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ORIGINAL ARTICLE

Rest and exercise oxygen uptake and cardiac output changes 6 months after successful transcatheter mitral valve repair

Carlo Vignati[1,2], Fabiana De Martino[1], Manuela Muratori[1], Elisabetta Salvioni[1], Gloria Tamborini[1], Antonio Bartorelli[1,3], Mauro Pepi[1], Francesco Alamanni[1,2], Stefania Farina[1], Gaia Cattadori[4], Valentina Mantegazza[1] and Piergiuseppe Agostoni[1,2]*

[1]*Centro Cardiologico Monzino, IRCCS, Milan, Italy;* [2]*Department of Clinical Sciences and Community Health, Cardiovascular Section, University of Milan, Milan, Italy;* [3]*Department of Biomedical and Clinical Sciences "Luigi Sacco", University of Milan, Milan, Italy; and* [4]*IRCCS Multimedica, Milan, Italy*

Abstract

Aims Changes in peak exercise oxygen uptake (VO_2) and cardiac output (CO) 6 months after successful percutaneous edge-to-edge mitral valve repair (pMVR) in severe primary (PMR) and functional mitral regurgitation (FMR) patients are unknown.

The aim of the study was to assess the efficacy of pMVR at rest by echocardiography, VO_2 and CO (inert gas rebreathing) measurement and during cardiopulmonary exercise test with CO measurement.

Methods and results We evaluated 145 and 115 patients at rest and 98 and 66 during exercise before and after pMVR, respectively.

After successful pMVR, significant reductions in MR and NYHA class were observed in FMR and PMR patients. Cardiac ultrasound showed reverse remodelling (left ventricular end-diastolic volume from 158 ± 63 mL to 147 ± 64, $P < 0.001$; ejection fraction from 51 ± 15 to 48 ± 14, $P < 0.001$; pulmonary artery systolic pressure (PASP) from 43 ± 13 to 38 ± 8 mmHg, $P < 0.001$) in the entire population. These changes were significant in PMR (n = 62) and a trend in FMR (n = 53), except for PASP, which decreased in both groups. At rest, CO and stroke volume (SV) increased in FMR with a concomitant reduction in arteriovenous O_2 content difference [$\Delta C(a\text{-}v)O_2$]. Peak exercise, CO and SV increased significantly in both groups (CO from 5.5 ± 1.4 L/min to 6.3 ± 1.5 and from 6.2 ± 2.4 to 6.7 ± 2.0, SV from 57 ± 19 mL to 66 ± 20 and from 62 ± 20 to 69 ± 20, in FMR and PMR, respectively), whereas peak VO_2 was unchanged and $\Delta C(a\text{-}v)O_2$ decreased.

Conclusions These data confirm pMVR-induced clinical improvement and reverse ventricular remodelling at a 6-month analysis and show, in spite of an increase in CO, an unchanged exercise performance, which is achieved through a 'more physiological' blood flow distribution and O_2 extraction behaviour. Direct rest and exercise CO should be measured to assess pMVR efficacy.

Keywords Oxygen uptake; Cardiac output; Transcatheter mitral valve repair; Percutaneous edge-to-edge mitral valve repair; Exercise

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**Correspondence to: Piergiuseppe Agostoni, Department of Clinical Sciences and Community Health, Cardiovascular Section, University of Milan. Via Parea, 4. 20138 Milan, Italy. Phone: 0039 02 58002772; Fax: 0039 02 58002008. Email piergiuseppe.agostoni@unimi.it; piergiuseppe.agostoni@ccfm.it*

Introduction

Percutaneous edge-to-edge mitral valve repair (pMVR) therapy is now established as a safe, feasible treatment option for patients with severe mitral regurgitation (MR) at high surgical risk. At present, although they are characterized by different underlying pathophysiological mechanisms, both primary mitral regurgitation (PMR) and functional mitral regurgitation (FMR) have been treated with pMVR[1] without relevant outcome differences between the two MR

aetiologies.[2,3] MR in PMR is due to mitral leaflet prolapse either with or without elongation of chordae tendineae/papillary muscles. On the other hand, in FMR, the mitral valve has a normal structure, but, in parallel with left ventricular (LV) dysfunction and remodelling, a displacement of the papillary muscle is present, causing leaflet tethering and reduction of closing forces. Moreover, as a consequence of LV enlargement, the mitral annulus dilates and loses its shape, inducing a failure of mitral leaflet coaptation.[4,5]

On top of the MITRA-FR and the COAPT trials, which mainly focused on pMVR-induced changes in prognosis,[6,7] several other studies were published on the efficacy of pMVR. Overall, these studies suggest that pMVR treatment is associated with an improvement in symptoms, quality of life, functional status and, in some but not all studies, exercise capacity.[8–12] Indeed, although MR directly impairs exercise performance,[13] both the COAPT and the MITRA-FR trials reported a null effect of pMVR on the 6-min walk test (6MWT).[6,7,14] Differently, several other studies suggested an improved exercise performance,[11,15] assessed in the great majority of reports by 6MWT. Moreover, a severely impaired exercise performance seems to be associated with poor pMVR outcome at least in FMR patients.[16] From a physiological point of view, successful MR repair is associated with LV reverse remodelling, reduction in pulmonary pressure and possibly improvement of forward stroke volume.[17,18] The latter has been shown at rest by haemodynamic monitoring shortly after pMVR.[19] At present, data on pMVR-induced forward stroke volume changes in the long term, both at rest and during exercise, are lacking. Indeed, the precise evaluation of forward stroke volume with relevant differences in MR by cardiac ultrasound is technically difficult during exercise.[20] Regardless, an increase of forward CO, both at rest and during exercise, is likely one of the major links between structural cardiac and functional improvements after pMVR and likely among the main reasons for the reported improvement of patients' exercise performance and well-being.

Accordingly, with the present study, we sought to evaluate the medium term effects of successful pMVR in PMR and FMR cases in terms of long-term forward stroke volume changes both at rest and at peak exercise. Successful pMVR therapy was defined as post-procedural reduction of MR $\geq$2 as well as absence of acute pMVR complications or patients' death.

Methods

We evaluated, before and 6 months after pMVR, patients admitted to Centro Cardiologico Monzino IRCCS (Milan, Italy), suffering from either FMR or PMR, with indication to pMVR therapy according to guidelines. Traditional surgery was excluded by the Heart Team due to high operative risk. In all cases, transcatheter edge-to-edge mitral valve repair was performed with the mitral clip system (Abbott Vascular, Santa Clara, CA, USA).[21]

To be enrolled in the study, patients had to be in stable clinical conditions. Drug treatment had to be optimal, uptitrated to target doses and stable. Study exclusion criteria were unstable clinical condition or drug treatment, urgent pMVR, impossibility to instruct patients for cardiac output (CO) measurements by inert gas rebreathing (IGR) method and the presence of any comorbidity directly affecting patients' prognosis and/or exercise performance, or of any scheduled or recent ($<$6 months) cardiac or extra-cardiac surgery. The study was approved by the Ethics Committee of Centro Cardiologico Monzino and registered as R272/15-CCM 288.

At baseline, patients underwent full clinical, laboratory and cardiac ultrasound evaluation. Specifically, patients underwent two-dimensional (2D) transthoracic echocardiography (TTE) using an iE33 ultrasound system (Philips Medical Systems, Andover, MA), with S5-1 probe. The comprehensive 2D TTE evaluation allowed quantifying LV volumes and function, left atrial dimensions, systolic pulmonary artery pressure, right ventricular function and right atrial pressure (RAP) and grading the severity of mitral and tricuspid regurgitation according to the European guidelines.[20] Specifically, RAP was estimated by means of the inferior vena cava collapsibility index. Patients also underwent non-invasive CO measurement at rest by IGR (Innocor rebreathing system, Innovision A/S, Odense, Denmark).[22] Patients able to perform a maximal cardiopulmonary exercise test (CPET), which was considered as a familiarization procedure, repeated a maximal CPET including CO measurement at rest and at peak of exercise by IGR. CPET and CO data were analysed by CPET experts using a standard methodology.[23] Peak oxygen uptake (VO_2) data were collected immediately before CO measurements. The IGR technique has been previously described in detail.[24] In brief, IGR uses an oxygen-enriched mixture of an inert soluble gas (0.5% nitrous oxide, N_2O) and an inert insoluble gas (0.1% sulfur hexafluoride, SF_6). SF_6 is insoluble in blood, and it is used to determine lung volume. N_2O is soluble in blood, and its concentration decreases during rebreathing with a rate proportional to pulmonary blood flow, that is, the blood flow that perfuses the alveoli participating in gas exchange, that is, ventilated and perfused. Cardiac output is equal to pulmonary blood flow in the absence of pulmonary shunt. Shunt flow can be estimated from arterial O_2 saturation. Patients underwent several IGR teaching sessions to obtain reliable CO measurements.

Over the 6 months after pMVR, patients were regularly followed up, and appropriate blood analyses or tests were carried out as clinically needed. To be able to assess the effects of pMVR, we did our best to avoid confounding factors.

Accordingly, patients were advised not to be involved in any structured rehabilitation programme and not to undergo treatment changes unless clinically needed. All tests were repeated at a 6-month evaluation.

Continuous variables are expressed as mean ± standard deviation unless differently specified, whereas categorical variables are expressed as numbers and percentages. CPET variables are reported as a 20-s average or as relationship slopes as appropriate. Only subjects who have pre- and post-pMVR evaluations were considered for the present analysis (*Figure 1*). Differences between baseline and 6-month evaluation were analysed by paired *t*-test. Statistical significance was accepted at $P < 0.05$. All tests were performed using Microsoft Excel or IBM SPSS Statistics 22.0.

Results

One hundred and forty-five consecutive patients who underwent pMVR procedure at our institute and met the study inclusion/exclusion criteria were included in the study. All were evaluated at rest, and 98 were also evaluated during exercise. The 6-month follow-up was completed in 115 cases with analyses limited to rest and in 66 cases with exercise evaluation (*Figure 1*). Forty-seven out of 145 patients did not perform CPET before the pMVR procedure. Twenty-three patients were considered too severely ill to perform a maximal CPET, 15 refused to exercise, and in 9 cases, a reliable CO measurement by IGR at peak exercise was not obtained. The 6-month follow-up rest evaluation was not carried out in 30 out of 145 patients due to residual severe MR in 3 cases, death of patients in 6 cases, end-stage heart failure (HF) in 1 case, mediastinal infection in 1 case, mitral valve thrombosis in 1 case and lung cancer in 1 case. Accordingly, not successful pMVR was observed in 8 cases. Study informed consent was withdrawn in the remaining 17 cases. Exercise evaluation at 6-month follow-up was not made in 32 of the 98 cases who performed CPET before pMVR for the following reasons: death, 2 cases; clip failure, 2 cases; lung cancer, 1 case; withdrawn study consent, 17 cases; failure of peak exercise measurements, two cases; too severely ill to perform a maximal CPET, 3 cases; and refused to exercise, 5 cases.

We report the data of the patients with successful pMVR who completed the 6-month follow-up, 115 for resting data analysis and 66 for exercise evaluation (*Table 1*). Sixty-two patients had PMR, and 53 had FMR. Ischaemic HF was diagnosed in 54 cases (PMR = 21 and FMR = 33). In ischaemic HF patients, flow-limiting coronary artery disease was assessed before pMVR by visual analysis of coronary imaging and, if needed, by functional flow reserve analysis or IVUS. In case of a haemodynamically relevant coronary stenosis, vessel stenting was performed before pMVR. Patients with FMR had severe HF (*Table 1*). Patients with PMR were older (*Table 1*). On average, both groups of patients had a definite exercise limitation, albeit more severe in FMR cases (*Table 1*).

Data at rest before and 6 months after pMVR for the entire population and for the two groups of MR patients are reported in *Tables 2 and 3*, respectively. Patients with FMR showed a larger left ventricle and lower ejection fraction than PMR patients. After pMVR, clinical conditions

Figure 1 Protocol enrolment flowchart.

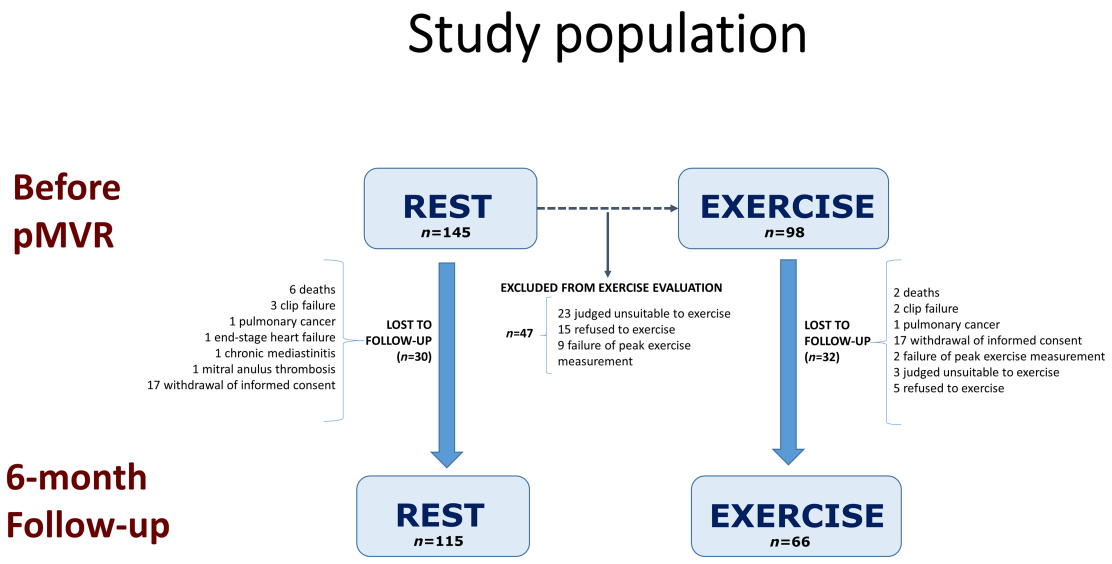

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Table 1 Population characteristics

	Total population		Functional mitral regurgitation		Primary mitral regurgitation		
	n	Mean ± SD	*n*	Mean ± SD	*n*	Mean ± SD	*P*
Age (years)	115	77 ± 8	53	71 ± 8	62	82 ± 5	<0.001
Sex (male/female)	115	75/40	53	39/14	62	36/26	0.082
BMI kg/m^2	106	25 ± 4	52	26 ± 4	54	25 ± 5	0.125
VO_2% of predicted	66	56 ± 16	30	51 ± 14	36	60 ± 17	0.02
VE/VCO_2 slope	66	34.2 ± 6.6	30	36.1 ± 7.3	36	32.7 ± 5.7	0.032
Hb (g/dL)	115	13 ± 1	53	13.1 ± 1.3	62	13.7 ± 1.3	0.042
BNP (pg/mL)	110	480 ± 669	52	655 ± 873	58	322 ± 345	0.012
NTproBNP (pg/mL)	2	6031 ± 4624	2	6031 ± 4624	0		
MR	115	4 [3–4][a]	53	4 [3–4][a]	62	4 [4–4][a]	<0.001
EF (%)	115	51 ± 15	53	38 ± 10	62	62 ± 9	<0.001
NYHA	115	2.65 ± 0.61	53	2.79 ± 0.66	62	2.53 ± 0.53	0.030
ACEI	115	50%	53	58%	62	44%	0.132
ARB	115	24%	53	21%	62	26%	0.561
ARNI	115	2%	53	4%	62	0%	0.210
Beta blocker	115	63%	53	79%	62	50%	0.001
MRA	115	40%	53	55%	62	28%	0.004
Loop diuretic	115	77%	53	96%	62	61%	<0.001
Ivabradine	115	4%	53	10%	62	0%	0.018
Digoxin	115	10%	53	12%	62	8%	0.532
CCB	115	10%	53	0%	62	18%	0.001
Antiplatelet drug	115	46%	53	62%	62	32%	0.002
Oral anticoagulant	115	37%	53	40%	62	34%	0.473
Amiodarone	115	26%	53	44%	62	11%	<0.001
Statin	115	43%	53	60%	62	29%	0.001
Antidiabetic treat.	115	8%	53	13%	62	3%	0.077
Bronchodilator	115	15%	53	13%	62	16%	0.690

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BMI, body mass index; BNP, B-type natriuretic peptide; CCB, calcium channel blocker; EF, ejection fraction; Hb, haemoglobin; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; NTproBNP, N-terminal B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation; VO_2, oxygen uptake.
[a]Median [interquartile range].

Table 2 Total population rest measurements

	Total population				
	PRE-MC		POST-MC		
	n	Mean ± SD	*n*	Mean ± SD	*P*
NYHA	115	2.7 ± 0.6	115	2.1 ± 0.6	0.001
MR	115	4 [3–4][a]	115	1 [1–2][a]	<0.001
EDV (mL)	115	157 ± 63	115	146 ± 64	<0.001
EDVi (mL/m^2)	115	86 ± 31	115	80 ± 33	<0.001
ESV (mL)	115	83 ± 55	115	82 ± 56	0.410
ESVi (mL/m^2)	115	45 ± 29	115	45 ± 30	0.601
EF (%)	115	51 ± 15	115	49 ± 14	<0.001
SV (mL)	115	74 ± 21	115	63 ± 17	<0.001
TAPSE (mm)	108	22 ± 5	108	23 ± 5	0.449
PASP (mmHg)	111	43 ± 13	111	38 ± 8	<0.001
TR	115	2 [1–3][a]	115	1 [1–2][a]	<0.001
RAP (mmHg)	113	7.2 ± 2.7	113	6.5 ± 2.0	0.009
Hb (g/dL)	114	13.4 ± 1.4	114	13.4 ± 1.4	0.654
BNP (pg/mL)	110	480 ± 669	110	523 ± 766	0.655
VO_2 (mL/min)	115	281 ± 62	115	286 ± 55	0.389
CO (L/min)	115	3.1 ± 0.9	115	3.3 ± 0.8	0.008
SV_{IGR} (mL)	115	44 ± 13	115	48 ± 14	<0.001
HR (bpm)	115	72 ± 13	115	70 ± 12	0.081
$\Delta C(a\text{-}v)O_2$ (mL/100 mL)	115	9.7 ± 2.8	115	9.2 ± 2.5	0.103

BNP, B-type natriuretic peptide; CO, cardiac output; EDV, end-diastolic volume; EDVi, end-diastolic volume indexed; EF, ejection fraction; Hb, haemoglobin; HR, heart rate; MR, mitral regurgitation; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; RAP, right atrial pressure; SD, standard deviation; SV, stroke volume; SV_{IGR}, stroke volume measured by inert gas rebreathing technique; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; VO_2, oxygen uptake at rest; $\Delta C(a\text{-}v)O_2$, arteriovenous O_2 difference.
[a]Median [interquartile range].

Table 3 Comparison of rest measurements according to the aetiology of mitral regurgitation

	Functional mitral regurgitation					Primary mitral regurgitation				
	PRE-pMVR		POST-pMVR			PRE-pMVR		POST-pMVR		
	n	Mean ± SD	*n*	Mean ± SD	*P*	*n*	Mean ± SD	*n*	Mean ± SD	*P*
NYHA	53	2.7 ± 0.7	53	2.1 ± 0.6	0.001	62	2.7 ± 0.7	62	2.1 ± 0.5	0.001
MR	53	4 [3–4][a]	53	1 [1–2][a]	<0.001	62	4 [4–4][a]	62	1 [1–2][a]	<0.001
EDV (mL)	53	194 ± 66	53	189 ± 64	0.105	62	126 ± 39	62	111 ± 39	<0.001
EDVi (mL/m^2)	53	105 ± 33	53	102 ± 34	0.199	62	71 ± 18	62	62 ± 19	<0.001
ESV (mL)	53	123 ± 53	53	121 ± 55	0.433	62	49 ± 25	62	48 ± 27	0.782
ESVi (mL/m^2)	53	67 ± 27	53	66 ± 30	0.570	62	27 ± 12	62	27 ± 13	0.971
EF (%)	53	38 ± 10	53	38 ± 10	0.419	62	62 ± 9	62	58 ± 9	<0.001
SV (mL)	53	70 ± 19	53	66 ± 16	0.034	62	77 ± 21	62	63 ± 18	<0.001
TAPSE (mm)	50	20 ± 4	50	21 ± 5	0.151	58	24 ± 6	58	24 ± 5	0.873
PASP (mmHg)	51	44 ± 13	51	40 ± 8	0.040	60	43 ± 13	60	37 ± 7	<0.001
TR	51	2 [1–3][a]	51	1 [1–2][a]	0.001	63	2 [1–3][a]	63	1 [1–2][a]	0.003
RAP (mmHg)	50	7.8 ± 3.1	50	6.7 ± 2.1	0.005	63	6.7 ± 2.2	63	6.3 ± 1.8	0.315
Hb (g/dL)	53	13.1 ± 1.3	53	13.0 ± 1.3	0.560	61	13.6 ± 1.4	61	13.6 ± 1.4	0.982
BNP (pg/mL)	49	660 ± 898	49	816 ± 1050	0.155	56	330 ± 349	56	296 ± 245	0.665
VO_2 (mL/min)	53	294 ± 64	53	298 ± 56	0.705	62	269 ± 59	62	276 ± 54	0.412
CO (L/min)	53	3.0 ± 0.8	53	3.4 ± 0.8	0.002	62	3.1 ± 0.9	62	3.2 ± 0.9	0.559
SV_{IGR} (mL)	53	44 ± 13	53	51 ± 14	0.001	62	43 ± 14	62	45 ± 13	0.127
HR (bpm)	53	69 ± 14	53	68 ± 13	0.453	62	74 ± 12	62	71 ± 11	0.094
$\Delta C(a\text{-}v)O_2$ (mL/100 mL)	53	10.2 ± 2.9	53	9.2 ± 2.3	0.038	62	9.3 ± 2.7	62	9.2 ± 2.7	0.907

BNP, B-type natriuretic peptide; CO, cardiac output; EDV, end-diastolic volume; EDVi, end-diastolic volume indexed; EF, ejection fraction; Hb, haemoglobin; HR, heart rate; MR, mitral regurgitation; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; RAP, right atrial pressure; SD, standard deviation; SV, stroke volume; SV_{IGR}, stroke volume measured by inert gas rebreathing technique; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; VO_2, oxygen uptake at rest; $\Delta C(a\text{-}v)O_2$, arteriovenous O_2 difference.
[a]Median [interquartile range].

improved as shown by New York Heart Association (NYHA) class improvement from 2.7 ± 0.7 to 2.1 ± 0.6 in the overall population and from 2.7 ± 0.7 to 2.1 ± 0.7 and from 2.7 ± 0.7 to 2.1 ± 0.5 in FMR and PMR, respectively ($P < 0.001$ for all). MR decreased from 4 (3–4) to 1 (1–2), $P < 0.001$ (median and IQR), similarly in the two MR groups. In the overall population, LV reverse remodelling was observed with a reduction of LV volume, pulmonary pressure, ejection fraction and total stroke volume at echocardiography. These changes were statistically significant and relevant in the overall population and in PMR cases, but they were minor in FMR patients. On the contrary, resting CO, as measured by IGR, and forward stroke volume increased, but only in FMR.

Exercise performance (*Tables 4 and 5*), did not improve after pMVR in terms of peak VO_2 and workload, in spite of a relevant increase of CO and forward stroke volume observed in both PMR and FMR cases. Consequently, the arteriovenous O_2 content differences [$\Delta C(a\text{-}v)O_2$] decreased after pMVR. Of note, peak exercise CO and forward stroke volume increased similarly in both MR groups. The graphical representation of the Fick principle [$VO_2 = CO \times \Delta C(a\text{-}v)O_2$] at rest and during exercise before and after pMVR is reported in *Figure 2a and 2b* for PMR and FMR, respectively. The black curvilinear lines are isoVO_2 curves. When CO increased, $\Delta C(a\text{-}v)O_2$ decreased at rest in FMR cases and at peak exercise in both FMR and PMR cases.

Table 4 Total population exercise measurements

	Total population				
	PRE-pMVR		POST-pMVR		
	n	Mean ± SD	*n*	Mean ± SD	*P*
Workload (watt)	66	57 ± 19	66	59 ± 21	0.081
Peak VO_2 (mL/min)	66	936 ± 260	66	962 ± 241	0.240
Peak CO (L/min)	66	5.9 ± 2.0	66	6.5 ± 1.8	<0.001
$\Delta C(a\text{-}v)O_2$ (mL/100 mL)	66	16.4 ± 4.0	66	15.2 ± 4.1	0.009
Peak SV_{IGR} (mL)	66	60 ± 20	66	67 ± 20	<0.001
Peak HR (bpm)	66	102 ± 22	66	101 ± 21	0.557
RER	66	1.02 ± 0.10	66	1.05 ± 0.11	0.136
AT VO_2 (mL/min)	59	708 ± 180	59	740 ± 180	0.177
VE/VCO_2 slope	66	34.2 ± 6.6	66	33.9 ± 6.5	0.674

AT VO_2, oxygen uptake at anaerobic threshold; CO, cardiac output; HR, heart rate; RER, respiratory exchange ratio; SD, standard deviation; SV_{IGR}, stroke volume measured by inert gas rebreathing technique; VE/VCO_2 slope, minute ventilation-to-carbon dioxide output slope;VO_2, oxygen uptake; $\Delta C(a\text{-}v)O_2$, arteriovenous O_2 difference.

Discussion

The present paper reports data of patients who underwent successful pMVR, excluding acute technical failures and patients who for any reason were unable or unwilling to perform a clinical evaluation at 6 months (*Figure 1*). In line with several previous studies, it shows that pMVR effectively reduces MR, with a significant residual MR observed in a very limited number of cases. After pMVR, clinical condition improved and LV reverse remodelling, as suggested by a

Table 5 Comparison of exercise parameters according to the aetiology of mitral regurgitation

	Functional mitral regurgitation					Primary mitral regurgitation				
	PRE-pMVR		POST-pMVR			PRE-pMVR		POST-pMVR		
	n	Mean ± SD	*n*	Mean ± SD	*P*	*n*	Mean ± SD	*n*	Mean ± SD	*P*
Workload (watt)	30	57 ± 19	30	59 ± 19	0.356	36	56 ± 20	36	59 ± 22	0.129
Peak VO_2 (mL/min)	30	932 ± 204	30	968 ± 224	0.222	36	938 ± 302	36	957 ± 258	0.581
Peak CO (L/min)	30	5.6 ± 1.4	30	6.3 ± 1.5	0.001	36	6.2 ± 2.4	36	6.7 ± 2.0	0.030
$\Delta C(a\text{-}v)O_2$ (mL/100 mL)	30	17.3 ± 4.1	30	15.7 ± 3.7	0.013	36	15.7 ± 3.8	36	14.9 ± 4.4	0.198
Peak SV_{IGR} (mL)	30	57 ± 19	30	66 ± 20	0.003	36	62 ± 20	36	69 ± 20	0.006
Peak HR (bpm)	30	102 ± 26	30	100 ± 20	0.438	36	102 ± 19	36	101 ± 22	0.858
RER	30	1.01 ± 0.13	30	1.06 ± 0.12	0.044	36	1.03 ± 0.08	36	1.03 ± 0.10	0.908
AT VO_2 (mL/min)	24	705 ± 170	24	724 ± 182	0.577	35	710 ± 189	35	751 ± 181	0.214
VE/VCO_2 slope	30	36.1 ± 7.3	30	35.6 ± 7.2	0.763	36	32.7 ± 5.7	36	32.4 ± 5.5	0.769

AT VO_2, oxygen uptake at anaerobic threshold; CO, cardiac output; HR, heart rate; RER, respiratory exchange ratio; SD, standard deviation; SV_{IGR}, stroke volume measured by inert gas rebreathing technique; VE/VCO_2 slope, minute ventilation-to-carbon dioxide output slope; VO_2, oxygen uptake; $\Delta C(a\text{-}v)O_2$, arteriovenous O_2 difference.

significant volume reduction, was observed in PMR, and only as a trend in FMR. Of note, the reduction of LV volumes was associated with a reduction of ejection fraction and total stroke volume at cardiac ultrasound evaluation. This is due to pre- and post-pMVR regurgitant volume differences. Differently, forward stroke volume, as measured by IGR, increased at rest after pMVR in FMR. A relevant post-pMVR increase of stroke volume was observed at peak exercise in both FMR and PMR patients, but the consequent CO increase did not translate into an improvement of exercise performance as assessed by peak workload or VO_2 achieved.

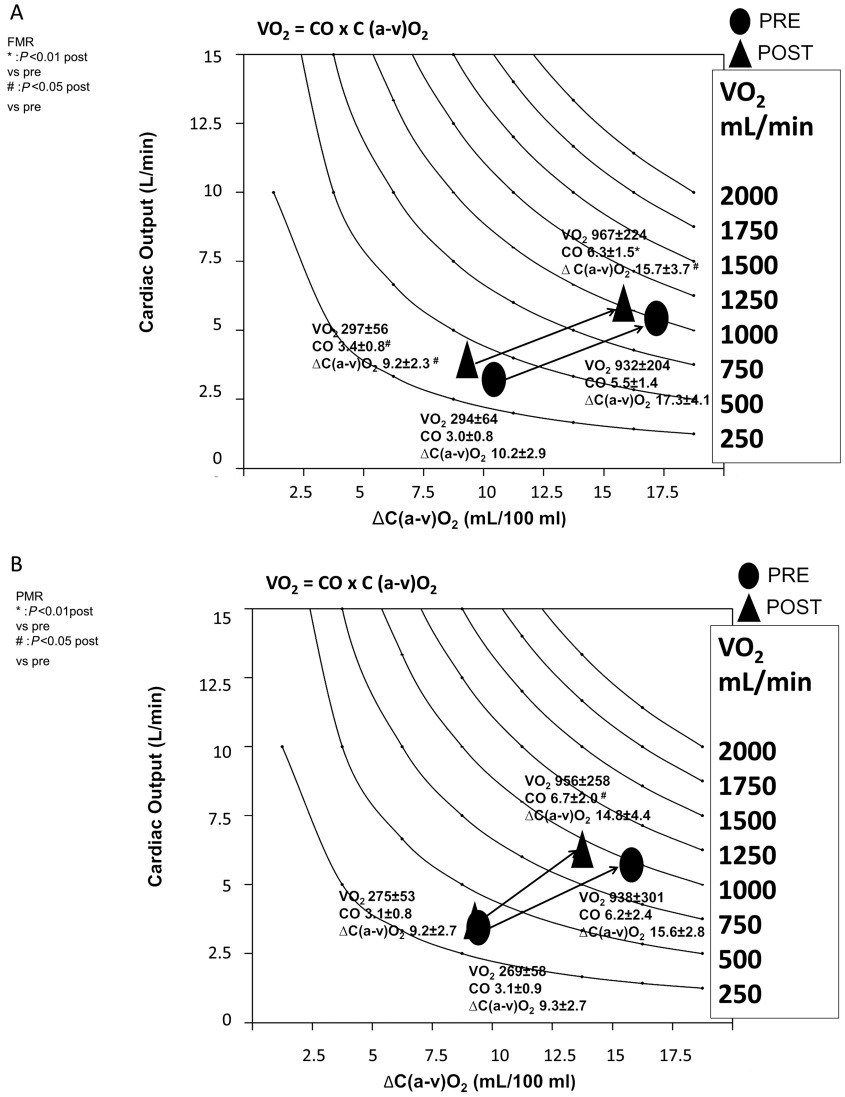
The FMR population we studied was characterized by advanced HF, as shown by natriuretic peptide values, with LV volumes and function similar on average to the ones reported by Stone et al. in the COAPT study.[7] Similarly, peak VO_2 (51 ± 14% of the predicted value) confirmed a severe exercise impairment, but not as severe as that reported to be a negative pMVR prognosticator.[16] The PMR population we studied was older and had a less evident exercise performance limitation (peak VO_2 60 ± 17% of the predicted value).

In the overall population, pMVR was associated with a reverse cardiac remodelling, in line with several previous reports. This LV reverse remodelling was more evident in PMR patients, in whom MR is likely the main cause of ventricular dysfunction. Regardless, in parallel with MR reduction, estimated pulmonary systolic pressure decreased in both groups, and a trend towards a reduction in LV diastolic volume was observed also in FMR cases. The LV reverse remodelling we observed with pMVR was associated with reduced (PMR) or unchanged (FMR) ejection fraction and stroke volume at cardiac ultrasound measurement. The reduction of LVEF and LV stroke volume is a consequence of the increased afterload and decreased preload due to MR volume reduction. Of note, LV reverse remodelling was associated with an improvement of patients' clinical status (NYHA class). pMVR also allowed an improvement of the right heart performance, as shown by the reduction of PASP, RAP and tricuspid regurgitation in the overall population. PASP and tricuspid regurgitation decreased in both groups, whereas RAP only decreased in FMR patients.

The IGR technique is a nowadays well-known technique to non-invasively measure forward CO at rest and during exercise. Specifically, several studies have shown the reliability of CO measurements by IGR[24–26] and their application in several clinical settings.[27–30] It should be noticed that, to measure peak exercise CO, patients must inform medical personnel that they have almost exhausted their exercise capacity to allow the rebreathing manoeuvre to be performed during loaded, active pedalling. Peak exercise ventilatory and gas exchange data are recorded immediately before. Thus, the recorded data might anticipate a little the true peak data as suggested by the respiratory exchange ratio reported (*Table 3*).

The discrepancy we observed in both study groups between peak CO improvement after pMVR and peak VO_2 or peak workload—both of which remained unchanged—is difficult to understand at a first glance, and it deserves a physiologically based discussion. Indeed, we reported, after pMVR, an improvement of patients' clinical conditions and an increase of peak CO but not of peak VO_2 or workload. This is different from any other successful treatment of HF, where VO_2 changes are considered the cornerstone of exercise improvement. In patients with severe HF, such as the FMR patients of the present population, the low CO at rest is compensated by a $\Delta C(a\text{-}v)O_2$ increase. Indeed, the $\Delta C(a\text{-}v)O_2$ values we observed at rest, both in PMR and FMR cases, were almost twice those usually observed in healthy individuals, showing that patients had to rely on compensatory mechanisms of low CO to maintain aerobic metabolism even at rest. When CO increased, as happened in FMR patients even at rest, $\Delta C(a\text{-}v)O_2$ decreased, suggesting that because VO_2 was constant, a reduction of O_2 extraction in the peripheral tissue and possibly a diversion, as a percentage, of blood flow from high-extraction to low-extraction tissues. This allowed a 'more physiological' blood flow distribution and O_2 extraction behaviour. A more evident but similar

Figure 2 Cardiac output (CO, L/min), arteriovenous oxygen content difference [$\Delta C(a\text{-}v)O_2$; a = arterial oxygen; v = mixed venous oxygen content, mL/dL] and oxygen uptake (VO_2, mL/min). Cardiac output is plotted against $\Delta C(a\text{-}v)O_2$. The solid lines are lines with the same VO_2. $\Delta C(a\text{-}v)O_2$ can be estimated from measured VO_2 and CO. (A) Data comparison at rest and at peak of exercise before and after pMVR in functional mitral regurgitation patients. (B) Data comparison at rest and at peak of exercise before and after pMVR in primary mitral regurgitation patients.



behaviour is observed at peak exercise, when, in spite of a relevant CO increase (≈10%), VO_2 is unchanged, and $\Delta C(a\text{-}v)O_2$ decreases in the presence of an unchanged haemoglobin level. Indeed, it is well known that the major determinants of exercise performance impairment in advanced HF patients are located in the periphery, and mainly in the muscles, which are unable to increase their aerobic ATP production.[31,32] However, an increase of CO and a reduction of $\Delta C(a\text{-}v)O_2$ are a favourable background for an effective rehabilitation programme or pharmacological treatment upgrading, both of which were not carried out in the present study.

The discrepancy between peak CO, which increased, and peak VO_2, which remained unchanged, was also observed in PMR patients. Again, in these patients, $\Delta C(a\text{-}v)O_2$ decreased at peak exercise. It is of note that exercise performance, relatively to age and gender, was less compromised in PMR patients even before pMVR, because peak VO_2 was ≈60% of the predicted value, that is, closer to a normal range than in FMR cases. Moreover, the respiratory exchange ratio was 1.02 ± 0.1 and 1.04 ± 0.1 before and after pMVR, that is, a somewhat low value likely due to the rebreathing manoeuvre needed for IGR; thus, peak VO_2 was likely underestimated. We speculate that, with severe MR, PMR patients redistribute blood flow towards the exercising muscles that have an O_2 extraction higher than other tissues to preserve exercise performance so that overall $\Delta C(a\text{-}v)O_2$ increases. When

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forward CO is higher, as happens after pMVR, this compensatory mechanism is no longer needed, and peak exercise $\Delta C(a\text{-}v)O_2$ decreases.

The relevance of blood flow redistribution towards the exercising muscles has been described for many years,[32–34] but its presence has been neglected in the general literature, likely because of the difficulties intrinsic to its measurement, analysis and interpretation, which imply the simultaneous measurement of forward CO and VO_2. However, a discrepancy between peak VO_2 and peak CO changes has been previously reported after exercise training, and more recently after cardiac resynchronization (CRT),[28,29] where, in spite of an effective LV reverse remodelling, peak VO_2 increases only in patients with most severe exercise limitation.[35]

The ventilation to carbon dioxide production relationship slope (VE/VCO_2) is another CPET-derived parameter associated with HF severity and prognosis.[23] The VE/VCO_2 we observed was higher in FMR than in PMR patients, in line with a more severe HF, but it was overall moderately elevated before pMVR. In both groups, VE/VCO_2 did not decrease after pMVR. Of note, in chronic HF, VE/VCO_2 increase is due to sympathetic tone increase and unrelated to cardiac haemodynamics. As a matter of fact, the specific behaviour of VE/VCO_2 in chronic HF is directly linked to the activity of chemoreceptors and other receptors.[36] Accordingly, because we limited our intervention to MR reduction, the unchanged VE/VCO_2 slope is not surprising.

This study has some limitations that need to be acknowledged. First, IGR implies an active role of patients, requiring at least a familiarization session for patients with medical personnel, so a large-scale clinical applicability of IGR is questionable and likely frail, and patients who are not fully motivated are unsuitable for this technique. Of note, the need for a respiratory manoeuvre did not influence the recorded VO_2 values, although peak data are anticipated.[37] Second, differently from several previous studies, the 6MWT was not carried out, so a comparison between studies as regards exercise performance changes after pMVR is impossible. Of note, both major studies on pMVR, the COAPT and the MITRA-FR studies, did not report an improvement of 6MWT distance after pMVR. Regardless, CPET is the recognized gold standard for the evaluation of exercise performance. Third, the echocardiographic measurement of stroke volume in the LV outflow tract was not performed. This measurement is likely more comparable with IGR volume in the presence of severe MR. Finally, the study was demanding for patients in terms of IGR methodology training and exercise evaluation. Consequently, there might be some selection bias. This also explains the relatively large number of cases who did not perform the final evaluation for various reasons (*Figure 1*).

In conclusion, we demonstrated that, in both PMR and FMR patients treated with successful pMVR, peak exercise CO and forward stroke volume significantly increase although peak VO_2 remains unchanged, suggesting a more physiological exercise performance. Most importantly the present study underlines the need to measure in parallel, during exercise, both VO_2 and CO to properly assess exercise performance in HF. Indeed, limiting the analysis to VO_2 does not allow to properly judge therapeutic interventions with a relevant blood flow distribution change during exercise such as pMVR, CRT or training.[23,28,29,38]

Conflict of interest

None declared.

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