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SHORT COMMUNICATION

MitraClip improves cardiopulmonary exercise test in patients with systolic heart failure and functional mitral regurgitation

Tomás Benito-González[1], Rodrigo Estévez-Loureiro[1]*, Carmen Garrote-Coloma[1], Ignacio Iglesias Garriz[1], Javier Gualis[2], Laura Álvarez-Roy[1], Miguel Rodriguez-Santamarta[1], Armando Pérez de Prado[1] and Felipe Fernández-Vázquez[1]

[1]*Department of Cardiology, University Hospital of León, Altos de Nava SN, 24071, León, Spain;* [2]*Department of Cardiovascular Surgery, University Hospital of León, León, Spain*

Abstract

Aims The aim of this study is to evaluate changes in cardiopulmonary exercise test (CPET) after percutaneous mitral valve repair (PMVR) with MitraClip in patients with heart failure with reduced ejection fraction who are potentially candidates for heart transplantation or destination left ventricular assist device.

Methods and results Prospective registry of all consecutive patients with heart failure with reduced ejection fraction and functional mitral regurgitation (MR) underwent elective PMVR between October 2015 and March 2018 in our institution. Patients with preserved or mid-range left ventricular ejection fraction (>40%), advanced age (>75 years old), or severe co-morbidities (end-stage organ damage) were not included. Treadmill exercise testing with respiratory gas exchange analysis was carried out in 11 patients (male, 72.7%; median age, 67 years old) within the month prior to the procedure and at 6 month follow-up. PMVR was successfully performed in all patients. At 6 month follow-up, PMVR was associated with an improvement in New York Heart Association functional class (P = 0.021) and a reduction in MR severity (P = 0.013) and N-terminal pro-brain natriuretic peptide levels (2805 [1878–5022] vs. 1485 [654–3032] pg/mL; P = 0.012). All patients completed pre-procedural and post-procedural CPET, and all the studies showed a respiratory exchange ratio ≥1 and were consistent with sufficient exercise effort. Compared with pre-procedural CPET, patients showed a significant increase in exercise time (295 [110–335] vs. 405 [261–540] s; P = 0.047), VO_2 (9.8 [9.1–13.4] vs. 13.5 [12.1–16.8] mL/kg/min; P = 0.033), ventilatory anaerobic threshold (510 [430–950] vs. 850 [670–1070] mL/kg/min; P = 0.033), peak O_2 pulse (7.2 [4.3–8.6] vs. 8.3 [6.2–11.8] mL/beat; P = 0.033), and workload (5 [3–6] vs. 6 [5–8] metabolic equivalents; P = 0.049).

Conclusions Percutaneous mitral valve repair with MitraClip was associated with an enhancement in cardiopulmonary performance in patients with systolic heart failure and secondary MR.

Keywords MitraClip; Cardiopulmonary stress test; Functional mitral regurgitation; Maximal O_2 consumption

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**Correspondence to: Rodrigo Estévez-Loureiro, Department of Cardiology, University Hospital of León, Altos de Nava SN, 24071, León, Spain. Tel: +34 987237683. Email: roiestevez@hotmail.com*

Introduction

Percutaneous mitral valve repair (PMVR) with MitraClip has proven to effectively reduce mitral regurgitation (MR) and improve symptoms in patients at high risk for conventional surgery.[1] Cardiopulmonary exercise test (CPET) is a valuable key tool to evaluate functional capacity, determine prognosis, and guide therapies in patients with heart failure with reduced ejection fraction (HFrEF).[2,3] To the best of our knowledge, no data are available regarding changes in CPET after PMVR.

Aim

Our aim was to evaluate changes in CPET after PMVR in patients with HFrEF who are potentially candidates for heart transplantation or destination left ventricular assist device.

Methods

We conducted a prospective registry of all consecutive patients with functional MR (FMR) and HFrEF who underwent elective PMVR between October 2015 and March 2018 in our institution. Patients with preserved or mid-range left ventricular ejection fraction (LVEF $>$ 40%), advanced age ($>$75 years old), or severe co-morbidities (end-stage organ damage) were not included. Patients with unimpaired preprocedural VO_2 $>$ 18 mL/kg/min were excluded (*Figure 1*). All patients underwent invasive angiogram before PMVR to exclude significant coronary artery disease, with two patients being revascularized within prior 90 days before clip implantation. Treadmill exercise testing with respiratory gas exchange analysis was carried out in 11 patients within the month prior to the procedure and at 6 month follow-up using a Schiller MTM-1500 ergometer (Polymed Chirurgical, Montreal, Canada). Current recommendations for CPET in this scenario were followed.[4] Wasserman's equation was used to estimate predicted VO_2 in each subject according to sex, predicted weight, and the use of treadmill test.[5] Patients breathed exclusively through a face mask and exhaled gases were analysed using sensors that allow breath-by-breath analysis with real-time plotting of the mean values. Respiratory exchange ratio (RER), defined as the ratio between carbon dioxide output and oxygen uptake, was estimated as a 10 to 60 s averaged value depending on the exercise protocol. A cut-off point $\geq$1.05 was set as an optimal exercise effort for maximal oxygen consumption (VO_2) estimation. In case of a RER between 1 and 1.05, the exercise was considered sufficient for peak VO_2 calculation if fulfilling one of the following criteria: achievement ventilatory anaerobic threshold, plateau in the VO_2, maximal heart rate $\geq$90%, or perceived exertion with the Borg scale $\geq$8. CPETs with a RER below 1 were excluded. Clinical, echocardiographic, and laboratory features were also collected.

Continuous variables were summarized as medians and interquartile range and compared using paired non-parametric Wilcoxon sign rank sum tests. Categorical variables were described as percentages and compared using paired McNemar test. A *P*-value of $<$0.05 was considered statistically significant.

Results

Baseline characteristics of included cohort are shown in *Table 1*. All patients were at optimal medical therapy at maximum dose tolerated according to heart failure (HF) guidelines before PMVR: 100% were on beta-blockers, and all but two patients with severe chronic kidney disease were on inhibitors of the renin–angiotensin system. No significant changes in medical therapy were observed at 6 month follow-up (*Table 2*). PMVR was successfully performed in all patients. At 6 month follow-up, PMVR was associated with an improvement in New York Heart Association functional class and LVEF and a reduction in MR severity and N-terminal pro-brain natriuretic peptide (*Table 2*). All patients completed preprocedural and post-procedural CPET, and all the studies

Figure 1 Inclusion and exclusion criteria: flow chart for selection of patients. FMR, functional mitral regurgitation; GFR, glomerular filtrate rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; OMT, optimal medical therapy; PMVR, percutaneous mitral valve repair; VO_2, maximal peak oxygen consumption.

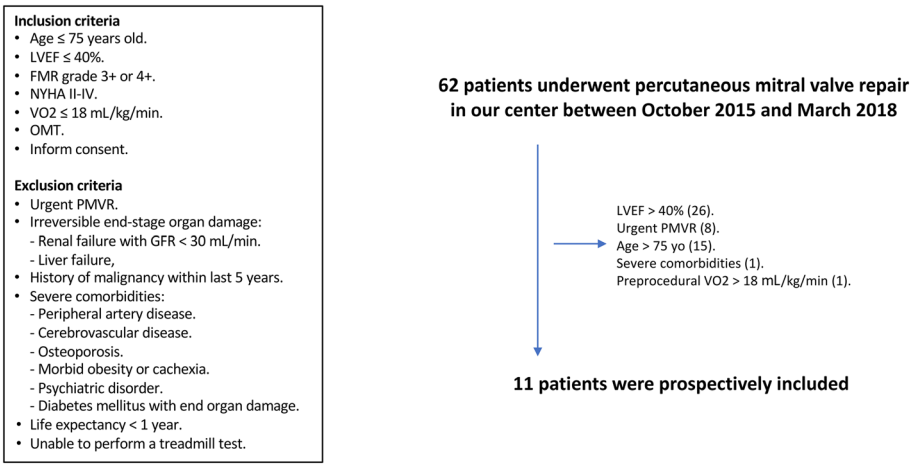

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Table 1 Baseline characteristics of patiets included in the study

Age (years)	Sex	BMI (kg/m^2)	DM	DCM	Prior coronary revascularization	Cardiac implantable device	AF	COPD	CKD	SHFM (%)	HFSS (%)	MAGGIC HF risk score (%)	Pre-PMVR HF Admissions (12 months)	MR	LVEF (%)	GLS (%)	NYHA functional class	VO_2 before (mL/kg/min)	VO_2 after (mL/kg/min)
67	Female	22.4	No	Non-ischaemic	—	ICD	Permanent	No	No	93.2	Low	9.3	0	4+	20	−6.0	2	13.4	7.7
71	Female	22.9	No	Non-ischaemic	—	ICD	No	No	Yes	92.6	Low	8.4	1	4+	30	−6.0	2	9.8	15.8
72	Male	31.1	No	Non-ischaemic	—	No	Permanent	No	Yes	91.9	Low	9.3	1	4+	35	−6.1	3	6.7	13.3
55	Male	25.9	No	Ischaemic	PCI	No	No	No	Yes	78.7	Low	8.4	2	4+	38	−11.6	3	18.0	23.5
55	Male	23.6	No	Ischaemic	PCI	ICD	Paroxysmal	No	No	95.7	Low	5.2	3	4+	35	−10.2	2	16.3	29.1
73	Male	24.9	Yes	Ischaemic	PCI	No	No	Yes	No	86.3	High	22.7	1	4+	27	−9.5	3	7.6	13.5
73	Male	25.2	No	Non-ischaemic	—	ICD	Paroxysmal	No	No	91.0	Medium	20.9	2	4+	25	−4.7	3	9.5	16.8
67	Male	24.9	Yes	Ischaemic	CABG	No	Permanent	No	Yes	70.3	Medium	22.7	2	4+	35	−8.7	3	9.2	12.1
59	Male	27.2	No	Ischaemic	PCI	ICD	Paroxysmal	No	No	87.9	Medium	11.1	2	3+	25	−6,6	3	9.1	13.9
69	Female	34.9	Yes	Non-ischaemic	—	No	No	No	No	93.2	Low	9.3	0	4+	33	−14.8	3	12.2	8.6
63	Male	25.2	Yes	Non-ischaemic	—	ICD/CRT	Paroxysmal	No	Yes	79.3	Low	19.1	4	4+	25	−7.2	3	11.9	13.4

AF, atrial fibrillation; BMI, body mass index; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; DM, diabetes mellitus; DCM, dilated cardiomyopathy; GLS, global longitudinal strain; HF, heart failure; HFSS, Heart Failure Survival Score; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PMVR, percutaneous mitral valve repair; SHFM, Seattle Heart Failure Model.

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Table 2 Changes in cardiopulmonary exercise test and clinical, echocardiographic, and biochemical follow-up

	Pre-procedural	Post-procedural	*P*-value
Reason for stopping	90.9	72.7	NS
Exhaustion/dyspnoea	9.1	18.2	
Claudication	0	9.1	
Time (s)	295 [110–335]	405 [261–540]	0.047
Peak heart rate (b.p.m.)	130 [110–153]	130 [115–141]	NS
Peak SBP (mmHg)	140 [120–150]	140 [110–150]	NS
Double product	17980 [13200–2950]	16100 [13300–21150]	NS
VO_2 (mL/kg/min)	9.8 [9.1–13.4]	13.5 [12.1–16.8]	0.033
VO_2/predicted VO_2 (%)	39.2 [30.3–6.3]	52.6 [44.2–68.8]	0.033
VAT (mL/kg/min)	510 [430–950]	850 [670–1070]	0.033
RER	1.18 [1.13–1.24]	1.16 [1.07–1.29]	NS
VE/VO_2 slope	30.0 [27.0–38.6]	31.5 [23.7–39.7]	NS
Peak O_2 pulse (mL/beat)	7.2 [4.3–8.6]	8.3 [6.2–11.8]	0.013
OUES	1035 [754–1657]	1135 [997–2324]	0.033
Workload (METs)	5 [3–6]	6 [5–8]	0.049
NYHA (%)			0.021
1	0	36.4	
2	27.3	54.6	
3	72.7	9.1	
4	0	0	
MR (%)			0.013
1+	0	36.4	
2+	0	45.5	
3+	9.1	9.1	
4+	90.9	9.1	
LVEF (%)	33 [25–35]	35 [29–45]	0.040
NT-proBNP (pg/mL)	2805 [1878–5022]	1485 [654–3032]	0.012
Beta-blockers (%)	100	90.9	NS
ACE/angiotensin II/neprilysin inhibitors (%)	81.8	90.9	NS
ACE inhibitors (%)	36.4	36.4	NS
Angiotensin II inhibitors (%)	27.3	9.1	NS
Neprilysin inhibitors (%)	18.2	36.4	NS
Mineralocorticoid receptor antagonists (%)	81.8	90.9	NS
Furosemide dose (mg/day)	80 [40–80]	40 [40–80]	NS

ACE, angiotensin-converting enzyme; LVEF, left ventricular ejection fraction; METs, metabolic equivalents; MR, mitral regurgitation; NS, not significant; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; OUES, oxygen uptake efficiency slope; RER, respiratory exchange ratio; SBP, systolic blood pressure; VAT, ventilatory anaerobic threshold; VE, ventilation; VO_2, maximal peak oxygen consumption.

showed a RER $\geq$ 1 and were consistent with sufficient exercise effort. Compared with pre-procedural CPET, patients showed a significant increase in exercise time (P = 0.047), VO_2 (P = 0.033), ventilatory anaerobic threshold (P = 0.033), peak O_2 pulse (P = 0.033), and workload (P = 0.049) (*Table 2* and *Figures 2–4*).

Discussion

Some reports have already highlighted the effectiveness of PMVR in patients with advanced HF candidates for heart transplantation or left ventricular assist device.[6,7] In our cohort, elective PMVR was related to an improved overall cardiopulmonary performance, including an increase in VO_2 as the most robust prognostic parameter of CPET. Some aspects should be pointed out regarding these findings. First, interpretation of pre-procedural and post-procedural CPETs results might be challenging, especially in patients with advanced age and severe co-morbidities.[3,8] Those patients were not included in this study. Second, FMR is a common finding among patients with HFrEF and has a negative impact on exercise capacity and clinical outcomes on standalone medical therapy.[9] Third, from a physiopathological perspective, PMVR reduces MR, thus decreasing left-side volume overload and pulmonary pressures and increasing cardiac output.[10] And fourth, this haemodynamic enhancement has translated into positive left ventricular remodelling and improvement in clinical symptoms, quality of life, and 6 min walk test in different series.[11–13] Although only modest increments in LVEF have been reported in this scenario, these changes, alongside the reduction in regurgitant volume, imply an improvement in antegrade ejection flow that might be one of the underlying mechanisms for a better cardiopulmonary performance.[14] Given the good correlation reported between 6 min walk test and estimated VO_2,[15] this result go alongside with prior findings. Because improvement in VO_2 has always been considered a relevant prognostic factor in patients with HFrEF, our observation may explain some of the benefits of the MitraClip therapy. At this regard, to date, larger randomized controlled trial addressing prognosis impact of PMVR

Figure 2 Changes in VO_2 before and after percutaneous mitral valve repair (PMVR).

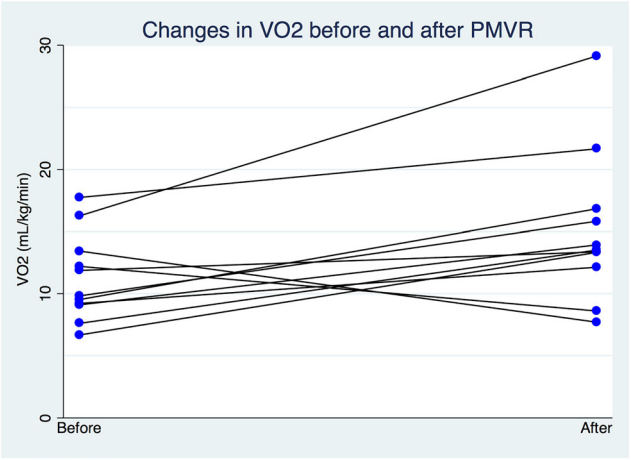


Figure 3 Changes in oxygen uptake efficiency slope (OUES) before and after percutaneous mitral valve repair (PMVR).

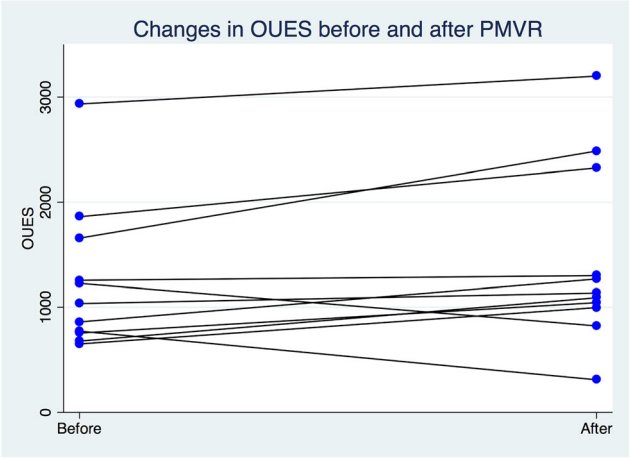
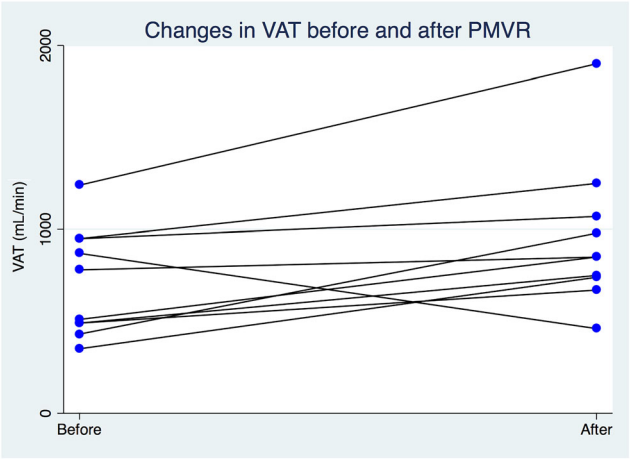


Figure 4 Changes in ventilatory anaerobic threshold (VAT) before and after percutaneous mitral valve repair (PMVR).



over medical therapy in patients with FMR showed a reduction in the need for advanced HF therapies, as well as an improved survival after clip implantation.[16] Conversely, the study of Obadia *et al.*[17] failed to show an improvement in prognosis after PMVR, which has been related to the inclusion of patients with very severely dilated left ventricular and less significant MR in this late study. Therefore, further trials are required to better discriminate best candidates for PMVR and determined if clinical improvement in patients with FMR translates in better survival outcomes and safe deference of advanced HF therapies.

Conclusions

In conclusion, although limited for the small number of patients included and the lack of a matched cohort, PMVR was related to an enhancement in cardiopulmonary performance in patients with systolic HF and no contraindication for advanced HF therapies in our series.

Conflict of interest

None declared.

Funding

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References

1. Nickenig G, Estevez-Loureiro R, Franzen O, Tamburino C, Vanderheyden M, Lüscher TF, Moat N, Price S, Dall'Ara G, Winter R, Corti R, Grasso C, Snow TM, Jeger R, Blankenberg S, Settergren M, Tiroch K, Balzer J, Petronio AS, Büttner HJ, Ettori F, Sievert H, Fiorino MG, Claeys M, Ussia GP, Baumgartner H, Scandura S, Alamgir F, Keshavarzi F, Colombo A, Maisano F, Ebelt H, Aruta P, Lubos E, Plicht B, Schueler R, Pighi M, di Mario C, Transcatheter Valve Treatment Sentinel Registry Investigators of the EURObservational Research Programme of the European Society of Cardiology. Percutaneous mitral valve edge-to-edge repair: in-hospital results and 1-year follow-up of 628 patients of the 2011–2012 Pilot European Sentinel Registry. *J Am Coll Cardiol* 2014; **64**: 875–884.
2. Mehra MR, Canter CE, Hannan MM, Semigran MJ, Uber PA, Baran DA, Danziger-Isakov L, Kirklin JK, Kirk R, Kushwaha SS, Lund LH, Potena L, Ross HJ, Taylor DO, Verschuuren EAM, Zuckermann A. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: a 10-year update. *J Heart Lung Transplant* 2016; **35**: 1–23.
3. Corrà U, Agostoni PG, Anker SD, Coats AJS, Crespo Leiro MG, de Boer RA, Harjola VP, Hill L, Lainscak M, Lund LH, Metra M, Ponikowski P, Riley J, Seferović PM, Piepoli MF. Role of cardiopulmonary exercise testing in clinical stratification in heart failure. A position paper from the Committee on Exercise Physiology and Training of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2018; **20**: 3–15.
4. Guazzi M, Arena R, Halle M, Piepoli MF, Myers J, Lavie CJ. 2016 focused update: clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *Eur Heart J* 2018; **39**: 1144–1161.
5. Guazzi M, Adams V, Conraads V, Halle M, Mezzani A, Vanhees L, Arena R, Fletcher GF, Forman DE, Kitzman DW, Lavie CJ, Myers J, EACPR, AHA. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *Eur Heart J* 2012; **33**: 2917–2927.
6. Godino C, Scotti A, Agricola E, Pivato CA, Chiarito M, Stella S, Maccherini M, Margonato A, Colombo A. Young patient with advanced heart failure no longer a candidate for heart transplantation after MitraClipÂ® procedure. *J Heart Valve Dis* 2017; **26**: 234–236.
7. Sündermann SH, Van Praet K, Kukucka M, Meyer A, Schönrath F, Knierim J, Kempfert J, Falk V, Jacobs S. MitraClip implantation in high risk heart failure patients with functional mitral valve regurgitation in a surgical department as first line treatment for patients evaluated for assist device implantation and/or heart transplantation. *Thorac Cardiovasc Surg* 2017; **65**: S1–S110.
8. Lund LH, Mancini DM. Peak VO_2 in elderly patients with heart failure. *Int J Cardiol* 2008; **125**: 166–171.
9. Szymanski C, Levine RA, Tribouilloy C, Zheng H, Handschumacher MD, Tawakol A, Hung J. Impact of mitral regurgitation on exercise capacity and clinical outcomes in patients with ischemic left ventricular dysfunction. *Am J Cardiol* 2011; **108**: 1714–1720.
10. Geis NA, Pleger ST, Bekeredjian R, Chorianopoulos E, Kreusser MM, Frankenstein L, Ruhparwar A, Katus HA, Raake PWJ. Haemodynamic effects of percutaneous mitral valve edge-to-edge repair in patients with end-stage heart failure awaiting heart transplantation. *ESC Heart Fail* 2018; **5**: 892–901.
11. Megaly M, Khalil C, Abraham B, Saad M, Tawadros M, Stanberry L, Kalra A, Goldsmith SR, Bart B, Bae R, Brilakis ES. Impact of transcatheter mitral valve repair on left ventricular remodeling in secondary mitral regurgitation: a meta-analysis. *Struct Hear* 2018; **2**: 541–547.
12. Maor E, Raphael CE, Panaich SS, Reeder GS, Nishimura RA, Nkomo VT, Rihal CS, Eleid MF. Acute changes in left atrial pressure after MitraClip are associated with improvement in 6-minute walk distance. *Circ Cardiovasc Interv* 2017; **10**: e004856.
13. Iliadis C, Lee S, Kuhr K, Metze C, Matzik AS, Michels G, Rudolph V, Baldus S, Pfister R. Functional status and quality of life after transcatheter mitral valve repair: a prospective cohort study and systematic review. *Clin Res Cardiol* 2017; **106**: 1005–1017.
14. Kubo S, Nakamura M, Shiota T, Itabashi Y, Mizutani Y, Nakajima Y, Meemook K, Hussaini A, Makar M, Siegel RJ, Kar S. Impact of forward stroke volume response on clinical and structural outcomes after percutaneous mitral valve repair with MitraClip. *Circ Cardiovasc Interv* 2017; **10**: e004909.

15. Ross RM, Murthy JN, Wollak ID, Jackson AS. The six minute walk test accurately estimates mean peak oxygen uptake. *BMC Pulm Med* 2010; **10**: 31.
16. Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, Whisenant B, Grayburn PA, Rinaldi M, Kapadia SR, Rajagopal V. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med* 2018; **379**: 2307–2318.
17. Obadia J-F, Messika-Zeitoun D, Leurent G, Iung B, Bonnet G, Piriou N, Lefèvre T, Piot C, Rouleau F, Carrié D, Nejjari M. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med* 2018; **379**: 2297–2306.