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

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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), VO2 (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 O2 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 O2 consumption

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 pre-procedural 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 ≥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 ≥90%, or perceived exertion with the Borg scale ≥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 pre-procedural and post-procedural CPET, and all the studies were completed within 90 days after the procedure.

![Figure 1](image-url) 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.
| Age (years) | Sex | BMI (kg/m²) | 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 | VO₂ before (mL/kg/min) | VO₂ 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 | 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 | Medium | 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 | No | 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.
showed a RER ≥ 1 and were consistent with sufficient exercise effort. Compared with pre-procedural CPET, patients showed a significant increase in exercise time (P = 0.047), VO₂ (P = 0.033), ventilatory anaerobic threshold (P = 0.033), peak O₂ 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. In our cohort, elective PMVR was related to an improved overall cardiopulmonary performance, including an increase in VO₂ 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. 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. Third, from a physiopathological perspective, PMVR reduces MR, thus decreasing left-side volume overload and pulmonary pressures and increasing cardiac output. 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. 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. Given the good correlation reported between min walk test and estimated VO₂, this result go alongside with prior findings. Because improvement in VO₂ 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

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

| Reason for stopping       | Pre-procedural | Post-procedural | P-value |
|---------------------------|----------------|-----------------|---------|
| Exhaustion/dyspnoea       | 9.0           | 7.2             | NS      |
| Claudication              | 0.1           | 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      |
| VO₂ (mL/kg/min)           | 9.8 [9.1–13.4] | 13.5 [12.1–16.8] | 0.033   |
| VO₂/predicted VO₂ (%)     | 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/VO₂ slope              | 30.0 [27.0–38.6] | 31.5 [23.7–39.7] | NS      |
| Peak O₂ 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; VO₂, maximal peak oxygen consumption.

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**Figure 2** Changes in VO₂ 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. Conversely, the study of Obadia et al. 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.

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References

1. Nickenig G, Estezev-Loureiro R, Franzens O, Tamburino C, Vanderheiden DA, Lüscher TF, Moat N, Price S, Dall’Ara G, Winter R, Corti R, Grasso C, Snow TM, Jeger R, Blankenberg S, Settergren M, Tirol K, Balzer J, Petronio AS, Böttner HJ, Ettori F, Sievert H, Florino MG, Claey S, Usia GP, Baumgartner H, Scandura S, Alamir 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 EUOResearch 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, Lavi 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, Lavi 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 L, 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.

7. Sündermann SH, Van Praet K, Kukucka M, Meyer A, Schönath F, Knieper 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–S11.

8. Lund LH, Mancini DM. Peak VO₂ 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, Bekererdjian R, Chorianopoulos E, Kreusser MM, Frankenlein L, Ruhrparwar 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 Heart 2018; 2: 541–547.

12. Maor E, Raphael CE, Panaich SS, Reeder GS, Nishimura RA, Nikomo 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, Matzuk AS, Michels G, Rudolph V, Baldus S, Pieter 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, Nejjar M. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med* 2018; 379: 2297–2306.