

Transcatheter mitral valve repair with MitraClip in patients with pulmonary hypertension: hemodynamic and prognostic perspectives

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Transcatheter mitral valve repair with MitraClip has emerged as a possible therapeutic option for patients with severe mitral regurgitation (MR) with high risk for surgical valve repair. MitraClip intervention has demonstrated to improve haemodynamics and clinical outcomes in selected patients in observational and randomized studies. Preoperative pulmonary hypertension (PH) is known to affect prognosis in patients undergoing surgical mitral valve intervention. The aim of the present review is to discuss the available literature focused on the haemodynamic and clinical effects of MitraClip in patients with severe MR and PH.

Keywords

MitraClip; Pulmonary hypertension; Mitral valve regurgitation

1. Introduction

Mitral regurgitation (MR) is the second most frequent indication for valve surgery in Europe [1] with an estimated prevalence of 5% among the adult population [2, 3]. The most widely used classification distinguishes between primary and secondary (or functional) MR: the former is caused by a damage to the mitral valve leaflets or *chordae tendinae*, whereas the latter presents a normal valve apparatus and is the consequence of annular enlargement/dysfunction and leaflet tethering caused in the majority of cases by left ventricular dysfunction [4].

Long-term increase in left-sided filling pressures due to MR can lead to pulmonary hypertension (PH). The prevalence of PH in patients with severe primary MR is 23%, while the prevalence among patients with secondary MR is unknown. PH due to any left heart disease (LHD) is the most

common form of PH [5], representing the second group of the WHO classification and being characterized by a mean pulmonary arterial pressure (mPAP) ≥ 20 mmHg and a pulmonary arterial wedge pressure (PAWP) > 15 mmHg (i.e. post-capillary PH) [6]. Indeed, severe MR induces an increase in left ventricular filling pressures and a reduction in left atrial compliance, causing an increase in left atrial pressure and causes pulmonary vascular congestion. Long-standing elevations in pulmonary pressures can cause an initial reactive vasoconstriction, which can eventually lead to irreversible remodelling of both pulmonary arterioles and veins [7], thus causing the evolution from an isolated post-capillary PH to a combined pre- and post-capillary PH, representing an advanced stage of the disease.

No pharmacological strategy showed to reduce mortality in patients with corrected MR and PH [8, 9] and the cornerstone in the management of these patients is represented by treating the valvular defect [10].

Preoperative PH is known to affect prognosis in patients undergoing surgical mitral valve intervention [11]. Most of the studies on the effect of PH on outcomes after mitral valve surgery are retrospective and used different definitions of PH. However, regardless of the invasive or non-invasive measurement or the defined thresholds [12], PH has been associated with significant reduction in post-operative left ventricular ejection fraction in patients with primary MR [13] and with increased mortality in both primary and secondary MR [11, 14].

Positive	Controversial	Negative
↑ Cardiac Index ↑ Cardiac Output ↓ PA Wedge Pressure ↓ Mean PA Pressure ↓ Pulmonary Vascular Resistance ↑ RV Stroke Work Index	Iatrogenic Septal Defects	Mitral Valve Pressure Gradient (potential)

Fig. 1. Haemodynamic effects of MitraClip. The green column shows the favourable haemodynamic effects after MitraClip; the yellow one the effects whose hemodynamic significance is still controversial; the red one the negative effects. Legend. CI, cardiac index; CO, cardiac output; iASD, iatrogenic atrial septal defect; mPAP, mean pulmonary artery pressure; MVPG, mitral valve pressure gradient; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RVSWI, right ventricular stroke work index.

Transcatheter mitral valve repair (TMVR) with MitraClip (Abbott Vascular, Inc.) has emerged as a possible therapeutic option for patients at high risk for surgical mitral valve repair. In primary MR, MitraClip is reserved for patients with symptoms who present contraindications to surgery [15]. In the setting of secondary MR, MitraClip has demonstrated to be effective in reducing symptoms and improving clinical outcomes in selected patients in observational and randomized studies [16, 17].

Since PH represents an important risk factor for right ventricular (RV) failure and peri-operative mortality in patients undergoing mitral valve surgery [18], great interest has been raised for TMVR in these high-risk patients.

The aim of the present review is to expose the available literature focused on MitraClip in patients with severe MR and PH, specifically evaluating the haemodynamic and clinical effects of MitraClip in this setting.

2. Haemodynamic effects of MitraClip

MitraClip intervention has been associated with favourable acute hemodynamic changes in patients with severe MR [19–21] (Fig. 1).

A successful reduction of MR causes a decrease of the regurgitant volume, which yields unloading of left atrium. An initial concern of TMVR was the possible increase in left ventricular (LV) afterload following elimination of the low resistance regurgitant flow into the left atrium, possibly resulting in a post-procedural low cardiac output (CO) [22, 23]. However, the first studies focused on the hemodynamic effects of MitraClip, performed by repeating right heart catheterization before and after the procedure, reported an acute increase in CO and cardiac index (CI) [21, 24, 25] (Table 1).

Data on the hemodynamic effects of MitraClip in patients with severe MR and PH are limited. In a cohort of patients with baseline low CI and elevated mean pulmonary artery pressure (mPAP), Kottenberg *et al.* showed that MitraClip resulted in CI, mPAP and right ventricular stroke work in-

dex (RVSWI) improvement at the end of the procedure [20]. These results allowed to assume that eliminating the regurgitant flow into the left atrium and pulmonary veins can improve cardiac forward output and reduce pulmonary pressures. Interestingly, the decrease in PAP values were reported in the first 90 days after MitraClip in patients with FMR and PH receiving hemodynamic telemonitoring with an implanted PAP sensor [27]. RVSWI is a surrogate parameter for RV function, representing the pressure-volume work of the right ventricle [28]. In this study RVSWI increase was mainly driven by decreased pulmonary vascular resistance (PVR) [20]. Indeed, in patients with PH, in whom the right ventricle chronically works against high pulmonary artery pressures, a reduction in PVR may be linked with an improvement in RV function by reducing RV afterload. This finding is particularly relevant in patients with chronic heart failure (HF), where the negative impact of PH on prognosis is mainly driven by the eventual worsening of RV function [29].

The reduction of PVR may be of particular relevance for patients with advanced HF who are not eligible for heart transplantation (HTx) due to elevated PVR. HTx represents the treatment of choice for end-stage HF [30], but patients with PH and elevated PVR are not suitable for HTx because of the risk of post-operative RV failure and poor outcome [26]. In this setting, a persistent reduction of PVR may lead to eligibility for HTx. Thus, since MitraClip has been associated with a sustained reduction of PVR, it has been proposed as a “bridge to candidacy” strategy [31–33]. The selected use of MitraClip as a bridge strategy to HTx has been recently investigated by a multicenter registry, which reported that 15% of patients underwent elective HTx, 15.5% became suitable for HTx and 23.5% was removed from HTx list because of clinical improvement [34].

By approximating the two mitral valve leaflets, MitraClip can increase mitral valve pressure gradient (MVPG) thus counterbalancing the benefit of unloading the left atrium by

Table 1. Main studies investigating the haemodynamic effects of MitraClip on pulmonary circulation and RV

Study (year) (reference)	Patients (n)	MR aetiology	Time of assessment	Hemodynamic effects
Siegel <i>et al.</i> (2011) [21]	107	Degenerative 79%	Intraprocedural,	↑ CO
		Functional 21%	Under general anaesthesia	↑ CI ↓ LVEDP
Gaemperli <i>et al.</i> (2012) [24]	50	Degenerative 30%	Intraprocedural,	↑ CI
		Functional 56%	Under general anaesthesia	↓ mPAP
		Mixed 14%		↓ PAWP
		Degenerative 55%	Intraprocedural,	
		Functional 42%	Under general anaesthesia	- Overall: ↑ CI ↓ mPAP ↓ PVR ↑ RVSWi
Kottenberg <i>et al.</i> (2014) [20]	81	Mixed 3%		- Subgroup analysis in patients with PH: ↓ mPAP ↓ PVR ↑ RVSWi ↓ PAWP
Crimi <i>et al.</i> (2018) [26]	3	Functional 100%	Before and 6 months after MitraClip,	↑ CI
		(case series of patients with end-stage CHF not eligible for HTx)	Conscious patients	↓ mPAP
				↓ PAWP ↓ PVR

CHF, cardiac heart failure; CI, cardiac index; CO, cardiac output; LVEDP, left ventricular end-diastolic pressure; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistances; RVSWi, right ventricular stroke work index.

MR reduction [35, 36]. Indeed, the residual MVPG after MitraClip implantation can influence long-term outcome proportionally to the degree of the MVPG. Neuss *et al.* found that MVPG > 5 mmHg after MitraClip implantation was associated with poor long-term outcomes [37]. Interestingly, also a reduction in mitral valve area (MVA) after MitraClip can influence patients' hemodynamics and outcome. In particular, Utsunomiya *et al.* showed that a post-procedural MVA ≤ 1.94 cm² was independently associated with a blunted post-procedural decrease in systolic PAP (sPAP), as well as with increased all-cause mortality and hospitalization for HF [36]. For these reasons, it is crucial to carefully assess MVPG during the intervention by echocardiography, thus guiding the operators for MitraClip repositioning and implantation.

MitraClip procedure requires inter-atrial trans-septal access of the left atrium with a steerable 24F sheath, sometimes leading to the development of a post-procedural iatrogenic atrial septal defect (iASD). The persistence of iASD has been described in up to 50% patients after interventional mitral valve repair [37]; however, the clinical and hemodynamic relevance of this iASD remains debated [38, 39]. Theoretically, a left-to-right shunting may increase RV preload and, in the presence of PH, this could further worsen RV loading and function. However, Eden *et al.* recently found that MitraClip did not induce a relevant inter-atrial left-to-right shunt through the iASD in a cohort of patients including

both degenerative and functional MR [39]. However, data on the hemodynamic effects of iASD are non-conclusive and the eventual indication for post-procedural iASD closure still remains unsettled.

Data on hemodynamic effects of MitraClip are limited. Indeed, most hemodynamic studies included both patients with degenerative and functional MR, in which the pathophysiologic and hemodynamic contribution of MR and, consequently, the hemodynamic effects of mitral valve intervention may be different. Furthermore, the hemodynamic effects of MitraClip have been collected acutely at the end of the procedure, during general anaesthesia and with different dosages of inotropes and vasopressors, which could influence measurements. Importantly, previous studies did not consider PH sub-types (isolated post-capillary and combined pre- and post-capillary PH), which have significant pathophysiologic differences and may have different hemodynamic responses to MitraClip. Beyond all these considerations, the promising results from the early studies focused on the hemodynamic modifications after MitraClip should prompt future research in collecting invasive data, in order to characterize preoperative PH and to identify specific hemodynamic effects for specific subsets of patients.

3. Prognostic impact of PH in patients treated with MitraClip

Data regarding the prognostic impact of pre-operative PH in MitraClip patients are limited. Randomized clinical trials focused on MitraClip intervention did not systematically investigate the prognostic impact of pre-operative PH [16, 17, 40]. The EVEREST II trial did not report outcomes based on pre-operative PH [16], while sPAP > 70 mmHg represented an exclusion criterion in the COAPT trial [17]. Literature on PH in MitraClip patients is mostly based on retrospective studies which evaluated the prognostic differences between patients with and without PH, using different cut-offs for PH definition, including both degenerative and functional MR, and reporting controversial results [41–44].

Matsumoto *et al.* [41] stratified 91 patients undergoing MitraClip into two groups based on pre-operative sPAP estimated with echocardiography: 50 mmHg was used as a cut-off to define patients with PH. The two groups showed similar reduction in sPAP, as well as similar safety and short-term mortality. However, all-cause mortality was higher in the PH-group at long-term follow-up (84.7% vs 63.0% at 2 years, 84.7% vs 45.4% at 3 years, log-rank P -value = 0.005). In the German Transcatheter Mitral valve Interventions (TRAMI) registry, including 643 patients, Tigges *et al.* [42] divided the study population into three groups based on sPAP (group 1 \leq 36 mmHg, group 2 from 37–50 mmHg, group 3 > 50 mmHg). They found no significant difference among the groups in 30-day mortality or 30-day major adverse cardiac events (MACCEs) defined as the composite of death, myocardial infarction and stroke. However, the study showed a significant difference in MACCEs among groups after 1 year (34.7% in group 3 vs 33.1% in group 2 vs 20.3% in group 1, $P < 0.01$). An analysis of the Society of Thoracic Surgery/American College of Cardiology Transcatheter Therapy (STS/ACC TVT) registry stratified 4071 patients treated with MitraClip into four groups based on pre-operative mPAP assessed invasively (group 1 < 25 mmHg, group 2 25–34 mmHg, group 3 35–44 mmHg, group 4 > 45 mmHg). In-hospital, 30-day and 1-year mortality all significantly and progressively worsened across the groups, with a hazard ratio of 1.05 every 5 mmHg increase in mPAP (95% CI: 1.01–1.09, $P = 0.017$) [43]. However, a retrospective analysis from the National Inpatient Sample (NIS), which studied 1037 patients undergoing MitraClip, found that in-hospital mortality and all the secondary outcomes (vascular complications, bleeding requiring transfusion, ischemic stroke, acute kidney injury requiring dialysis, deep venous thrombosis and infectious complications) were comparable between patients with and without pre-operative PH [44].

Recently, a post-hoc analysis of the COAPT trial reported the prognostic implication of echocardiographic evidence of elevated sPAP [45]. The Authors investigated the relationship between sPAP and prognosis by evaluating sPAP as a both continuous and dichotomized variable (50 mmHg was used as cut-off). Patients treated with MitraClip and opti-

mal medical therapy showed a lower incidence of the combined endpoint (death and HF-related hospitalization) at 2 years follow-up across sPAP values (when considered as continuous variable) and in both groups (group with sPAP < 50 mmHg: adjusted hazard ratio 0.59; 95% confidence interval: 0.42–0.82; group with sPAP > 50 mmHg: adjusted hazard ratio 0.49; 95% confidence interval: 0.32–0.72. P for interaction = 0.45) compared with patients treated only with medical therapy. Of note, a higher sPAP was associated with higher incidence of the composite endpoint at 2-years follow-up regardless of the intervention arm of the study, confirming that patients with PH are at higher risk of mortality and hospitalization for HF. This study is of great importance since, for the first time, it shows that MitraClip could improve prognosis in patients with functional MR and PH. Nevertheless, it is important to underline that the study defined PH based on sPAP evaluated by echocardiography, which represents an incomplete evaluation as it does not provide a complete characterization of the patients' hemodynamics and pathophysiology. Indeed, PH is not a single disease and it would be of utmost importance to understand whether clinical benefit after MitraClip is present in both patients with isolated post-capillary PH and with combined pre- and post-capillary PH, or it is limited to patients without elevated PVR. However, this study importantly expands the knowledge on the usefulness of MitraClip in patients with PH and should encourage research in this area.

4. Conclusions

MitraClip represents a promising therapeutic option for selected patients with MR at high surgical risk. For patients with pre-operative PH, there is no conclusive evidence in literature on the clinical and hemodynamic effects and the appropriateness of MitraClip. Despite the promising results shown by recent analyses focusing on hemodynamic and clinical outcomes, the available studies are methodologically heterogeneous and, specifically, they do not consider the different pathophysiological entities which are collected under the name of PH. Invasive hemodynamic data could provide a comprehensive hemodynamic evaluation and PH characterization in patients with MR, thus helping in identifying hemodynamic features showing probable benefit from MitraClip and supporting clinical evaluations for patient selection.

Author contributions

EA, AB, SC conceived and designed the content; AMM, LT, LA, AD, AS, GT, GC, wrote the manuscript; EA, AB, SC supervised and prepared the final version for submission.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors have no relationship with industry to disclose.

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