillation (AF), and pulmonary hypertension. According to current European Society of Cardiology (ESC) Guidelines [2], surgical treatment of primary MR is recommended in symptomatic patients or in asymptomatic patients with systolic dysfunction (ejection fraction, EF ≤60%) and ventricular dilatation (LV end-systolic diameter, ESD ≥40 mm). Treatment should be considered in asymptomatic patients with AF or pulmonary hypertension secondary to MR (systolic pulmonary artery pressure, sPAP >50 mmHg at rest) or significant LA dilatation (LA

* Corresponding author at: Department of Medical Biotechnologies, Division of Cardiology, University of Siena, Viale Bracci 1, Siena, Italy.
E-mail address: mariaconce.pastore@unisi.it (M.C. Pastore).

[1] These authors takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

https://doi.org/10.1016/j.ijcard.2024.131772
Received 6 September 2023; Received in revised form 22 December 2023; Accepted 7 January 2024
Available online 9 January 2024

volume indexed,LAVI ≥60 ml/m2 or diameter ≥ 55 mm). Echocardiography is the first-line method for the evaluation of patients with MR. [3] Beyond basic indices, speckle tracking echocardiography (STE) has shown to be a useful tool to provide reliable assessment of myocardial damage and fibrosis in MR before the development of irreversible LV dysfunction, and to predict worse prognosis, with suggested potential value as a marker for early surgery [4].

Recently, myocardial work (MW) emerged as a new echocardiographic method to assess myocardial performance [5]. MW is based on integration of STE with arterial blood pressure and is calculated from pressure-strain loop areas constructed from LV pressure combined with global longitudinal strain (GLS) curves. MW could estimate LV contractile proprieties by overcoming limitation of load dependency characterizing GLS with the advantage of incorporating after-load information.

MW has proved to be useful and superior to GLS and LV EF as a measure of systolic function, especially in clinical settings characterized by frequent hemodynamic changes, such as HF [6], and in high afterload conditions such as hypertension [7], aortic stenosis [8], or hypertrophic obstructive cardiomyopathy [9]. Furthermore, MW demonstrated to be effective in predicting response to cardiac resynchronization therapy (CRT) [10]. MW evaluation showed interesting results in ischemic heart disease, hypertrophic or dilated cardiomyopathy as a predictor of outcome and as a valid method for early LV dysfunction evaluation even with preserved EF [5,11].

To date, the role of MW in identifying cardiac dysfunction in MR has not been studied. The aim of this study was to evaluate the changes in MW indices and left heart chamber deformation parameters with relation to the stages of MR and their association with patients' symptoms.

2. Methods

2.1. Patient population

In this observational study, we consecutively enrolled outpatients with primary MR referred to the echo-labs of the Le Scotte University Hospital in Siena between January 2021 and December 2022. Demographic characteristics, medical history, cardiovascular risk factors and laboratory test data were collected for each patient. Each patient underwent physical examination, vital signs measurement (including blood pressure), ECG and echocardiographic examination on the same day of enrollment. Patients with chronic AF, history of previous valve surgery, congenital heart disease or more than moderate other valve diseases were excluded. New York Heart Association (NYHA) class was used as index of the burden of patients' symptoms [12].

Patients were divided into three groups based on MR degree according to the current American Society of Echocardiography (ASE) guidelines [13] (Fig.1). All patients signed informed consent for the study. All the study procedures were performed in accordance with the Declaration of Helsinki.

2.2. Echocardiographic measurements

Transthoracic echocardiography was performed in accordance with the recommendations of the ASE/European Association of Cardiovascular Imaging (ASE/EACVI) recommendations [14–16] in patients at rest in the left lateral decubitus position by experienced operators, using a using a high-quality ultrasound machine (Vivid E9; General Electric, Horten, Norway) equipped with an adult 1.5–4.3 MHz phased array transducer.

LV and LA diameters were measured in parasternal standard views. LV EF (by Simpson's method) and LA volume were assessed from the apical 4- and 2-chamber views, then, LAVI was obtained dividing for

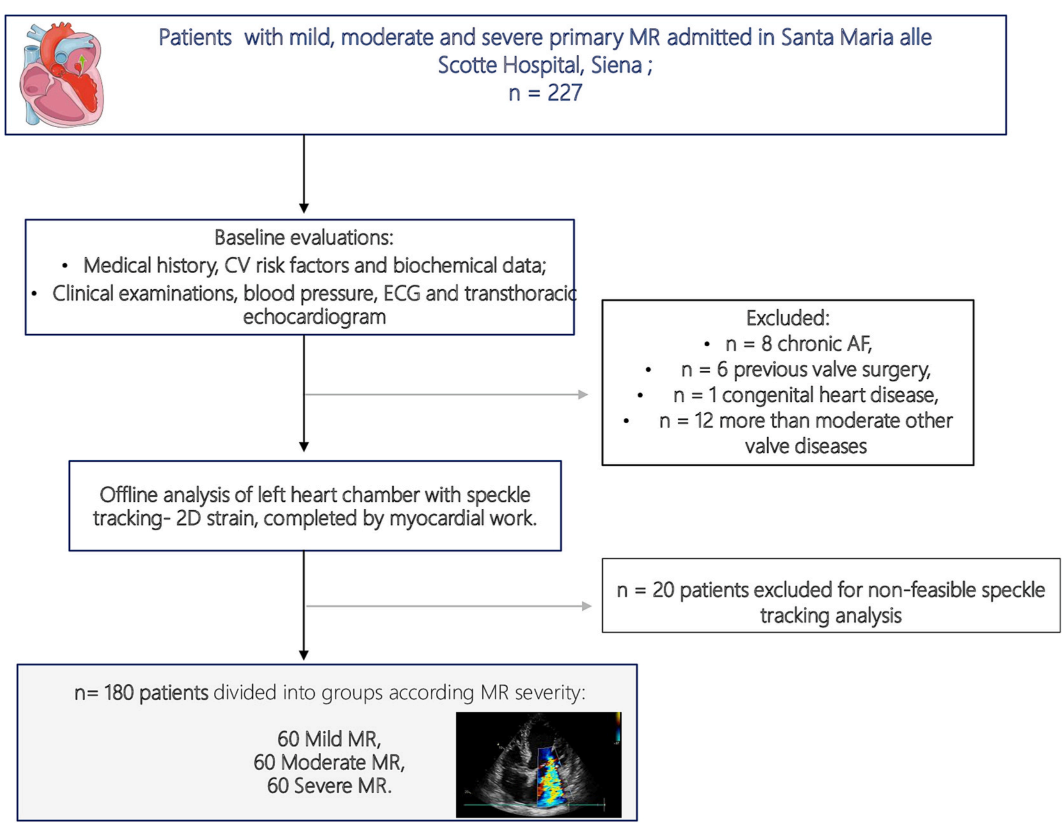

Fig. 1. Algorithm of enrolment of our study population. AF,atrial fibrillation;CV,cardiovascular,MR,mitral regurgitation.

body surface area. Tricuspid annulus plane systolic excursion (TAPSE) was measured using M-mode. *Trans*-Mitral pulsed-wave and tissue Doppler were used to assess LV filling pressure. Valvular heart diseases were quantified by bidimensional(2D)-echocardiography according to ASE/EACVI recommendation [14–16]. Presence of aortic/tricuspidal/pulmonary regurgitation has been defined in presence of at least moderate regurgitation.

2.3. Speckle-tracking and myocardial work analysis

For STE, apical 4-, 2- and 3-chamber 2-dimensional gray-scale images with a stable electrocardiographic recording were analyzed. Atrial strain was calculated using apical 4- and 2-chamber views, using the QRS wave as cardiac cycle starting point; dedicated views were utilized for LV, LA and right ventricular analysis, allowing a more reliable delineation of the atrial endocardial border. Three consecutive heart cycles were recorded and averaged. The frame rate was 60–80 frames/s. Analysis was performed off-line by a single experienced and independent echocardiographer, using a commercially available semiautomated 2-dimensional strain software (EchoPac, GE, Milwaukee, Wisconsin) with automated functional imaging (AFI) algorithms dedicated to LV and LA. LV GLS was calculated as the average of 4-chambers, 2-chambers and 3-chambers longitudinal strain curves. Global peak atrial longitudinal strain (PALS) was calculated at the end of the reservoir phase as an average of the values observed in all LA segments in the 4- and 2-chamber views. Free-wall right ventricular longitudinal strain was derived by a ROI of three segments (basal, medial, & apical) including only right ventricular free-wall.

For subsequent MW analysis, the operator confirms the event timing of aortic and mitral events by the apical three-chamber view synchronized with the ECG trace. Brachial arterial pressure was measured during the physical examination and just (few minutes) before performing the echocardiographic examination. Blood pressure is used by the software to fit a non-invasively estimated LV pressure curve [17] with peak blood pressure values and valvular events.

The software automatically creates a pressure-deformation loop, derived from the estimated LV pressure curve and GLS, and generates four myocardial performance indices: global work index (GWI), which is the total work done by the left ventricle during systole, calculated from MV closure to MV opening adding isovolumetric contraction and isovolumetric relaxation, global constructive work (GCW), which is the productive work done during systole and includes both muscle shortening in systole and muscle lengthening during isovolumetric relaxation, the global wasted work (GWW), which is the non-productive work done during systole and includes the muscle lengthening in systole and the shortening work during isovolumetric relaxation, and finally, the global work efficiency (GWE), which is a ratio of constructive work divided by the sum of constructive work and wasted work (GCW/GCW + GWW) [18–20] (Fig.2).

2.4. Statistical analysis

Data are expressed as means ± SD (continuous normal variables) or median [interquartile range, IQR] (continuous non-normal variables) or as counts and percentages (binary variables). Kolmogorov-Smirnov test was used to test parameters for normality. Patients were divided into three groups based on MR severity. Differences between the three groups for general and echocardiographic parameters were analyzed using independent sample Student *t*-tests for continuous variables (Mann-Whitney *U* test for non-normally distributed variables) and Chi-squared analyses for categorical variables.

Pearsons' coefficient was used to determine the correlation between echocardiographic parameters and NYHA class in patients' population, then, linear regression analysis was used to assess the value of strain parameters as a predictor of NYHA class.

Receiver operating characteristic (ROC) curves allowed to estimate the overall performance of echocardiographic parameters to predict NYHA class ≥2.

Analyses were performed using the Statistical Package for Social Sciences software, release 20.0 (SPSS, Chicago, Illinois). *P*-values <0.05 were considered statistically significant.

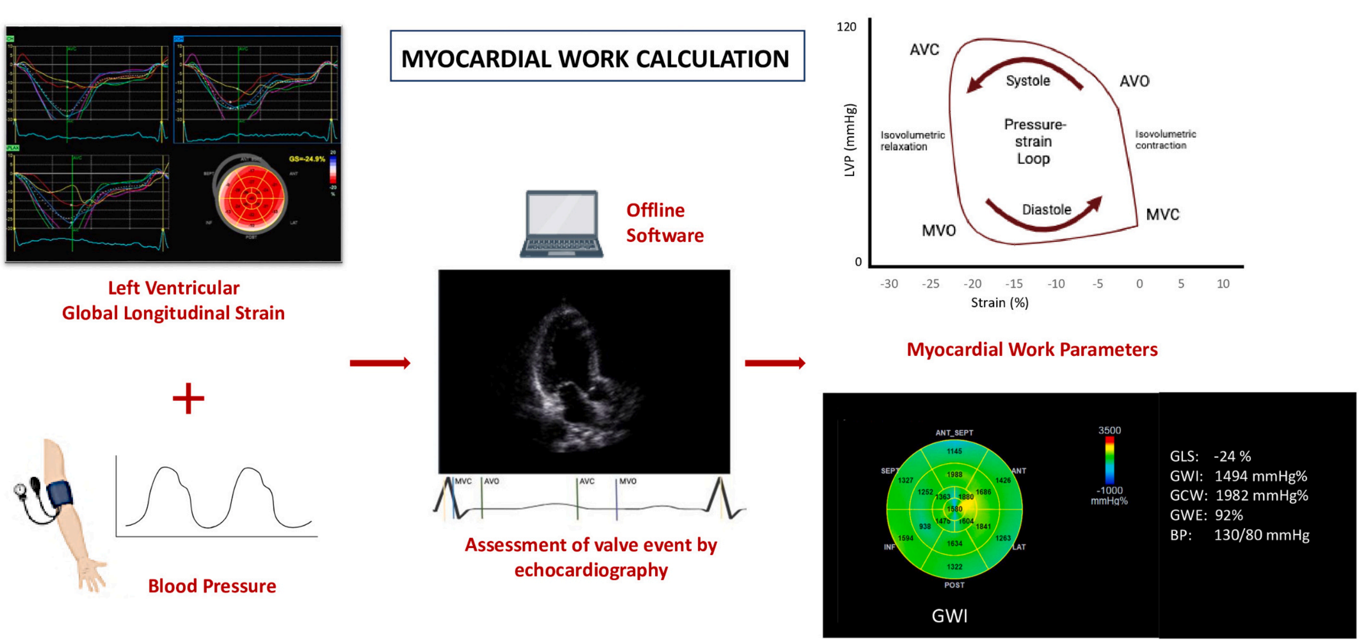

Fig. 2. Myocardial work calculation.
BP,blood pressure;GCW,global constructive work;GLS,global longitudinal strain;GWE,global work efficiency;GWI,global work index;GWW,global wasted work;LV, left ventricular.

3. Results

3.1. General population characteristics

A total of one hundred and eighty patients with primary MR were included: 60 patients with mild MR, 60 patients with moderate MR and 60 patients with severe MR. Median age was 67 ± 15 years, the majority were male (57%). Patients with moderate or severe MR were older than patients with mild MR. Heart rate was slightly higher in the severe MR group while systolic blood pressure was similar between the groups. The main cause of MR was the presence of leaflet prolapse while leaflet flail and annulus dilation were recorded mainly in patients with severe MR ($p < 0.0001$). Overall, 59% of the patients were in NYHA class I, 36% in NYHA class II and 5% in NYHA class III. Overall, 13.3% of the population had concomitant type 2 diabetes mellitus, 66.5% had systemic artery hypertension and 6.1% had paroxysmal AF episodes. Most of the population was on ACEi therapy (60%), 42% were taking beta-blockers and 7.8% spironolactone. Finally, patients with severe MR were older (69 ± 13 years), more symptomatic (73% in NYHA class II), had more paroxysmal AF episodes (15%), and a greater numbers were taking beta-blocker (57%) or MRA (15%) therapies than mild MR (Table 1**)**.

3.2. Echocardiographic parameters

The differences in echocardiographic parameters in our population are shown in Table 2. LV EF was preserved in all patients (57 ± 5%), however, patients with moderate or severe MR showed a slight reduction in EF compared to patients with mild MR ($p < 0.001$ and $p < 0.02$, respectively). Patients with severe MR had significantly increased LV end-diastolic volumes index (LV EDVi) than patients with mild and moderate MR ($p < 0.001$ and $p < 0.01$, respectively). LV concentric remodeling was observed in moderate and severe MR. Diastolic function was increasingly impaired in severe MR (mean E/e' = 11 ± 3) and in moderate MR (mean E/e' = 9 ± 4). Patients with moderate and severe MR also had a significant increase in estimated systolic pulmonary artery pressure (sPAP) and LAVI compared with patients with mild MR.

3.3. Deformation and myocardial work parameters

The mean global GLS was −19.5 ± 3, without a significant variation between the three severity groups. Global PALS and peak atrial contraction strain (PACS) showed a significant early and progressive reduction towards increasing severity. Right ventricular free wall strain (−20 ± 15%) showed no significant variation among the three groups (Table 2).

MW analysis showed similar values of GWI (mean 1884 ± 427 mmHg) across the three stages of MR. On the other hand, GCW was increased in severe MR compared with mild MR (2261 ± 333 mmHg % vs 2501 ± 632 mmHg %, $p < 0.01$). Importantly, a significant increase of GWW was recorded in patients with severe MR compared to moderate and mild MR ($p < 0.0001$ vs mild MR, $p < 0.002$ vs moderate MR). Moreover, GWE was significantly reduced in the higher severity grades ($p < 0.0001$ vs mild MR, $p < 0.001$ vs moderate MR) (Fig.3). Conversely no significant variation of MW parameters was observed between mild and moderate MR (Table 2).

MW reference values in healthy patients were described in the NORRE study [21]. Compared with reference values, GWI and GWC values were similar to healthy patients (GWI n.v. 1896 ± 308 mmHg%; GCW n.v. 2232 ± 331 mmHg %) even in severe MR stages. On the other hand, a significant increase in GWW (n.v. 53–122.2 mmHg%) is detected from the early stages of MR as well as a reduced GWE (n.v. 94–97%) is observed in mild MR.

3.4. Correlation analysis

We analyzed the potential correlation of echocardiographic and MW parameters with the presence of symptoms shown as NYHA class≥II. Significant correlations were found between the presence of symptoms and LAVi (Pearson's $P = 0.29$, Spearman's rho 0.32, $p < 0.0001$), average E/e' (Pearson's $P = 0.22$, Spearman's rho 0.25, $p < 0.002$), global PALS (Pearson's $P = -0.3$, Spearman's rho −0.35, $p < 0.0001$) and global PACS (Pearson's $P = -0.25$, Spearman's rho −0.21, $p < 0.001$). On the other hand, GLS showed no significant correlation with NYHA class (Pearson's P = 0.2, Spearman's rho 0.09, $p = 0.2$).

Regarding MW parameters, the best association with NYHA class ≥ II was found for GWE (Pearson's $P = -0.22$; Spearman's rho −0.22, $p = 0.003$), followed by GWW (Pearson's $P = 0.22$; Spearman's rho −0.24, $p = 0.001$). By contrast, there was no association between GWI (Pearson's $P = -0.1$, Spearman's rho −0.08, $p = 0.25$) and GCW (Pearson's $P = -0.015$, Spearman's rho −0.021, $p = 0.77$); and symptoms.

With ROC curve analysis, global PALS (AUC = 0.7, CI 0.62–0.77, *p < 0.0001*) emerged as the best echocardiographic predictor of NYHA

Table 1
Baseline clinical characteristics in the overall study population and in the three severity groups.

	Overall (*n* = 180)	Group 1 Mild MR (*n* = 60)	Group 2 Moderate MR (n = 60)	Goup 3 Severe MR (n = 60)	*p* value overall	*p* value (1 vs 2)	*p* value (1 vs 3)	*p* value (2 vs 3)
Age (years)	67 ± 14.5	62 ± 16	69 ± 13	69 ± 13		**0.004**	**0.003**	0.93
BMI (kg/m^2)	25 ± 4	25 ± 4	25 ± 5	25 ± 4		0.82	0.93	0.78
SBP (mmHg)	128 ± 17	128 ± 15	127 ± 15	130 ± 20		0.65	0.60	0.36
HR (bpm)	69 ± 13	69 ± 12	65 ± 10	73 ± 15		0.07	0.07	**0.0008**
Male (%, n)	57%(102)	58%(35)	57%(34)	55%(33)	0.64			
NYHA class I (%, n)	59%(107)	80%(48)	72%(43)	26%(16)	**<0.0001**			
NYHA class II (%, n)	36%(64)	17%(10)	28%(17)	62%(37)	**<0.0001**			
NYHA class III (%, n)	5%(9)	3%(2)	–	12%(7)	**<0.0001**			
Diabetes (%, n)	13.3% (24)	18%(11)	17%(10)	5%(3)	0.065			
Hypertension (%,n)	66.5%(119)	57%(34)	80%(48)	63%(37)	**0.019**			
paroxysmal AF (%,n)	6.1%(11)	–	3%(2)	15%(9)	**0.002**			
ACEi (%, n)	60%(108)	53%(32)	67%(40)	60%(36)	0.329			
Beta Blockers (%,n)	42%(75)	30%(18)	38%(23)	57%(34)	**0.010**			
Spironolattone (%,n)	7.8%(14)	3%(2)	5%(3)	15%(9)	**0.032**			
MR flail (%, n)	8%(14)	–	–	23%(14)	**<0.0001**			
MR prolapse (%, n)	68%(123)	40%(24)	78%(47)	87%(52)	**<0.0001**			
MR degenerative (%, n)	32%(57)	60%(36)	22%(13)	13%(8)	**<0.0001**			
MR anulus >35 mm (%, n)	33%(59)	13%(8)	17%(10)	69%(41)	**<0.0001**			

AF,atrial fibrillation;BMI, body mass index;BSA,body surface area;HR,heart rate;MR,mitral regurgitation;NYHA,New York Heart Association;SBP,systolic blood pressure.

Table 2
Echocardiographic parameters in the overall study population and in the three severity groups.

	Overall (n = 180)	Group 1 Mild MR (n = 60)	Group 2 Moderate MR (n = 60)	Group 3 Severe MR (n = 60)	*p* value overall	*p* value (1 vs 2)	*p* value (1 vs 3)	*p* value (2 vs 3)
LV EF (%)	57 ± 5	59 ± 4	56 ± 5	57 ± 6		**0.001**	**0.02**	0.60
IVS (mm)	11 ± 2.0	11 ± 1.8	12 ± 2.0	11 ± 1.8		**0.01**	**0.05**	0.45
EDDi (mm/m^2)	28 ± 5	25 ± 3	29 ± 6	28 ± 4		0.17	0.73	0.24
EDVi (ml/m^2)	54.6 ± 15.4	50 ± 14	52 ± 14	59 ± 16		0.42	**0.001**	**0.01**
Mitral E/A ratio	1.1 ± 1.2	0.9 ± 0.4	1.2 ± 0.5	1.2 ± 0.5		**0.0004**	**<0.0001**	0.66
E/e'm	9 ± 3.4	8 ± 2	9 ± 4	11 ± 3		**0.008**	**<0.0001**	0.06
LAVi (ml/m2)	40 ± 17	30 ± 7	40 ± 13	53 ± 20		**0.000**	**<0.0001**	**<0.0001**
TAPSE (mm)	24 ± 5	23 ± 4	21 ± 4	22 ± 4		**0.05**	0.81	0.11
TDI s' (m/s)	0.14 ± 0.03	0.14 ± 0.03	0.14 ± 0.03	0.14 ± 0.04		0.95	0.90	0.94
Mild RVEDD (mm)	28 ± 5	26 ± 5	29 ± 5	29 ± 4		**0.004**	**0.003**	0.61
RVFAC (%)	44 ± 6	45 ± 6	44 ± 7	44 ± 7		0.18	0.17	0.96
sPAP (mmHg)	30 ± 9	26 ± 5	29 ± 8	35 ± 11		**0.03**	**<0.0001**	**0.0008**
Presence of AR (%, n)	52%(94)	32%(19)	65%(39)	60%(36)	**0.001**			
Presence of TR (%, n)	88%(159)	83%(50)	85%(51)	97%(58)	**<0.0001**			
Presence of AS (%, n)	7%(12)	5%(3)	10%(6)	5%(3)	0.366			
Speckle tracking parameters								
GLS	(−)19.5 ± 3	(−)19.7 ± 2.0	(−)19.4 ± 2.5	(−)19.3 ± 4		0.47	0.48	0.87
Global PALS	28.2 ± 9	34.8 ± 7.7	26.9 ± 7.8	23.1 ± 8.2		**<0.0001**	**<0.0001**	**0.01**
Global PACS	15 ± 7	17.8 ± 7.2	14.8 ± 5.4	11.6 ± 5.2		**0.01**	**<0.0001**	**0.001**
fwRVLS	(−)23 ± 6	(−)23 ± 6	(−)24 ± 7	(−)23 ± 7		0.66	1.00	0.68
GWI (mmHg%)	1884 ± 427	1890 ± 299	1867 ± 364	1895 ± 574		0.70	0.96	0.75
GCW (mmHg %)	2341 ± 484	2261 ± 333	2261 ± 400	2501 ± 632		0.99	**0.01**	0.15
GWW (mmHg %)	211 ± 178	156 ± 110	184 ± 135	294 ± 234		0.22	**0.0001**	**0.002**
GWE (%)	91 ± 5	93 ± 4	91 ± 5	88 ± 6		0.18	**<0.0001**	**0.001**

AR,aortic regurgitation;AS,aortic stenosis;EDDi,end-diastolic diameter index;EDVi,end-diastolic volume index;E/E',peak early diastolic"E" wave/medium early mitral annular velocity by tissue doppler imaging;fwRVLS,free wall right ventricular longitudinal strain;GLS,global longitudinal strain;GWI,global work index;GCW,global constructive work;GWW,global wasted work;GWE,global work efficiency;IVS,interventricular septum;LAVi,left atrium volume index;LV EF,left ventricle ejection fraction;PACS,peak atrial contraction strain;PALS, peak atrial longitudinal strain;RVEDD,right ventricular end-diastolic diameter;RVFAC,right ventricular fractional area change;sPAP,systolic pulmonary artery pressure;TAPSE,tricuspid annular plane systolic excursion;TDI,tissue doppler imaging;TR,tricuspid regurgitation.

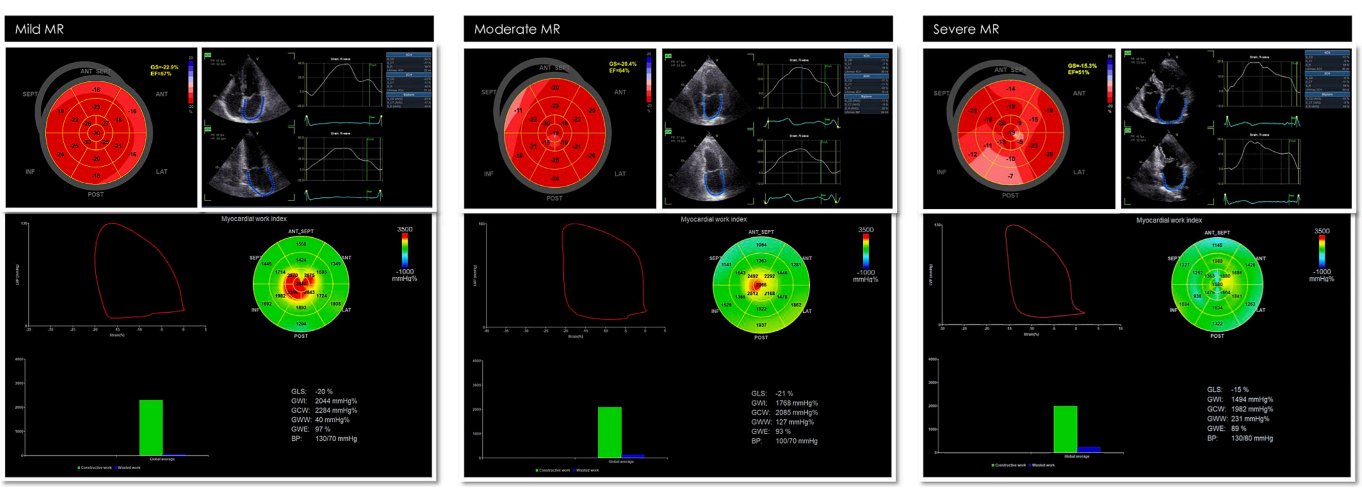

Fig. 3. Representative cases showing left heart deformation parameters (global longitudinal strain up(GLS)-left, left atrial strain up-right, myocardial work down) in patients with different stages of mitral regurgitation. BP,blood pressure;GCW,global constructive work;GWE,global work efficiency;GWI,global work index;GWW, global wasted work;MR,mitral regurgitation.

class. Among MW parameters only GWW (AUC 0.634, CI 0.55–0.72, *p = 0.002*) was significantly associated with NYHA class (Fig. 4)**).**

4. Discussion

Our study was the first to evaluate differences in MW across different severity stages of primary MR and its impact on symptoms. Overall, we found a significant change of GCW, GWW and GWE in patients with higher grades of MR which may reflect the response to gradual hemodynamic changes characterizing the disease. LV GCW was found to be less impaired, while GWW was higher, in severe MR. This suggests a progressive increase in contractility as a compensatory mechanism to volume overload resulting in early increased wasted work. In addition, MW indices showed an association with the appearance of symptoms in patients with MR, however, PALS gradually decreased from patients with moderate MR and showed the best association with symptoms.

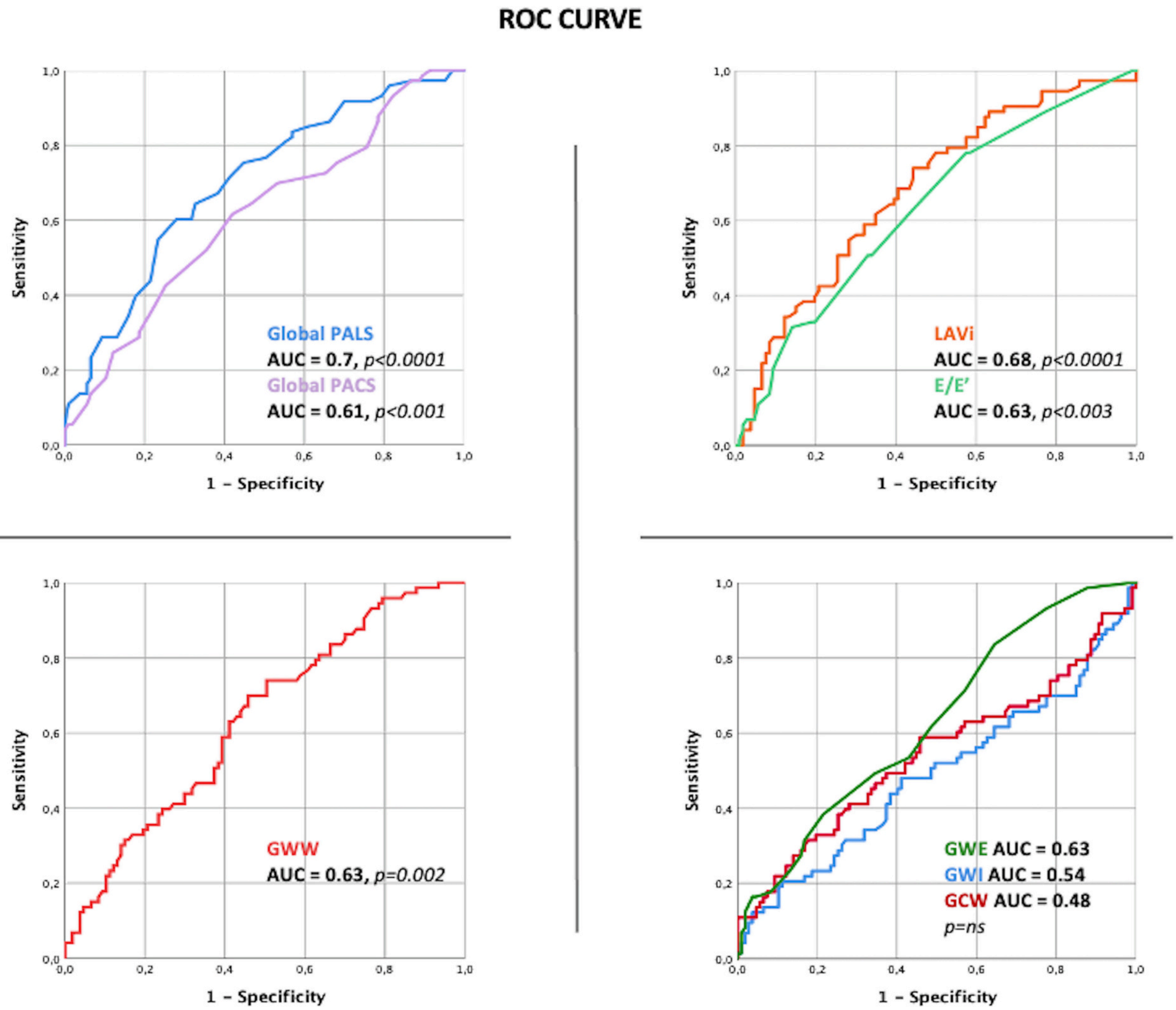

Fig. 4. Receiver operating characteristic (ROC) curves show the correlation of echocardiographic and MW parameters with symptoms (NYHA class ≥ II). AUC,area under the curve;E/E',peak early diastolic "E" wave/medium early mitral annular velocity by tissue doppler imaging;GCW,global constructive work;GWE,global work efficiency;GWI,global work index;GWW,global wasted work;LAVI,left atrium volume index;PALS,peak atrial longitudinal strain.

4.1. Evaluation of MW in primary MR

Primary MR is characterized by progressive volume overload in the left chambers leading to eccentric LV remodeling and an increase in end-diastolic volume. These changes can significantly affect LV diastolic and systolic function without LV EF impairment until the advanced stages when fibrosis has already established. Moreover, despite the progression of the disease, many patients remain asymptomatic, while others rapidly develop symptoms with or without the presence of echocardiographic criteria for surgical treatment. Several new parameters have been proposed over the years as predictors of disease progression and myocardial impairment [4].

Many authors have shown the role of GLS as an index of subclinical cardiac dysfunction compared with LV EF. In a meta-analysis involving 5267 patients (from 24 studies, of which 16 in primary MR), all studies except for one showed a significant association between impaired LV GLS and worse clinical and echocardiographic outcomes in primary MR. [22] In addition, GLS proved to be useful to optimize the timing of intervention [23]: preoperative LV GLS ≥ -20.9% predicted worse long-term survival in 593 patients with MR undergoing surgery [24]. Furthermore, in another meta-analysis [25] involving 2358 patients (8 studies), reduced baseline GLS was associated with worse long-term survival and lower LV EF after surgery.

On the other hand, further evidence has shown that left atrial strain could reveal myocardial damage caused by MR earlier than LV GLS [23].

Left atrial deformation by STE (i.e. global PALS) is now a validated parameter, with high feasibility (95% for senior operators and 90% for young operators) [26,27]. Global PALS has been applied in various clinical scenarios showing good prognostic power. It has been described as an early prognostic marker in MR of different severity, even superior to GLS [23,28]. PALS was also correlated with functional capacity measured by NYHA class and Borg scale [28] and with peak oxygen consumption in patients with severe MR [29] and was found to be a useful parameter to stratify the risk of AF [23,26,30] as well.

LA is the first chamber affected by the hemodynamic overload in MR, therefore, in the first stages it compensates volume overload increasing its performance, but the chronic increase in LV filling pressures eventually leads to LA remodeling and fibrosis [31]. Global PALS has shown to be a reliable marker of LV filling pressure and LA fibrosis [30], it has been recommended as an additional parameter to assess LV diastolic function in the EACVI consensus for the evaluation of HF with preserved ejection fraction (HFpEF) [32]. In several studies, it also showed to be correlated with the onset of HF symptoms [33] and with functional capacity [34].

In our study, we confirmed the association of LA strain with symptomatic status (i.e. NYHA class) in patients with MR, over other echocardiographic parameters. This suggests that the gradual reduction of LA strain mirrors the appearance of ultrastructural changes in LA wall in response to increasing hemodynamic overload, until LA capability to compensate high LV filling pressures is compromised and symptoms appear. This is a crucial point for MR treatment, which should be early recognized to provide prompt medical or surgical therapy, before irreversible cardiac damage take place.

MW may provide additional value for the assessment of myocardial function, considering both myocardial deformation and afterload [17]. In recent years, an increasing number of studies have evaluated the application of MW indices in different clinical settings that have shown the good reproducibility (intraclass correlation coefficient = 0.99) of this technique [10,35].

The clinical application of MW has been studied in various conditions, among which the first and most studied is the prediction of cardiac resynchronization therapy (CRT) response in HF [10] . Also, Coisine A. et al [35] evaluated MW indices in patients with acute ischemic heart disease, in which low GWE (<91%) at 1 month after acute myocardial infarction was associated with major event rate. MW seems to be useful also in non-obstructive hypertrophic cardiomyopathy (HCM) to assess myocardial performance [9] and LV fibrosis as compared to cardiac magnetic resonance. MW has shown promising results in aortic valve disease, being correlated with the extent of fibrosis and symptoms due to pressure overload in aortic stenosis [8,36]. In chronic aortic regurgitation, an afterload-dependent condition, MW may offer additional information. In fact, Meucci et al. [37] showed that LV GWI and GCW correlated with aortic regurgitation severity and, after valve repair/ replacement, LV GWI, GCW and GWE decreased significantly. Finally, MW was evaluated in patients with severe secondary MR. Those patients had lower LV GWI and LV GCW but higher LV GWW and GWE, which were associated with worse long-term survival [38]. In addition, MW has been shown to be useful in detecting the impact of MV repair with MitraClip in patients with functional MR as an increase of GWI and GCW [39].

Changes in MW across MR severity has never been investigated. In our study, among different stages of primary MR, there were no significant differences in LV function assessed by LV EF and LV GLS. By contrast, we observed an increase in GCW and in GWW according to severity. The significant increase in GCW could be an early marker of the higher LV contractile performance required in case of increased afterload conditions. Probably, as the severity of MR increases, LV emptying in a low-pressure chamber (the LA) triggers a compensatory mechanism of increased LV contractility to pump blood volume into a higher-pressure chamber (the aorta). This effect, however, has limited efficacy in increasing LV stroke volume. In fact, in our study, a significant increase in GWW was found in moderate stages of MR, attributable to an increase in wall distress reflecting an inefficient myocyte contraction despite an attempt to increase LV performance from the mid-gravity stages. These findings reflect into a significant decrease in GWE (i.e. GCW/ GCW + GWW ratio), thus the increase in both parameters results in an overall decreased MW efficiency.

On the other hand, changes in MW in patients with functional MR (FMR) has already been evaluated [38]. An impairment of LV GWI and GCW was observed, while LV GWW and GWE were significantly less impaired in severe FMR than mild FMR. These results can be explained by the different pathophysiology underlying FMR. In fact, LV function, described by a falsely preserved LV EF but an underlying dysfunction (reduced LV GLS) according to severity, and global LV work are impaired due to eccentric remodeling, which is unable to generate constructive work, but apparently facilitated by the emptying of blood volume in the LA at low pressure. In addition, LV is not able to generate enough work to pump blood volume into a higher-pressure district (aorta) due to the LV underlying disease. This translates into less wasted energy and greater global efficiency.

4.2. MW in primary MR: clinical implications

In patients with primary MR, a more accurate assessment of LV systolic function remains a current clinician interest since basic echocardiographic parameters are not sensitive enough for an early characterization of progressive myocardial impairment and show a reduction only in advanced stages of the disease. MW currently represents a precise and additional measure to GLS that could reveal underlying LV dysfunction accounting for different hemodynamic conditions with more sensitive parameters. Our findings suggest that the evaluation of both parameters in the context of primary MR could help stratifying the intrinsic myocardial damage, beyond MR grading and LV EF. Particularly, in moderate and severe stage, this technique could be used as additional tool to early recognize patients who do not achieve the standard echocardiographic parameters of severity but who show early LV dysfunction and could benefit from therapeutic modifications, stricter follow up or earlier surgical intervention.

4.3. Limitations

Even though our study results are unique and promising, some limitations should be recognized. First, this is a single-center study with a limited number of patients, therefore larger and multicenter studies are warranted to confirm our findings. Moreover, ambulatory patients analyzed were mainly hemodynamically stable and with low burden of symptoms (in fact, no patient had NYHA class = IV). Patients with AF were excluded for greater population homogeneity and to focus our analysis of strain parameters in MR patients without any confounders. Further analysis is needed to assess changes in LA deformation and MW parameters in these settings. Then, as a speckle tracking-based method, MW is not applicable in patients with poor acoustic window. Moreover, MW is currently available only on Echopac software, which may limit its applicability in all centers. However, we hope that increasing evidence on the potential value of these parameters would lead to the diffusion of this technique to all vendors, resulting in an increasing availability in first and second level centers.

5. Conclusions

Patients with primary MR are subject to increasing volume overload and wall stress parallel to disease severity. Our study showed differences in MW indices according to MR severity. More severe stages of primary MR are characterized by higher values of GCW and GWW with a reduction of GWE. Furthermore, MR increasing severity is also associated with an early reduction in PALS which is associated symptomatic status. Evaluation of MW indices can allow better stratification of patients with primary MR with the aim of identifying patients who could benefit from therapeutic modifications, stricter follow-up or earlier surgical intervention. However, studies with larger numbers of patients are needed to confirm the proposed method for non-invasive estimation of MW in MR patients and to better define the role of MW parameters in predicting disease progression.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2024.131772.

Fundings

none.

CRediT authorship contribution statement

Maria Concetta Pastore: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing. **Francesca Vannuccini:** Data curation, Writing – original draft, Writing – review & editing. **Giulia Elena Mandoli:** Data curation, Visualization, Writing – review & editing. **Matteo Lisi:** Data curation, Investigation, Supervision, Visualization, Writing – review & editing. **Maria Alma Iuliano:** Data curation, Investigation. **Alfonso Santoro:** Data curation, Investigation. **Francesco Paolo Niglio:** Data curation, Investigation. **Enrico Emilio Diviggiano:** Data curation, Investigation. **Veronica Lorenz:** Data curation, Investigation. **Gianfranco Montesi:** Supervision, Validation, Visualization. **Luna Cavigli:** Validation, Visualization. **Marta Focardi:** Supervision, Validation, Visualization. **Flavio D'Ascenzi:** Supervision, Validation, Visualization. **Matteo Cameli:** Conceptualization, Methodology, Project administration, Supervision, Validation, Visualization, Writing – review & editing.

Declaration of competing interest

The authors report no relationships that could be construed as a conflict of interest.

Acknowledgements

None.

References

[1] B. Slostad, G. Ayuba, J.J. Puthumana, Primary mitral regurgitation and heart failure: current advances in diagnosis and management, Heart Fail. Clin. 19 (3) (2023) 297–305, https://doi.org/10.1016/J.HFC.2023.02.006.
[2] A. Vahanian, F. Beyersdorf, F. Praz, et al., 2021 ESC/EACTS guidelines for the management of valvular heart disease, Eur. Heart J. 43 (7) (2022) 561–632, https://doi.org/10.1093/eurheartj/ehab395.
[3] M.C. Pastore, G.E. Mandoli, A. Sannino, et al., Two and three-dimensional echocardiography in primary mitral regurgitation: practical hints to optimize the surgical planning, Front. Cardiovasc. Med. (2021) 8, https://doi.org/10.3389/fcvm.2021.706165.
[4] M.C. Pastore, G.E. Mandoli, A. Dokollari, et al., Speckle tracking echocardiography in primary mitral regurgitation: should we reconsider the time for intervention? Heart Fail. Rev. 27 (4) (2022) 1247–1260, https://doi.org/10.1007/s10741-021-10100-1.
[5] F. Ilardi, A. D'andrea, F. D'ascenzi, et al., Myocardial work by echocardiography: principles and applications in clinical practice, J. Clin. Med. 10 (19) (2021), https://doi.org/10.3390/jcm10194521.
[6] J. Chan, N.F.A. Edwards, B.K. Khandheria, et al., A new approach to assess myocardial work by non-invasive left ventricular pressure–strain relations in hypertension and dilated cardiomyopathy, Eur. Heart J. Cardiovasc. Imaging 20 (1) (2019) 31–39, https://doi.org/10.1093/ehjci/jey131.
[7] M. Tadic, C. Cuspidi, B. Pencic, G. Grassi, V. Celic, Myocardial work in hypertensive patients with and without diabetes: an echocardiographic study, J. Clin. Hypertens. 22 (11) (2020) 2121–2127, https://doi.org/10.1111/jch.14053.
[8] F. Fortuni, S.C. Butcher, F. van der Kley, et al., Left ventricular myocardial work in patients with severe aortic stenosis, J. Am. Soc. Echocardiogr. 34 (3) (2021) 257–266, https://doi.org/10.1016/j.echo.2020.10.014.
[9] E. Galli, E. Vitel, F. Schnell, et al., Myocardial constructive work is impaired in hypertrophic cardiomyopathy and predicts left ventricular fibrosis, Echocardiography. 36 (1) (2019) 74–82, https://doi.org/10.1111/echo.14210.
[10] E. Galli, C. Leclercq, M. Fournet, et al., Value of myocardial work estimation in the prediction of response to cardiac resynchronization therapy, J. Am. Soc. Echocardiogr. 31 (2) (2018) 220–230, https://doi.org/10.1016/j.echo.2017.10.009.
[11] D. Abawi, T. Rinaldi, A. Faragli, et al., The non-invasive assessment of myocardial work by pressure-strain analysis: clinical applications, Heart Fail. Rev. 27 (4) (2022) 1261–1279, https://doi.org/10.1007/s10741-021-10119-4.
[12] C. Caraballo, N.R. Desai, H. Mulder, et al., Clinical implications of the New York heart association classification, J. Am. Heart Assoc. 8 (23) (2019), https://doi.org/10.1161/JAHA.119.014240.
[13] W.A. Zoghbi, D. Adams, R.O. Bonow, et al., Recommendations for noninvasive evaluation of native Valvular regurgitation: a report from the American Society of Echocardiography developed in collaboration with the Society for Cardiovascular Magnetic Resonance, J. Am. Soc. Echocardiogr. 30 (4) (2017) 303–371, https://doi.org/10.1016/j.echo.2017.01.007.
[14] R.M. Lang, L.P. Badano, M.A. Victor, et al., Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging, J. Am. Soc. Echocardiogr. 28 (1) (2015) 1–39.e14, https://doi.org/10.1016/j.echo.2014.10.003.
[15] C. Mitchell, P.S. Rahko, L.A. Blauwet, et al., Guidelines for performing a comprehensive transthoracic echocardiographic examination in adults, J. Am. Soc. Echocardiogr. (2018), https://doi.org/10.1016/j.echo.2018.06.004.
[16] W.A. Zoghbi, D. Adams, R.O. Bonow, et al., Recommendations for noninvasive evaluation of native Valvular regurgitation: a report from the American Society of Echocardiography developed in collaboration with the Society for Cardiovascular Magnetic Resonance, J. Am. Soc. Echocardiogr. 30 (4) (2017) 303–371, https://doi.org/10.1016/j.echo.2017.01.007.
[17] K. Russell, M. Eriksen, L. Aaberge, 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, https://doi.org/10.1093/eurheartj/ehs016.
[18] K. Papadopoulos, Ö.Ö. Tok, K. Mitrousi, I. Ikonomidis, Myocardial work: methodology and clinical applications, Diagnostics. 11 (3) (2021), https://doi.org/10.3390/diagnostics11030573.
[19] O.A. Smiseth, E. Donal, M. Penicka, O.J. Sletten, How to measure left ventricular myocardial work by pressure-strain loops, Eur. Heart J. Cardiovasc. Imaging 22 (3) (2021) 259–261, https://doi.org/10.1093/ehjci/jeaa301.
[20] N. Marzlin, A.G. Hays, M. Peters, et al., Myocardial work in echocardiography, Circ. Cardiovasc. Imag. 16 (2) (2023) E014419, https://doi.org/10.1161/CIRCIMAGING.122.014419.
[21] R. Manganaro, S. Marchetta, R. Dulgheru, et al., Echocardiographic reference ranges for normal non-invasive myocardial work indices: results from the EACVI NORRE study, Eur. Heart J. Cardiovasc. Imaging 20 (5) (2019) 582–590, https://doi.org/10.1093/ehjci/jey188.
[22] H. Ueyama, T. Kuno, H. Takagi, et al., Prognostic value of left ventricular global longitudinal strain in mitral regurgitation: a systematic review, Heart Fail. Rev. (2022), https://doi.org/10.1007/s10741-022-10265-3.
[23] M. Cameli, G.E. Mandoli, D. Nistor, et al., Left heart longitudinal deformation analysis in mitral regurgitation, Int. J. Cardiovasc. Imaging 34 (11) (2018) 1741–1751, https://doi.org/10.1007/s10554-018-1391-4.
[24] Y.L. Hiemstra, A. Tomsic, S.E. van Wijngaarden, et al., Prognostic value of global longitudinal strain and etiology after surgery for primary mitral regurgitation, JACC Cardiovasc. Imaging 13 (2P2) (2020) 577–585, https://doi.org/10.1016/j.jcmg.2019.03.024.
[25] M. Canessa, R. Thamman, C. Americo, G. Soca, V. Dayan, Global longitudinal strain predicts survival and left ventricular function after mitral valve surgery: a Meta-analysis, Semin. Thorac. Cardiovasc. Surg. 33 (2) (2021) 337–342, https://doi.org/10.1053/j.semtcvs.2020.09.024.
[26] M. Cameli, M. Lisi, F.M. Righini, M. Focardi, O. Alfieri, S. Mondillo, Left atrial speckle tracking analysis in patients with mitral insufficiency and history of paroxysmal atrial fibrillation, Int. J. Card. Imaging 28 (7) (2012) 1663–1670, https://doi.org/10.1007/s10554-011-9987-y.
[27] M. Cameli, M.H. Miglioranza, J. Magne, et al., Multicentric atrial strain COmparison between two different modalities: MASCOT HIT study, Diagnostics. 10 (11) (2020), https://doi.org/10.3390/diagnostics10110946.
[28] G.E. Mandoli, M.C. Pastore, G. Benfari, et al., Left atrial strain as a pre-operative prognostic marker for patients with severe mitral regurgitation, Int. J. Cardiol. 324 (2021) 139–145, https://doi.org/10.1016/j.ijcard.2020.09.009.
[29] T. Sugimoto, F. Bandera, G. Generati, et al., Left atrial dynamics during exercise in mitral regurgitation of primary and secondary origin: pathophysiological insights by exercise echocardiography combined with gas exchange analysis, JACC Cardiovasc. Imaging 13 (1) (2020) 25–40, https://doi.org/10.1016/j.jcmg.2018.12.031.
[30] M. Cameli, G.E. Mandoli, F. Loiacono, S. Sparla, E. Iardino, S. Mondillo, Left atrial strain: a useful index in atrial fibrillation, Int. J. Cardiol. 220 (2016) 208–213, https://doi.org/10.1016/j.ijcard.2016.06.197.
[31] M. Lisi, M. Cameli, G.E. Mandoli, et al., Left atrial myocardial intrinsic function remodeling response to repair of primary mitral regurgitation, Echocardiography. 39 (10) (2022) 1264–1268, https://doi.org/10.1111/echo.15452.
[32] O.A. Smiseth, D.A. Morris, N. Cardim, et al., Multimodality imaging in patients with heart failure and preserved ejection fraction: an expert consensus document of the European Association of Cardiovascular Imaging, Eur. Heart J. Cardiovasc. Imaging 23 (2) (2022) E34–E61, https://doi.org/10.1093/ehjci/jeab154.
[33] M. Cameli, C. Sciaccaluga, F. Loiacono, et al., The analysis of left atrial function predicts the severity of functional impairment in chronic heart failure: the FLASH multicenter study, Int. J. Cardiol. 286 (2019) 87–91, https://doi.org/10.1016/j.ijcard.2019.03.063.
[34] T. Bekfani, A. Hamadanchi, S. Ijuin, et al., Relation of left atrial function with exercise capacity and muscle endurance in patients with heart failure, ESC Heart Fail. 8 (6) (2021) 4528–4538, https://doi.org/10.1002/ehf2.13656.
[35] A. Coisne, V. Fourdinier, G. Lemesle, et al., Clinical significance of myocardial work parameters after acute myocardial infarction, Eur. Heart J. Open 2 (3) (2022), https://doi.org/10.1093/ehjopen/oeac037.
[36] F. Ilardi, A. Postolache, R. Dulgheru, et al., Prognostic value of non-invasive global myocardial work in asymptomatic aortic stenosis, J. Clin. Med. 11 (6) (2022), https://doi.org/10.3390/jcm11061555.
[37] M.C. Meucci, S.C. Butcher, X. Galloo, et al., Noninvasive left ventricular myocardial work in patients with chronic aortic regurgitation and preserved left ventricular ejection fraction, J. Am. Soc. Echocardiogr. 35 (7) (2022) 703–711.e3, https://doi.org/10.1016/j.echo.2022.01.008.
[38] I. Yedidya, R.P. Lustosa, F. Fortuni, et al., Prognostic implications of left ventricular myocardial work indices in patients with secondary mitral regurgitation, Circ. Cardiovasc. Imag. 14 (9) (2021) E012142, https://doi.org/10.1161/CIRCIMAGING.120.012142.
[39] K. Papadopoulos, I. Ikonomidis, M. Chrissoheris, et al., MitraClip and left ventricular reverse remodelling: a strain imaging study, ESC Heart Fail. 7 (4) (2020) 1409–1418, https://doi.org/10.1002/ehf2.12750.