Article:

Gorecka, M., Craven, T.P., Jex, N. et al. (16 more authors) (2024) Mitral regurgitation assessment by cardiovascular magnetic resonance imaging during continuous in-scanner exercise: a feasibility study. The International Journal of Cardiovascular Imaging, 40 (7). pp. 1543-1553. ISSN 1569-5794

https://doi.org/10.1007/s10554-024-03141-8

The International Journal of Cardiovascular Imaging
https://doi.org/10.1007/s10554-024-03141-8

ORIGINAL PAPER

Mitral regurgitation assessment by cardiovascular magnetic resonance imaging during continuous in-scanner exercise: a feasibility study

Miroslawa Gorecka[1] · Thomas P. Craven[1] · Nick Jex[1] · Pei G. Chew[1] · Laura E. Dobson[2] · Louise A.E. Brown[1] · David M. Higgins[3] · Sharmaine Thirunavukarasu[1] · Noor Sharrack[1] · Wasim Javed[1] · Sindhoora Kotha[1] · Marilena Giannoudi[1] · Henry Procter[1] · Martine Parent[1] · Dominik Schlosshan[1] · Peter P Swoboda[1] · Sven Plein[1] · Eylem Levelt[1] · John P. Greenwood[1,4]

Received: 17 December 2023 / Accepted: 13 May 2024

Abstract

Purpose Exercise imaging using current modalities can be challenging. This was patient focused study to establish the feasibility and reproducibility of exercise-cardiovascular magnetic resonance imaging (EX-CMR) acquired during continuous in-scanner exercise in asymptomatic patients with primary mitral regurgitation (MR).

Methods This was a prospective, feasibility study. Biventricular volumes/function, aortic flow volume, MR volume (MR-Rvol) and regurgitant fraction (MR-RF) were assessed at rest and during low- (Low-EX) and moderate-intensity exercise (Mod-EX) in asymptomatic patients with primary MR.

Results Twenty-five patients completed EX-CMR without complications. Whilst there were no significant changes in the left ventricular (LV) volumes, there was a significant increase in the LVEF (rest 63 ± 5% vs. Mod-EX 68 ± 6%;$p = 0.01$). There was a significant reduction in the right ventricular (RV) end-systolic volume (rest 68 ml(60–75) vs. Mod-EX 46 ml(39–59);$p < 0.001$) and a significant increase in the RV ejection fraction (rest 55 ± 5% vs. Mod-EX 65 ± 8%;$p < 0.001$). Whilst overall, there were no significant group changes in the MR-Rvol and MR-RF, individual responses were variable, with MR-Rvol increasing by ≥ 15 ml in 4(16%) patients and decreasing by ≥ 15 ml in 9(36%) of patients. The intra- and inter-observer reproducibility of LV volumes and aortic flow measurements were excellent, including at Mod-EX.

Conclusion EX-CMR is feasible and reproducible in patients with primary MR. During exercise, there is an increase in the LV and RV ejection fraction, reduction in the RV end-systolic volume and a variable response of MR-Rvol and MR-RF. Understanding the individual variability in MR-Rvol and MR-RF during physiological exercise may be clinically important.

Keywords Exercise testing · Stress testing · Cardiovascular magnetic resonance · Mitral regurgitation

✉ John P. Greenwood
j.greenwood@leeds.ac.uk

1 Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds Teaching Hospitals NHS Trust, Leeds LS2 9JT, UK

2 Department of Cardiology, Wythenshawe Hospital, Manchester University NHS Trust, Manchester, UK

3 Philips, Farnborough, Farnborough, UK

4 Baker Heart and Diabetes Institute & Monash University, Melbourne, Australia

Abbreviations

AFF	Aortic forward flow
CMR	Cardiovascular magnetic resonance
C-SENSE	Compressed sensing
EX-CMR	Exercise cardiovascular magnetic resonance
EX-TTE	Exercise transthoracic echocardiography
HR	Heart rate
HRR	Heart rate reserve
Low-EX	Low-intensity exercise stage
LV	Left ventricle
LVEDV	Left ventricle end-diastolic volume
LVEF	Left ventricular ejection fraction
LVSV	Left ventricle stroke volume
Mod-EX	Moderate-intensity exercise stage
MR	Mitral regurgitation

Published online: 23 May 2024

PCMR	Phase-contrast CMR
RF	Regurgitant fraction
RV	Right ventricle
Rvol	Regurgitant volume
SD	Standard deviation
TTE	Transthoracic echocardiography

Introduction

In severe primary mitral regurgitation (MR), surgery is recommended in symptomatic patients or those with left ventricular (LV) dysfunction or dilated end-systolic cavity [1]. In patients with high likelihood of successful repair and low operative mortality, mitral valve repair is also recommended in those with new-onset atrial fibrillation or pulmonary hypertension [1]. However, in some cases, irreversible left ventricular remodelling may occur before the surgery. As such, appropriate timing of surgical intervention and identifying patients, who can potentially benefit from early surgery is crucial to prevent adverse outcomes and to improve prognosis.

Exercise testing plays an important role in patients with asymptomatic MR [1, 2]. Exercise transthoracic echocardiography (EX-TTE) can provide useful insights into the physiological LV response to exercise and examine changes in MR during exercise [1, 2]. However, EX-TTE has several limitations, such as poor acoustic windows [3], and can be very challenging due to motion artefact – in fact, quantification of MR during exercise has been found to be possible only in about 50% of cases [4].

Quantification of primary MR by cardiovascular magnetic resonance (CMR) imaging has been shown to have better prognostic association in asymptomatic MR than TTE [5, 6]. Moreover, CMR is the reference-standard for assessment of the LV and right-ventricular (RV) size and function [7, 8]. Exercise-CMR (EX-CMR) can, therefore, potentially overcome the limitations of EX-TTE and add diagnostic value in the assessment of asymptomatic patients with primary MR.

EX-CMR assessment of biventricular volumes has been shown to be feasible and reproducible in a small study of patients with primary MR [9]. Although in this study aortic flow measurements were not performed, which prevented assessment of MR severity and its response to exercise, we have also demonstrated the feasibility of bi-ventricular volumes and aortic flow assessment by EX-CMR in healthy volunteers [10].

EX-CMR enables assessment of the effective forward ejection fraction, a novel concept that has been previously demonstrated in resting CMR and shown to correlate better with the post-operative left ventricular ejection fraction (LVEF) [11]. This, however, has never been assessed during physiological exercise in patients with primary MR. EX-CMR could, therefore, potentially identify patients who would benefit from an early surgical referral as it may add diagnostic and prognostic information.

Therefore, we sought to describe (1) the feasibility and reproducibility of EX-CMR assessment of biventricular volumes and aortic flow volume in patients with asymptomatic primary MR, during continuous supine in-scanner exercise, utilising vendor provided pulse sequences and standard analysis software; and (2) the biventricular and MR regurgitant volume (MR-Rvol) and regurgitant fraction (MR-RF) changes that occur during exercise in this group of patients.

Materials and methods

Study population

This was a prospective, single-centre feasibility study. We recruited patients with at least moderate primary MR, who were asymptomatic and had LVEF > 55%. We excluded patients with (a) secondary MR (atrial, ischaemic) and those with rheumatic aetiology, (b) indication for surgery as per the 2017 European Society of Cardiology guidelines [1]: atrial fibrillation, evidence of pulmonary hypertension on TTE of ≥ 50mmHg or dilated LV cavity (LV end-systolic dimension ≥ 45 mm), (c) significant aortic valve disease on TTE (> mild), (d) prior myocardial infarction, (e) significant respiratory disease, (f) contraindications to exercise stress testing [12] and (g) general contraindications to CMR. Diagnosis of at least moderate MR was based on the American Society of Echocardiography guidelines [13]. The study was approved by the National Research Ethics Service (18/YH/0168), had institutional approval and complied with the Declaration of Helsinki. All patients provided written informed consent.

Exercise protocol

Patients exercised on a supine cycle ergometer (Lode BV, Netherlands) during the CMR scan. The exercise protocol used in this study was in accordance with the heart rate reserve (HRR) and an age predictive maximal heart rate model [14]. In line with this model, an individual low (30–39% HRR) and moderate (40–59% HRR) exercise intensity was defined for each patient. The age-predictive maximal heart rate was calculated as per the following formula [14]:

maximal heart rate = 208 – 0.7 x age. This method was chosen as it was developed from a population with a wide age range and fitness level.

The low and moderate intensities were calculated as per the Karvonen method according to the following equation:

%HRR=((maximal heart rate − heart rate at rest) x % desired intensity of exercise) + HR (heart rate) rest [15]. This method was used as it takes into account the lower resting and exercise heart rate, which occurs in supine position. Following resting imaging, patients exercised with no resistance (0 Watts) for 1 min, with a subsequent increase in the resistance by 25 Watts every 2 min and ideally 60–70 revolutions per minute. This was continued until the low intensity target heart rate was reached and stabilised for 1 min, at which point CMR scanning was performed. When required, small increases in resistance were carried out to maintain the target heart rate. Once the low intensity stage was complete, further increase in resistance of 25 Watts every 2 min were undertaken until the moderate intensity target heart rate was reached and stabilised for 1 min, whereupon further CMR scanning was performed. Patients exercised continuously with the CMR acquisition undertaken during exercise (rather than with exercise cessation), using a navigated free-breathing pulse sequence and with the receiver coil strapped to the patient to ensure consistency of the coil-to-body position. Patients were instructed to hold onto handrails mounted at the side of the scanner in order to stabilise themselves during the scan and reduce motion artefact. Optimal patient preparation also included instructions on consistent thoracic breathing, skin preparation to maximize interface between electrode and skin and securing vector electrocardiogram connections onto anterior chest wall with tape.

CMR protocol

All EX-CMR studies were conducted on a 1.5T Philips Ingenia (Best, The Netherlands) system. The CMR imaging protocols used were previously validated in healthy volunteers in our centre [10]. All images were acquired using retrospective ECG gating. CMR scan protocol (Fig. 1), which took about 45 min to complete, included:

CMR = cardiovascular magnetic resonance; CS3 = rate 3 compressed sensing; LV = left ventricle; THR = target heart rate.

Imaging at rest.

a) Survey images.
b) Free-breathing transverse Half-Fourier Acquisition Single-shot Turbo spin Echo imaging.
c) Cine images acquired with breath-hold balanced steady-state free precession sequence:

    a. 4-chamber view and vertical-long axis view.
    b. 2 orthogonal LV outflow tract views.
    c. LV short-axis stack. Sequence parameters: typical field-of-view 300 × 360 mm, 10 mm slice thickness with 0 mm gap, repetition time 3.2ms, echo time 1.58ms, flip angle 60°, sensitivity encoding (SENSE) factor 2, 30 reconstructed phases, acquired matrix 192 × 158 and acquired voxel size 1.88 × 1.88 mm, typical total scan duration 60s (6 breath-holds). Quantification of right ventricular volumes/function was performed on the short-axis cine images.

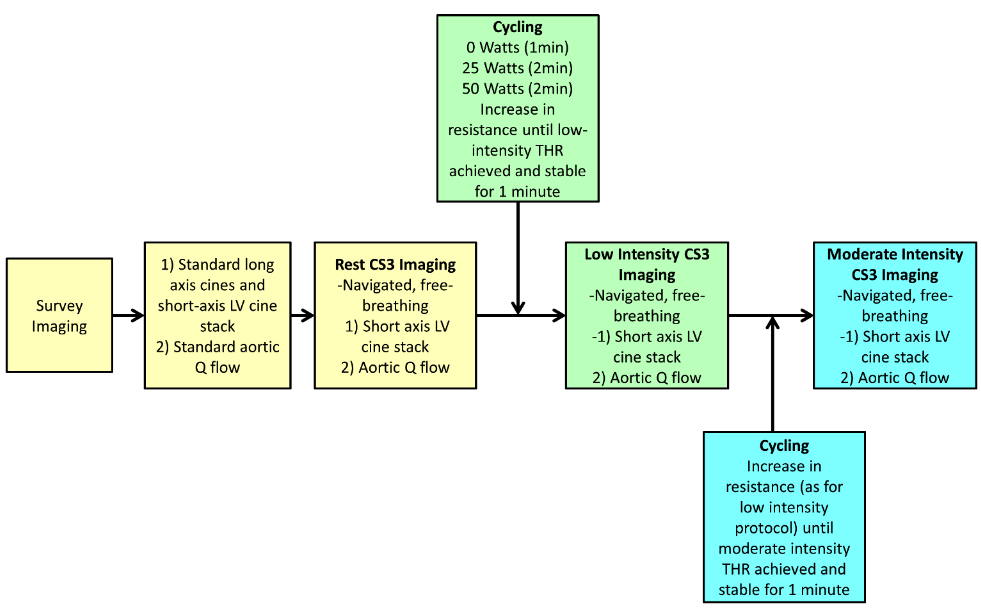

Fig. 1 Exercise-CMR scan protocol

d) Through-plane aortic phase contrast breath-held images (PCMR): planned at sino-tubular junction and orthogonal to the vessel [16]. Velocity encoding was set to 150 cm/s. Sequence parameters: typical field-of-view 350 × 282 mm, slice thickness 8 mm, repetition time 4.9ms, echo time 2.9ms, flip angle 15°, number of signal averages 1, SENSE factor 2, 30 reconstructed phases, acquired matrix 140 × 113, acquired voxel size 2.5 × 2.5 mm, Cartesian sampling, turbo field echo factor 3, typical total scan duration 20s.
e) Compressed-SENSE (C-SENSE) protocol:

   a. Rate 3 C-SENSE LV short-axis cine stack: free-breathing, respiratory navigator gated continuous imaging with rate 3 C-SENSE. Respiratory navigation was performed by means of the respiratory echo-based navigator, which was positioned on the right hemi-diaphragm. There was a 5 mm acceptance window with continuous gating level drift. Imaging parameters: typical field-of-view 300 × 300 mm, repetition time 2.4ms, echo time 1.2, flip angle 60°. Multishot turbo field echo factor 12, acquired heart phases 34, slice thickness 10 mm, 0 mm gap, acquired voxel size 2.5 × 3.45 mm, acquired matrix 120 × 87, typical total scan duration 39s.
   b. Rate 3 C-SENSE through-plane aortic phase contrast imaging stack: free-breathing, respiratory navigator gated continuous imaging with rate 3 C-SENSE. Velocity encoding was set to 150 cm/s. Three 8 mm overlapping slices were acquired with a -3 mm gap to account for increased motion during exercise, so that the centres of the individual slices were 5 mm apart. Imaging parameters: typical field-of-view 350 × 320 mm, repetition time 4.9ms, echo time 2.9ms, flip angle 15°, number of signal averages 1, turbo field echo factor 5, slice thickness 8 mm, 30 reconstructed phases, acquired voxel size 2.5 × 2.5 mm, acquired matrix 140 × 128, Cartesian sampling, typical total scan duration 27s.

Low-intensity exercise (Low-EX) imaging

a) Free-breathing 4-chamber view and a LV outflow tract view to allow re-planning of the short-axis cine imaging and phase-contrast imaging.
b) Rate 3 C-SENSE LV short-axis stack: as per rest imaging.
c) Rate 3 C-SENSE through-plane aortic phase contrast imaging stack: as per rest imaging, except for velocity encoding, which was increased to 250 cm/s.

Moderate-intensity exercise (Mod-EX) imaging

a) As per low-intensity exercise imaging.

CMR image analysis

Analysis was performed by MG and TC using post-processing software (cvi42, Circle Cardiovascular Imaging, Calgary, AB, Canada). Blinded intra-observer analysis was performed by MG and blinded inter-observer analysis was performed by TC and NJ. Left and right ventricular volumes were obtained by manually tracing the endocardial border in end-diastole and end-systole, with trabeculations and papillary muscles being included in the blood pool. Final volumes were obtained by the summation of discs method [17]. Aortic flow was quantified by manually tracing the endovascular border in every cardiac phase. The slice closest to the sinotubular junction was chosen from the exercise PCMR stack for quantification of aortic flow at exercise to ensure consistency of results. Mitral regurgitant volume was obtained indirectly, by substracting aortic forward flow (AFF) volume from the LV stroke volume (LVSV). Mitral regurgitant fraction was obtained by dividing the MR-RVol by LVSV. Effective forward LVEF was calculated as: AFF/LVEDV as previously described [11].

Statistical analysis

Continuous variables are presented as mean ± SD (standard deviation) or median with interquartile range as per normality of distribution. Normal distribution was determined by Anderson-Darling test. Categorical variables are expressed as numbers and percentages. Continuous variables were compared by means of Student t-test (normal distribution) or Mann-Whitney test (non-normal distribution). The differences in continuous variables between rest, low- and moderate-intensity exercise were compared by repeated measures Analysis of Variance with Bonferroni correction for normally distributed variables and Friedman's test with Bonferroni correction (if significant) for non-normally distributed variables. The reproducibility was assessed by intra-class correlation with a two-way random model for absolute agreement and a 95% confidence interval, it was defined as excellent when ICC was > 0.9, good > 0.75, moderate > 0.5 and poor < 0.5. Furthermore, it was assessed by coefficient of variation and mean biases obtained from Bland-Altman plots. All analyses were performed using IBM SPSS (version 27) and Minitab (version 19); statistical significance was defined with a two-sided $P < 0.05$.

Results

Twenty-nine patients were recruited to the study, of whom 4 were excluded from the final analysis (claustrophobia $n=2$, legs too long to use the ergometer $n=1$, severe artefact at low-intensity exercise $n=1$). All patients who underwent imaging had height < 185 cm.

Demographic and clinical characteristics

Baseline demographic and clinical characteristics of the patient population are presented in Table 1. With regard to severity of MR, almost half of the patients in our study had severe MR, with the remainder of patients having at least moderate MR. The most common aetiology was posterior mitral valve prolapse ($n=15$;60%).

Haemodynamic and imaging characteristics at rest and during exercise

Haemodynamic characteristics

Both, heart rate and systolic blood pressure increased significantly during exercise (Table 2). The increase in heart rate was significant between all stages: rest vs. Low-EX ($p=0.001$), Rest vs. Mod-EX ($p<0.001$) and Low-EX vs. Mod-EX ($p=0.001$). The systolic blood pressure increased significantly between Rest vs. Low-EX ($p<0.001$) and Rest vs. Mod-EX ($p<0.001$), but not between Low-Ex and Mod-EX ($p=1.0$). There was no significant change in the diastolic blood pressure during exercise.

Table 1 Baseline patient characteristics

Variable	All patients $n=25$
Age (years)	65(55–69)
Male	19(76)
BMI (kg/m^2)	24 ± 3
Weekly exercise (hours)	2(0–4)
Hypertension	5 [20]
Prior stroke/TIA	1 [4]
MR Severity as per TTE	
Severe	12(48)
Mod-severe	1 [4]
Moderate	12(48)
MR Aetiology	
Posterior MVP	15(60)
Bileaflet MVP	9(36)
Mitral valve cleft	1 [4]

Data are presented as mean ± SD, median(IQR1-IQR3) and n(%). BMI = body mass index; MR = mitral regurgitation; MVP = mitral valve prolapse; TIA = transient ischaemic attack; TTE = transthoracic echocardiography

Imaging characteristics

An example of Ex-CMR image quality during Low-EX and Mod-EX is presented in Fig. 2. The changes in the imaging parameters between rest, low-intensity exercise and moderate-intensity exercise are presented in Table 2. With regard to the changes in the LV parameters, there were no significant changes in the LV end-diastolic volume (LVEDV), end-diastolic volume index or stroke volume during exercise. Although, the LV end-systolic volume (LVESV) reduced numerically, especially between rest and Low-EX, this was not statistically significant ($p=0.11$). The LVEF, however, increased significantly between Rest vs. Low-EX (63%±5 vs. 68%±5, respectively; $p=0.01$), with no further increase between Low-EX vs. Mod-EX (68%±5 vs. 68%±6, respectively; $p=1.0$).

Similar to the LV parameters, there were no significant changes in the RV end-diastolic volume, end-diastolic volume index or the stroke volume. The RV end-systolic volume, however, reduced significantly during exercise (rest 68 ml(60–75) vs. Mod-EX 46 ml(39–59); $p<0.001$). The RV ejection fraction (RVEF) also increased significantly between Rest to Mod-EX stage of exercise (55%±5 vs. 65%±8, respectively; $p<0.001$).

With regard to the LV contractile reserve, 14 patients (56%) demonstrated LVEF increase of at least 4% at Low-EX, while 15 patients (60%) demonstrated LV contractile reserve at Mod-EX. There were 4 patients (16%), who did not have LV contractile reserve at Low-EX, but had an increase in LVEF of more than 4% in the Mod-EX stage. There were 3 patients (12%), who demonstrated LV contractile reserve at Low-EX, but subsequently had a decrease in the LVEF in the Mod-EX stage.

While there were no significant changes in the LVEDV and the AFF, the effective forward LVEF increased significantly between Rest vs. Mod-EX (39%±8 vs. 47%±10, respectively; $p=0.01$), but not between rest and Low-EX stage of exercise ($p=0.20$) or between Low-EX and Mod-EX stage ($p=0.76$).

There were no statistically significant changes in the MR-Rvol and MR-RF during exercise, although the MR-Rvol reduced numerically between Rest and Mod-EX stage (50 ml ± 26 vs. 42 ml ± 22, respectively; $p=0.39$). While overall, there were no significant changes in the MR-Rvol and MR-RF in this group, the individual response to exercise was quite variable. **(**Fig. 3**)** Mitral regurgitant volume increased by more than 15 ml from rest to Low-EX in 5(20%) patients and from rest to Mod-EX in 4(16%) patients. There was, however, reduction in severity of MR in 4(16%) patients at Low-EX and in 9(36%) patients at Mod-EX.

Table 2 Comparison of haemodynamic and CMR parameters at rest, low-intensity and moderate-intensity exercise

	Rest	Low-intensity exercise	Moderate-intensity exercise	Overall *p*-value*	Rest vs. Low-Intensity	Rest Vs. Moderate-Intensity	Low vs. Mod-Intensity
Haemodynamic parameters							
HR achieved (bpm)	63(59–68)	98(95–105)	112(109–118)	**< 0.001**	**0.001**	**< 0.001**	**0.001**
Systolic BP (mmHg)	130(121–138)	142(137–161)	159(138–170)	**< 0.001**	**< 0.001**	**< 0.001**	1.0
Diastolic BP (mmHg)	78 ± 8	79 ± 19	78 ± 13	0.91	-	-	-
Cycle resistance (W)	-	50(50–60)	75(55–75)	**< 0.001**	-	-	**< 0.001**
CMR parameters							
LV EDV (ml)	201 ± 41	201 ± 41	193 ± 39	0.69	-	-	-
LV EDV index (ml/m^2)	108 ± 19	108 ± 18	104 ± 19	0.63	-	-	-
LV ESV (ml)	74 ± 20	65 ± 20	63 ± 20	0.11	-	-	-
LV ESV index (ml/m^2)	40 ± 10	31 ± 10	34 ± 10	0.07	-	-	-
LV SV (ml)	127 ± 27	135 ± 26	130 ± 25	0.51	-	-	-
LV EF (%)	63 ± 5	68 ± 5	68 ± 6	**0.004**	**0.01**	**0.01**	1.0
RV EDV (ml)	151 ± 29	151 ± 28	145 ± 31	0.68	-	-	-
RV EDV index (ml/m^2)	81 ± 15	81 ± 13	78 ± 16	0.62	-	-	-
RV ESV (ml)	68(60–75)	57(47–71)	46(39–59)	**< 0.001**	0.10	**< 0.001**	**0.03**
RV SV (ml)	84 ± 19	92 ± 25	95 ± 26	0.21	-	-	-
RV EF (%)	55 ± 5	61 ± 9	65 ± 8	**< 0.001**	0.06	**< 0.001**	0.17
Aortic forward flow (ml)	77 ± 16	86 ± 18	88 ± 19	0.08	-	-	-
Effective forward LV EF (%)	39 ± 8	44 ± 8	47 ± 10	**0.01**	0.20	**0.01**	0.76
MR-Rvol (ml)	50 ± 26	49 ± 19	42 ± 22	0.39	-	-	-
MR-RF (%)	35(29–49)	37(28–43)	35(23–43)	0.18	-	-	-
Number of patients with LV contractile reserve, n(%)	-	14(56)	15(60)	-	-	-	-
Number of patients with an increase in MR-Rvol ≥ 15 ml, n(%)	-	5 [20]	4 [16]	-	-	-	-
Number of patients with a decrease in MR-Rvol ≥ 15 ml, n(%)	-	4 [16]	9(36)	-	-	-	-

Data are presented as mean ± SD and median(IQR1-IQR3). *Overall p-value – result of comparison between all groups. BP = blood pressure; CMR = cardiovascular magnetic resonance; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; HR = heart rate; LV = left ventricle; MR-Rvol = mitral regurgitant volume; MR-RF = mitral regurgitant fraction; RV = right ventricle; SV = stroke volume

Panel (A) presents individual responses of MR-Rvol during exercise in all patients. Dashed red line represents the mean and the black dashed lines represent the standard deviation. Panel (B) presents individual responses of MR-RF during exercise in all patients. Dashed red line represents the mean and the black dashed lines represent the standard deviation. MR-Rvol = mitral regurgitant volume; MR-RF = mitral regurgitant fraction.

Intra- and inter-observer reproducibility

These results are presented in Table 3.

Intra-observer reproducibility

As assesses by intraclass correlation coefficient, the intra-observer reproducibility was excellent for all imaging parameters at rest and at low-intensity exercise. At moderate-intensity exercise, it was excellent for all parameters, except the RV end-systolic volume, where it was good. Mean bias was very small for all parameters. Coefficient of variation was very good for all parameters (< 10%), with RV end-systolic volume at Mod-Ex demonstrating largest degree of dispersion.

Inter-observer reproducibility

As assessed by intraclass correlation coefficient, at rest, the inter-observer reproducibility was excellent for LV parameters and aortic forward flow, whereas it was moderate-to-good for right-ventricular parameters. At low-intensity exercise, it remained good-to-excellent for LV parameters, AFF and RV end-diastolic volume, whereas it was poor for the assessment of RV end-systolic volume. At moderate-intensity exercise, it was good-to-excellent for all parameters, except RV end-systolic volume, for which it was

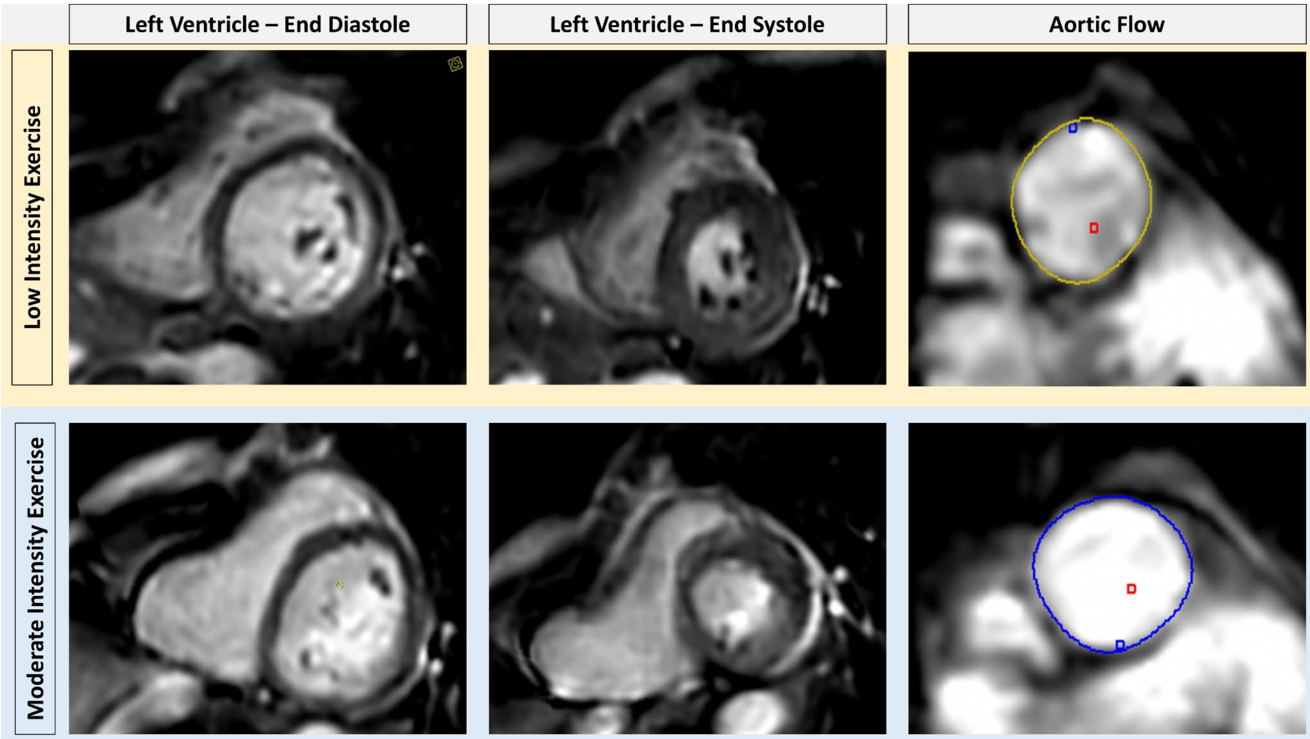

Fig. 2 An example of exercise-CMR image quality at low-intensity and moderate-intensity exercise. CMR = cardiovascular magnetic resonance

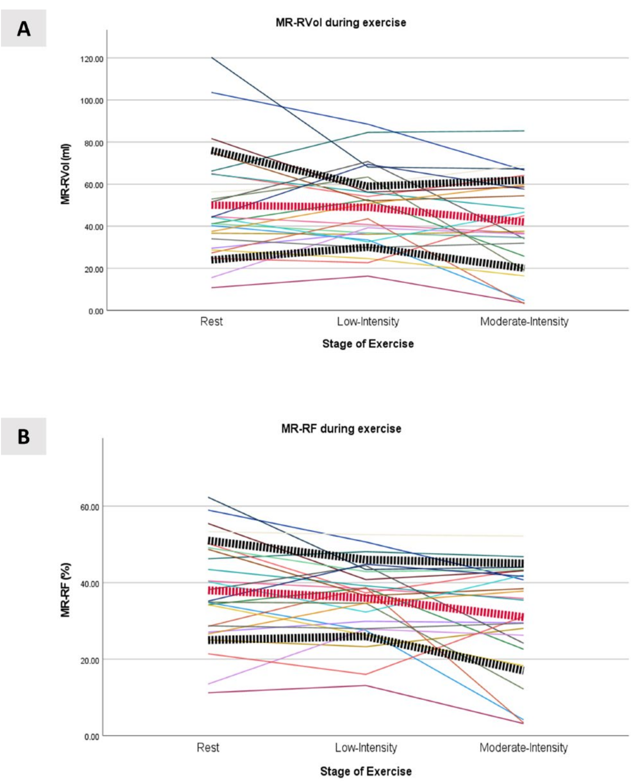

Fig. 3 Individual and group changes in MR-Rvol and MR-RF during exercise-CMR

moderate. The coefficient of variation was very good for all parameters, except end-systolic volumes at low-intensity exercise and RV end-systolic volume at moderate-intensity exercise.

Discussion

To our knowledge, this is the first study that allowed assessment of biventricular volume and function as well as quantification of MR during continuous supine EX-CMR in asymptomatic patients with primary MR. We have demonstrated not only that continuous supine EX-CMR with the use of C-SENSE is feasible in asymptomatic patients with primary MR, but also that there was good-to-excellent intra- and interobserver reproducibility for quantification of the LV volumes and aortic forward flow at low- and moderate-intensity exercise. We have also described the changes that occur in LV/RV volume and function, aortic forward flow, effective forward LVEF and MR-Rvol and MR-RF during supine in-scanner exercise. We have shown that while there was a significant augmentation of the LVEF and RVEF as well as the effective forward LVEF during exercise, there were no statistically significant changes in the MR-Rvol and MR-RF, although the individual responses were quite variable.

Table 3 Intra- and inter-observer reproducibility

		Intra-observer				Inter-observer			
Stage	Parameter	ICC	95% CI [lower, upper]	Mean bias [ml]	CoV (%)	ICC	95% CI [lower, upper]	Mean bias [ml]	CoV (%)
Rest	LVEDV	0.997	[0.989,0.999]	1.5	1.1	0.992	[0.971,0.998]	-2.8	2.0
	LVESV	0.993	[0.975,0.998]	0.9	2.4	0.977	[0.912,0.994]	-2.9	5.0
	RVEDV	0.997	[0.987,0.999]	-0.4	1.3	0.866	[0.480,0.966]	-4.2	5.5
	RVESV	0.986	[0.941,0.997]	-1.3	2.6	0.681	[-0.086,0.917]	-6.7	8.4
	AFF	0.995	[0.980,0.999]	0.0	1.9	0.989	[0.955,0.997]	0.2	1.8
Low-Intensity	LVEDV	0.993	[0.971,0.998]	-2.9	2.3	0.945	[0.791,0.986]	-4.5	3.5
	LVESV	0.994	[0.927,0.999]	-2.0	3.0	0.815	[0.228,0.954]	-1.9	11.1
	RVEDV	0.985	[0.943,0.996]	-1.5	4.1	0.837	[0.312,0.960]	8.9	4.6
	RVESV	0.992	[0.959,0.998]	-1.2	2.4	−0.319	[-3.461,0.656]	9.4	17.9
	AFF	0.995	[0.960,0.999]	-2.0	2.0	0.971	[0.878,0.993]	-2.5	3.3
Moderate-Intensity	LVEDV	0.989	[0.950,0.997]	3.9	2.7	0.984	[0.937,0.996]	-1.8	3.0
	LVESV	0.992	[0.967,0.998]	1.3	3.6	0.916	[0.680,0.979]	-3.3	9.0
	RVEDV	0.993	[0.914,0.999]	2.9	2.0	0.833	[0.366,0.958]	-5.2	6.3
	RVESV	0.885	[0.559,0.971]	0.9	5.1	0.575	[-0.329,0.886]	-9.8	15.9
	AFF	0.996	[0.981,0.999]	-1.3	2.0	0.954	[0.804,0.989]	3.1	4.08

AFF = aortic forward flow; CI = confidence interval; CoV = coefficient of variation; ICC = Intraclass Correlation Coefficient; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; RVEDV = right ventricular end-diastolic volume; RVESV = right ventricular end-systolic volume

Feasibility of EX-CMR in asymptomatic patients with primary MR

Although EX-CMR is not commonly utilised, as it is constrained by technical challenges and the availability of expensive exercise equipment [18], it offers several advantages over EX-TTE [9], such as superior image quality and reproducibility [9]. Utilising the above compressed-sensing pulse sequence to examine both, biventricular volumes and AFF during continuous in-scanner exercise, we have demonstrated its feasibility in asymptomatic patients with primary MR. All patients in our study, who were able to proceed with the EX-CMR scan, completed the examination in its entirety without complications.

Reproducibility

Similar to the aforementioned study in healthy volunteers [10], we have demonstrated excellent reproducibility for the assessment of LVEDV and AFF by intraclass correlation coefficient and coefficient of variation, at both, Low- and Mod-EX. This holds promise for the clinical utility of the effective forward LVEF, which relies solely on the LVEDV and AFF volume. A study by Chew et al. also demonstrated very good reproducibility of biventricular end-diastolic volumes, with poorer performance of end-systolic parameters [9]. Out of all the measurements, the lowest inter-observer reproducibility was noted in right-ventricular parameters, particularly right ventricular end-systolic volume as evidenced by larger biases and poorer coefficient of variation. The intraclass correlation coefficient for RV end-systolic volume at Low-EX resulted in a negative value, suggestive of divergence within the group. It, however, needs to be interpreted with caution.

Left ventricular volume and function during exercise

A meta-analysis of supine EX-CMR studies in healthy volunteers, demonstrated that the physiological response to exercise consisted of an increase in heart rate and LV stroke volume, which occurred as a result of reduction in the LVESV volume with no change in the LVEDV [19]. A small supine EX-CMR study, which evaluated 5 patients with severe MR found, similar to our study, a significant increase in the heart rate, no change in the LVEDV, non-significant reduction in the LVESV and a significant increase in the LVEF [9]. As this is the only prior study, which utilised EX-CMR in patients with primary MR, the majority of current evidence stems from studies in exercise echocardiography. In these echocardiographic studies however, where reduction in LVESV is seen, exercise was performed in an upright or semi-supine position rather than fully supine [20–23]. This is important, as the haemodynamic response to exercise differs, depending on the patient's position [24].

Furthermore, exercise imaging enables assessment of LV contractile reserve [25], which is defined as the ability to augment LVEF during exercise by more than 4%; lack of contractile reserve has been shown to be associated with LVEF impairment following mitral valve intervention as well as worsening of LVEF in those undergoing medical management [26]. As CMR is the reference-standard for assessment of LV volume and function at rest [7], EX-CMR has the potential for accurate measurement of LV contractile reserve in this group of patients, which may add value in the risk-stratification of patients with asymptomatic MR. In our study, more than half of the patients demonstrated contractile reserve at both, low- and moderate-intensity exercise. In some patients, however, while the contractile reserve was present at Low-EX, it was absent at Mod-EX, and vice versa. Future EX-CMR studies should aim to correlate not only the absence of the contractile reserve with clinical outcomes, but also evaluate the clinical significance of such a variable response in patients with primary MR.

Right ventricular volume and function during exercise

In asymptomatic patients with primary MR, the development of RV dysfunction during exercise showed prognostic associations in an EX-TTE study [27]. While RV assessment by TEE may be challenging, CMR can provide direct, accurate and reproducible measurements of RV volumes and function at rest [8]. This high level of accuracy and reproducibility at rest holds promise for the clinical utility of RV volume and function assessment during exercise. The only previous EX-CMR study in patients with asymptomatic, severe MR also demonstrated significant reduction in the RV end-systolic volume, but with no change in the RV end-diastolic volume and a non-significant increase in the RVEF [9]. While there was no significant change in the RV end-diastolic volume in our study, there was a significant decrease in the RV end-systolic volume, leading to a significant improvement in the RVEF. In our study, however, one half of the patients had moderate MR only, which may explain the more pronounced increase in the RVEF.

Mitral regurgitant volume and fraction during exercise

As the only prior EX-CMR study in primary MR did not assess AFF, it could not accurately quantify changes in MR-Rvol and MR-RF during exercise [9]. In our study, while overall there was no significant change in these parameters, the individual response to exercise was quite variable. This is in line with a prior study, which demonstrated variable responses, with MR-Rvol increasing in about a third of patients. Furthermore, increase in MR-Rvol by more than 15 ml during exercise was associated with reduced symptom-free survival [21]. This increase in severity during exercise is possibly related to the absence of the LV contractile reserve [28], which may also be responsible for the diminished functional capacity in these patients [29].

Effective forward left ventricular ejection fraction

Current guidelines recommend mitral valve intervention in asymptomatic patients with severe MR in the presence of reduced LVEF or increased LV end-systolic diameter, amongst others [1]. However, once LV dysfunction ensues, it may be irreversible. It is therefore crucial to detect subclinical LV impairment, which may be present despite normal LVEF [30, 31]. Effective forward LVEF has been proposed as a superior measure to predict outcomes and guide surgical intervention in this group of patients [30]. Significant impairment of effective forward LVEF prior to mitral valve surgery has been shown to be associated with post-operative LV dysfunction [11]. It may therefore provide means of accurate assessment of the actual LV function in patients with MR. While the above studies demonstrated the prognostic advantage of the effective forward LVEF assessment at rest, the response to exercise and its clinical significance have not been previously described. In the current study, there was a significant increase in the effective forward LVEF at moderate-intensity exercise, despite non-significant changes in the aortic forward flow and LVEDV, which may add clinical utility to this patient group.

Future perspectives

While EX-TTE provides additional diagnostic and prognostic information, it is bound by standard TTE limitations, such as poor acoustic windows, which become even more pronounced during exercise. Indeed, one EX-TTE study showed that it was not feasible to assess MR severity in almost half of the patients, and it was particularly challenging in those with MV prolapse [4]. As CMR is the reference-standard for biventricular volume/function assessment [7, 8] and has been shown to have prognostic associations in primary MR [6], EX-CMR hold promise as the exercise imaging modality of choice in this group of patients.

Limitations

This was a small, single-centre, feasibility study. All recruited patients were clinically well, able to exercise and did not have any significant co-existing conditions. EX-CMR may therefore be less well tolerated or even not possible in symptomatic patients or those with other comorbidities, such as respiratory disease or arthritis. We did, however, aim to evaluate the feasibility of EX-CMR in asymptomatic patients with primary MR, in whom it could theoretically assist in guiding surgical therapy decisions. All patients were in normal sinus rhythm, as the presence of atrial fibrillation was an exclusion criterion due to it being an indication for surgery. Presence of an arrhythmia could potentially lead to a significant reduction in image quality, in addition to motion artefact. While increased abdominal girth may be a problem for a standard, resting CMR, EX-CMR is further limited by patient's height, as very tall patients may not be able to cycle within the bore. Although the exclusion criteria were quite strict, this was still a very heterogenous group of patients. Therefore, the response to EX-CMR in these patients might have been very different. Furthermore, cycling whilst lying in a flat, supine position is an unorthodox form of exercise. As the study was performed in a supine position, this limits the interpretation of our results to exercise in the upright position. Also, it is important to note, that while the image quality during exercise is lower than at rest, the use of the above pulse sequence and appropriate patient preparation led to sufficient image quality. Lastly, as this was a feasibility study, clinical outcomes were not assessed, and prognostic information cannot be derived from this study.

Conclusions

In this pilot study, we demonstrated the feasibility of performing CMR imaging during continuous, supine, in-scanner exercise in asymptomatic patients with moderate and severe MR. We have also shown that the assessment of biventricular volumes and quantification of MR during exercise in this group of patients is not only feasible, but also reproducible, even at moderate-intensity exercise. We have also described the changes that occur in the biventricular volumes during exercise and demonstrated that primary MR is a dynamic entity. Future studies are needed to correlate these changes with clinical outcomes.

Acknowledgements We thank the patients and research staff in the Cardiac MRI Department, Leeds General Infirmary, Leeds, UK for their assistance with the cardiac MRI scans.

Author contributions MG was responsible for patient screening and recruitment, CMR acquisition and analysis, statistical analysis, literature review and write up of the draft manuscript. TPC was responsible for patient recruitment, patient consent, CMR acquisition and CMR analysis. NJ was responsible for performing the inter-observer analysis. DMH was responsible for oversight of scan protocol and provided exercise-CMR expertise from physics' perspective. AC, PGC, LED, LAEB, ST, NS, WJ, SK, MG, HP and MP helped with patient recruitment and scan supervision. PPS, SP, EL were responsible for reviewing and correcting the manuscript. JPG was the principal investigator responsible for the design of the study, oversight of the study and final approval of the submission.

Funding This work was funded by local funding, provided by the University of Leeds.

Data availability No datasets were generated or analysed during the current study.

Declarations

Ethical approval The study was approved by the National Research Ethics Service (18/YH/0168), had institutional approval and complied with the Declaration of Helsinki.

Informed consent was obtained from all individual participants included in the study.

Competing interests The authors declare no competing interests.

References

1. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ et al (2017) 2017 ESC/EACTS guidelines for the management of valvular heart disease. Eur Heart J 38(36):2739–2791
2. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP 3rd, Gentile F et al (2021) 2020 ACC/AHA Guideline for the management of patients with Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice guidelines. Circulation 143(5):e72–e227
3. Peteiro J, Bouzas-Mosquera A (2010) Exercise echocardiography. World J Cardiol 2(8):223–232
4. Coisne A, Levy F, Malaquin D, Richardson M, Quere JP, Montaigne D et al (2015) Feasibility of Doppler hemodynamic evaluation of primary and secondary mitral regurgitation during exercise echocardiography. Int J Cardiovasc Imaging 31(2):291–299
5. Myerson SG, d'Arcy J, Christiansen JP, Dobson LE, Mohiaddin R, Francis JM et al (2016) Determination of clinical outcome in Mitral Regurgitation with Cardiovascular magnetic resonance quantification. Circulation 133(23):2287–2296
6. Penicka M, Vecera J, Mirica DC, Kotrc M, Kockova R, Van Camp G (2018) Prognostic implications of magnetic resonance-derived quantification in asymptomatic patients with Organic Mitral Regurgitation: comparison with Doppler Echocardiography-Derived Integrative Approach. Circulation 137(13):1349–1360
7. Grothues F, Smith GC, Moon JC, Bellenger NG, Collins P, Klein HU et al (2002) Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. Am J Cardiol 90(1):29–34
8. Maceira AM, Prasad SK, Khan M, Pennell DJ (2006) Reference right ventricular systolic and diastolic function normalized to age, gender and body surface area from steady-state free precession cardiovascular magnetic resonance. Eur Heart J 27(23):2879–2888
9. Chew PG, Swoboda PP, Ferguson C, Garg P, Cook AL, Ibeggazene S et al (2020) Feasibility and reproducibility of a cardiovascular magnetic resonance free-breathing, multi-shot, navigated image acquisition technique for ventricular volume quantification during continuous exercise. Quant Imaging Med Surg 10(9):1837–1851
10. Craven TP, Jex N, Chew PG, Higgins DM, Bissell MM, Brown LAE et al (2021) Exercise cardiovascular magnetic resonance: feasibility and development of biventricular function and great vessel flow assessment, during continuous exercise accelerated by compressed SENSE: preliminary results in healthy volunteers. Int J Cardiovasc Imaging 37(2):685–698

11. Gelfand EV, Haffajee JA, Hauser TH, Yeon SB, Goepfert L, Kissinger KV et al (2010) Predictors of preserved left ventricular systolic function after surgery for chronic organic mitral regurgitation: a prospective study. J Heart Valve Dis 19(1):43
12. Fletcher GF, Ades PA, Kligfield P, Arena R, Balady GJ, Bittner VA et al (2013) Exercise standards for testing and training: a scientific statement from the American Heart Association. Circulation 128(8):873–934
13. Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA et al (2017) 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):303–371
14. Tanaka H, Monahan KD, Seals DR (2001) Age-predicted maximal heart rate revisited. J Am Coll Cardiol 37(1):153–156
15. Mj K (1957) The effects of training on heart rate: a longitudinal study. Ann med exp biol fenn 35:307–315
16. Garg P, Swift AJ, Zhong L, Carlhall CJ, Ebbers T, Westenberg J et al (2020) Assessment of mitral valve regurgitation by cardiovascular magnetic resonance imaging. Nat Rev Cardiol 17(5):298–312
17. Petersen SE, Aung N, Sanghvi MM, Zemrak F, Fung K, Paiva JM et al (2017) Reference ranges for cardiac structure and function using cardiovascular magnetic resonance (CMR) in caucasians from the UK Biobank population cohort. J Cardiovasc Magn Reson 19(1):18
18. Craven TP, Tsao CW, La Gerche A, Simonetti OP, Greenwood JP (2020) Exercise cardiovascular magnetic resonance: development, current utility and future applications. J Cardiovasc Magn Reson 22(1):65
19. Beaudry RI, Samuel TJ, Wang J, Tucker WJ, Haykowsky MJ, Nelson MD (2018) Exercise cardiac magnetic resonance imaging: a feasibility study and meta-analysis. Am J Physiol Regul Integr Comp Physiol 315(4):R638–R45
20. Suzuki K, Izumo M, Yoneyama K, Mizukoshi K, Kamijima R, Kou S et al (2015) Influence of exercise-induced pulmonary hypertension on exercise capacity in asymptomatic degenerative mitral regurgitation. J Cardiol 66(3):246–252
21. Magne J, Lancellotti P, Piérard LA (2010) Exercise-Induced changes in degenerative mitral regurgitation. J Am Coll Cardiol 56(4):300–309
22. Lee R, Haluska B, Leung DY, Case C, Mundy J, Marwick TH (2005) Functional and prognostic implications of left ventricular contractile reserve in patients with asymptomatic severe mitral regurgitation. Heart 91(11):1407–1412
23. Leung DY, Griffin BP, Stewart WJ, Cosgrove DM 3rd, Thomas JD, Marwick TH (1996) Left ventricular function after valve repair for chronic mitral regurgitation: predictive value of preoperative assessment of contractile reserve by exercise echocardiography. J Am Coll Cardiol 28(5):1198–1205
24. Kramer B, Massie B, Topic N (1982) Hemodynamic differences between supine and upright exercise in patients with congestive heart failure. Circulation 66(4):820–825
25. Lancellotti P, Dulgheru R, Go YY, Sugimoto T, Marchetta S, Oury C et al (2018) Stress echocardiography in patients with native valvular heart disease. Heart 104(10):807–813
26. Henri C, Pierard LA, Lancellotti P, Mongeon FP, Pibarot P, Basmadjian AJ (2014) Exercise testing and stress imaging in valvular heart disease. Can J Cardiol 30(9):1012–1026
27. Kusunose K, Popovic ZB, Motoki H, Marwick TH (2013) Prognostic significance of exercise-induced right ventricular dysfunction in asymptomatic degenerative mitral regurgitation. Circ Cardiovasc Imaging 6(2):167–176
28. Magne J, Mahjoub H, Dulgheru R, Pibarot P, Pierard LA, Lancellotti P (2014) Left ventricular contractile reserve in asymptomatic primary mitral regurgitation. Eur Heart J 35(24):1608–1616
29. Leung DY, Griffin BP, Snader CE, Luthern L, Thomas JD, Marwick TH (1997) Determinants of functional capacity in chronic mitral regurgitation unassociated with coronary artery disease or left ventricular dysfunction. Am J Cardiol 79(7):914–920
30. Dupuis M, Mahjoub H, Clavel MA, Cote N, Toubal O, Tastet L et al (2017) Forward Left Ventricular Ejection Fraction: a simple risk marker in patients with primary mitral regurgitation. J Am Heart Assoc. ;6(11)
31. Witkowski TG, Thomas JD, Delgado V, van Rijnsoever E, Ng AC, Hoke U et al (2012) Changes in left ventricular function after mitral valve repair for severe organic mitral regurgitation. Ann Thorac Surg 93(3):754–760