Curr Treat Options Cardio Med (2019) 21:60
DOI 10.1007/s11936-019-0768-6

Valvular Heart Disease (J Dal-Bianco, Section Editor)

Pulmonary Hypertension in Patients Eligible for Transcatheter Mitral Valve Repair: Prognostic Impact and Clinical Implications

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This article is part of the Topical Collection on *Valvular Heart Disease*

Keywords Mitral regurgitation · Transcutaneous mitral valve repair · MitraClip · Transcatheter mitral valve repair · Pulmonary hypertension

Abstract

Purpose of review Transcatheter edge-to-edge mitral valve repair (TMVr) has been increasingly used in the treatment of patients with severe symptomatic mitral regurgitation who are at high or prohibitive risk for surgical intervention. Pre-existing pulmonary hypertension is known to pertain worse prognosis for patients who are undergoing surgical intervention. The aim of this review is to discuss the current literature on the effects of pulmonary hypertension on the transcatheter edge-to-edge mitral valve repair outcomes.
Recent findings Large registry data in patients undergoing TMVr for treatment of severe mitral regurgitation reveal a significant negative impact of baseline pulmonary hypertension on post-procedural outcomes.
Summary Pulmonary hypertension is associated with increased mortality and heart failure readmissions in patients undergoing TMVr using MitraClip. Further prospective studies are needed to determine whether earlier intervention will improve clinical outcomes.

Published online: 10 September 2019

Introduction

An estimated 2.5 million people in the USA have moderate-to-severe mitral regurgitation (MR) [1]. Long-standing mitral regurgitation often leads to pulmonary hypertension (PH), which is typically a reflection of the hemodynamic severity of the valvular heart disease. PH is present in about 23% of the patients with severe primary MR [2] and in up to 64% of severely symptomatic patients. [3, 4••, 5] The true prevalence of PH in chronic secondary MR as a result of systolic or diastolic LV dysfunction is unknown. Over time, if left untreated, long-standing elevations in mean pulmonary pressure result in vasoconstriction and irreversible remodeling of the pulmonary arterioles. The use of diuretics can help improve symptoms. However, no medication has been proven to improve survival in patients with corrected MR and PH [6]. While the EuroSCORE includes PH as a risk factor when deriving the overall surgical risk score, the Society of Thoracic Surgery (STS) score does not. However, PH contributes to the decisions regarding candidacy for mitral valve surgery due to its effect on outcomes in surgical literature suggesting an increase in in-hospital mortality in patients with PH when they undergo mitral valve surgeries [3]. Despite differences in threshold for definition of PH in various studies, there is overall consensus that preoperative PH is associated with worse short- and long-term outcomes. Because of its impact on outcomes, pulmonary artery systolic pressure (PASP) > 50 mmHg at rest is a class IIa indication for surgery in patients with asymptomatic severe chronic primary MR [7].

Transcatheter mitral valve repair (TMVr) using a percutaneously implanted clip (MitraClip, Abbott Vascular) has emerged as an effective therapeutic intervention for patients who are at high risk for surgical mitral valve repair. The EVEREST II trial randomized patients with symptomatic moderate-to-severe and severe MR to percutaneous repair with MitraClip or conventional mitral surgery. In this cohort, the majority (73%) had primary MR and MitraClip was associated with reduced rates of adverse periprocedural events [8]. Similar improvements in symptoms, functional capacity, and quality of life were reported but the efficacy to reduce MR remained inferior to surgery. However, mid-term outcomes demonstrated that the increase in rate of recurrent MR was similar to surgical group beyond the first year [9]. Recent data from Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial demonstrate a mortality benefit of MitraClip repair versus guideline-directed medical therapy in carefully selected heart failure patients with severe secondary MR [10].

While pre-existing PH is known to be a predictor of outcomes after mitral valve surgery, the data on its impact on clinical outcomes after MitraClip are limited to observational studies. This article will review the current literature on the implications of pre-existing PH on outcomes after surgical and transcatheter mitral valve repair.

Prognostic importance of PH in mitral valve surgery

Most of the data regarding the effect of PH on outcomes after mitral valve surgery is retrospective and the definition of PH varies significantly between studies, some based on invasive measurements, while others use non-invasive PASP or right ventricular systolic pressure (RVSP) measurement by transthoracic echocardiography derived from the tricuspid regurgitation velocity. Regardless of the defined threshold, studies concur in their results that preoperative pulmonary hypertension is associated with worse outcomes after surgery. In chronic primary MR, preoperative PH was associated with significant reduction in postoperative left ventricular ejection fraction (LVEF) [11], persistence of PH and persistence of symptoms post-op [12], and increased operative mortality and long-term mortality even when PH was mild (defined as RVSP > 40 mmHg) [3]. These results were replicated in even low-risk patients who undergo surgery.

Mentias et al. reported on low-risk patients with primary MR and normal LVEF and showed that preoperative RVSP was associated with outcomes at 7 years. Out of the patients who died, 4% had RVSP < 35 mmHg, 12% had RVSP 35–50 mmHg, and 25% had RVSP > 50 mmHg. They also found that adding RVSP to the traditional STS score would improve their ability to predict poor prognosis better (integrated discrimination index 0.07; $p < 0.001$) [13•]. Similar patterns for mortality and major cardiac events were seen in patients with secondary MR undergoing mitral valve annuloplasty (multivariate HR 6.9; CI 1.1–44, $p = 0.04$) [14]. In the same study, Kainuma et al. showed that residual PH in patients who underwent restrictive annuloplasty was a major predictor of post-procedural adverse cardiac events, including readmission and heart failure.

Pathophysiological changes in patients with long-standing MR and PH

The pathogenesis of PH in patients with chronic (primary or secondary) MR involves a multitude of processes, dominated by an initially reversible transmission of increased left atrial pressure to the pulmonary system, which over time irreversibly alters the pulmonary vascular bed [4••, 5, 15]. Progressive structural alteration of the pulmonary vascular bed with increasing pulmonary vascular resistance (PVR) and increased pulmonary pressures ultimately result in right ventricular (RV) hypertrophy and dilation leading to poor prognosis [4••, 5, 15]. A timely intervention to treat MR is the key while still on the reversible portion of the PH curve and before irreversible RV dysfunction (Fig. 1a) [16].

Pathophysiological considerations of PH in transcatheter edge-to-edge mitral valve repair

In patients who are eligible for TMVr, several additional considerations apply (Fig. 1b). First, patients' characteristics in the current TMVr experience reflect a high-risk elderly population with severely symptomatic mitral regurgitation with some presenting at a later stage in their disease [8, 10, 17, 18]. Surgical series demonstrated a drop in mean PAP after surgical mitral valve repair with lower degrees of improvement in patients with more severe PH [3, 19]. One concern is that the structural alterations of the pulmonary vascular bed are already more pronounced in patients considered for TMVr than in some surgical series, with important prognostic implications.

Second, the positive effects of MR reduction on the left atrial pressure after successful TMVr with multiple clips can sometimes be blunted by an increase in transmitral pressure gradient [20–22]. Utsunomiya and colleagues found that a post-procedural mitral valve area ≤ 1.94 cm^2 was associated with less PH reduction and worse outcome [23]. This could be particularly relevant during exercise [24], similar to observations of increased exercise gradients and exercise pulmonary hypertension after restrictive annuloplasty for secondary MR [25–27]. In a prospective study

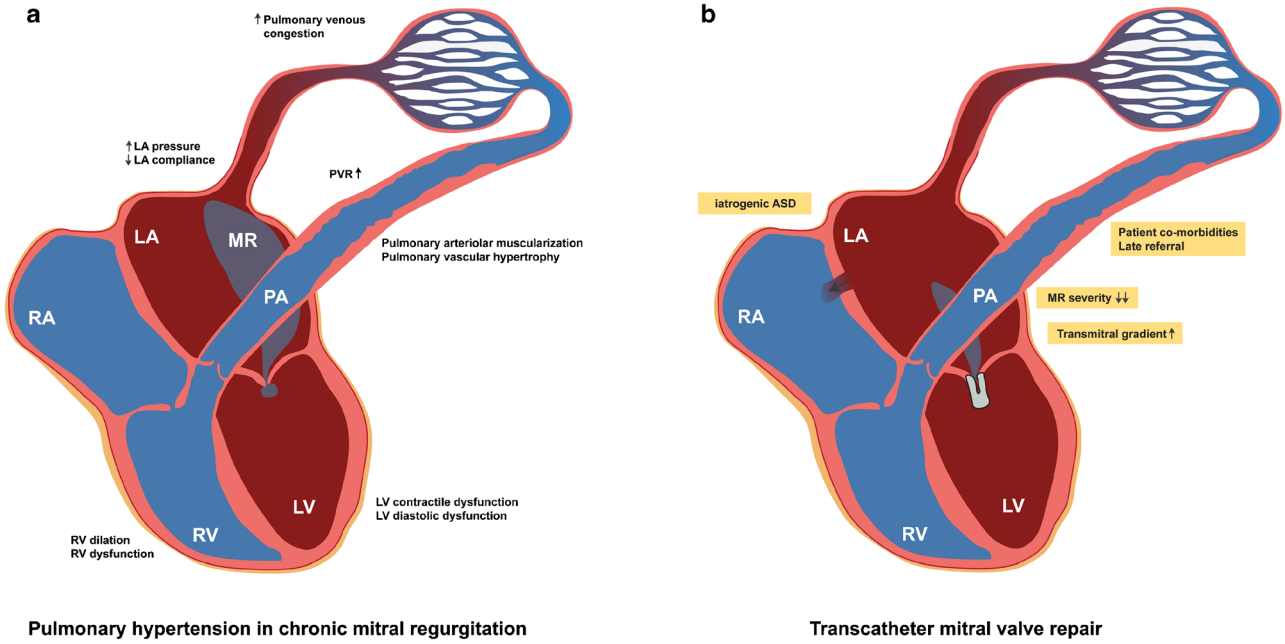

Fig. 1. Pathophysiology of pulmonary hypertension in mitral regurgitation, applied to transcatheter edge-to-edge mitral valve repair. **a** Chronic severe mitral regurgitation, over time, induces LV systolic and diastolic dysfunction, reduced left atrial compliance, and elevated left atrial pressure. Backward transmission of elevated left atrial pressures causes pulmonary venous congestion with passive pulmonary hypertension that (when chronic) can lead to structural changes in the distal pulmonary arterioles, with muscularization and medial hypertrophy, hence irreversibly increasing the pulmonary vascular resistance. Chronic right ventricular pressure overload resulting from pulmonary hypertension ultimately leads to RV dilation and dysfunction. **b** In transcatheter mitral valve repair (highlighted in yellow boxes): (1) late referral of patients at high risk of conventional interventions and with significant co-morbidities is likely associated with more prominent (irreversible) vascular remodeling and pulmonary vascular resistance; (2) the impact of the decrease in mitral regurgitation on left atrial pressures can be blunted by an increase in transmitral gradient after edge-to-edge repair; (3) the post-procedural iatrogenic atrium septal defect can impose increased preload to the right ventricle that is already exposed to high pulmonary vascular resistance, further stressing the right ventricular system. LA, left atrial; LV, left ventricle; PA, pulmonary artery; MR, mitral regurgitation; PVR, pulmonary vascular resistance; RA, right atrium; RV, right ventricle; ASD, atrium septum defect.

involving 31 secondary MR patients undergoing exercise echocardiography before and 6 months after MitraClip procedure, Van de Heyning et al. demonstrated significant hemodynamic improvement (systolic pulmonary artery pressure over cardiac output ratio) after MitraClip, both at rest and during exercise, related to successful MR reduction [28]. It remains to be determined whether exercise hemodynamic improvement is blunted in the subgroup of patients with high post-procedural transmitral gradients.

Finally, a post-procedural iatrogenic atrium septum defect (ASD) remains present in 25–50% of patients 6 months after the trans-septal procedure, typically with a degree of left-to-right shunting [29]. The clinical relevance of this ASD remains debated, either being a marker of persistently high LA pressures in advanced disease, or a mediator of disease causing progressive RV dilation and worse outcome [29, 30]. Theoretically, increased preload to a right ventricle already working against high pulmonary vascular resistance can further deteriorate the right ventricular function in those patients at highest risk. To date, it is unclear if and in whom closure of the ASD should be attempted.

Prognostic impact of pre-intervention PH in MitraClip patients

EVEREST II trial did not evaluate outcomes based on preoperative PASP and patients with significant PH (defined as RVSP >70 mmHg) were excluded from the COAPT trial. Therefore, current literature is based on the retrospective analysis of registries. In a single-center study, Matsumoto et al. reported on 91 patients with moderate-to-severe or severe functional MR who underwent MitraClip therapy and divided them into two groups on the basis of PASP (no PH: PASP <50 mmHg, and PH: PASP >50 mmHg on Doppler echocardiography). They showed reduction in pulmonary pressures and similar safety profile of the procedure including early mortality in the two groups. However, the PH group had significantly increased all-cause mortality at long-term follow-up (84.7% versus 63.0% at 2 years and 84.7% versus 45.4% at 3 years in the PH and non-PH groups, respectively; log-rank $p = 0.005$) despite the improvement in NYHA functional class and a trend towards improved reverse LV remodeling. In the PH group, despite an early improvement of PASP, PH did not resolve, likely owing to the irreversible pulmonary vascular remodeling [31].

Previous work by Tigges et al. on all patients ($n = 643$) in the German transcatheter mitral valve interventions (TRAMI) registry who had MitraClip repair did not find a statistically significant difference in 30-day major adverse cardiac or cardiovascular events (MACCEs: death, myocardial infarction, and stroke) in patients with advanced PH: 6.1% in group 1 (PASP ≤36 mmHg), 11.9% in group 2 (PASP of 37–50 mmHg), and 12.4% in group 3 (PASP of >50 mmHg), although there was a trend for higher adverse event rates with groups 2 and 3. However, 1-year follow-up MACCEs rates were significantly higher with advanced PH: 20.3% in group 1, 33.1% in group 2, and 34.7% group 3 ($p < 0.01$), but not re-hospitalization. Both groups 2 and 3 were independently predictive of mortality (group 2, HR 1.81, $p = 0.012$, group 3, HR 1.85, $p = 0.0092$) [32].

In a more recent analysis of the National Inpatient Sample (NIS), Ahmed et al. reported a retrospective study of 1037 patients who underwent TMVr with the MitraClip between 2011 and 2015 and reported on the immediate outcomes based on the presence of PH. The primary outcome was defined as the effect of PH on inpatient mortality and secondary outcomes included vascular complications requiring surgical intervention, bleeding requiring transfusion, ischemic strokes, respiratory complications, post-operative deep venous thrombosis/pulmonary embolism, acute kidney injury requiring dialysis, sepsis, and cardiac complications. Inpatient mortality rates were similar between the two groups (3.2% versus 2.1%, respectively; odds ratio [OR], 1.57; $p = 0.335$). Additionally, no significant differences were found between the PH and non-PH groups with regard to secondary outcomes or length of stay [33].

In addition, in the STS/ACC TVT registry, patients with mostly primary MR who underwent MitraClip repair across 232 US sites were stratified into 4 groups based on mean pulmonary artery pressure (group 1 no PH [<25 mmHg, $n = 1103$]; group 2 mild PH [25–34 mmHg, $n = 1399$]; group 3 moderate PH [35–44 mmHg, $n = 1011$]; group 4 severe PH [>45 mmHg, $n =$

558]). Out of the 2381 patients who had 1-year outcome data, in-hospital, 30-day, and 1-year mortality increased with worsening PH ($p < 0.001$ for all). One-year mortality was 20.5%, which was higher in those with worse PH (group 1 16.3%, group 2 19.8%, group 3 22.4%, group 4 27.8%, $p < 0.001$). Moreover, they showed that every 5-mmHg increase in mean pulmonary artery pressure has a hazard ratio of 1.05 for 1-year mortality (95% CI: 1.01–1.09, $p = 0.017$) [34••].

Finally, echocardiographic outcome data in the landmark COAPT trial demonstrate similar findings. In patients with heart failure and secondary MR treated with MitraClip, PASP at baseline (in mmHg) was the only independent echocardiographic predictor of worse outcome (HR 1.02, 95% CI 1.01, 1.04, $p = 0.005$). Intriguingly, the benefit of MitraClip versus medical therapy in terms of clinical outcome (24-month all-cause mortality or first HF hospitalization) remained significant even in the subgroup of patients with high PASP at baseline (≥ 43 mmHg, $n = 276$), with a hazard ratio of 0.62 (95% CI 0.45–0.84, $p = 0.79$ for interaction) [35].

Clinical implications

The current literature on the effect of pre-intervention PH on outcomes after TMVr is subject to significant variability in terms of etiology of MR (primary versus secondary), diagnostic method of PH (invasive versus non-invasive, use of systolic versus mean pulmonary arterial pressure), and differences in cut-off values. Therefore, this may explain some of the inconsistencies across all the studies. Nevertheless, although there are mixed outcomes in short term, the results obtained from registry data clearly suggest a negative long-term impact of PH in patients who are undergoing MitraClip procedures. One of the major limitations of the aforementioned studies is the lack of data on the pre-procedural right ventricular function, which has a significant prognostic implication in patients with PH [36, 37]. Furthermore, most of the outcome studies did not report data on post-procedure pulmonary pressure, so the efficacy of TMVr in reversing PH remains unclear. Some reports do suggest a decrease in pulmonary pressures after TMVr despite underlying pre-procedure PH [31, 38]. Finally, TMVr is feasible in patients with severe PH, but the negative impact on outcomes begs the question of whether patients should be referred earlier before PH develops, as it has been proposed in surgical mitral valve repair [13•]. Large randomized trials will hopefully better address this question.

Conclusions

Based on the available literature, PH, whether it is a consequence of MR (as seen in primary MR) or a consequence of adverse remodeling associated with cardiomyopathy (as seen in secondary MR), results in worse long-term outcomes in patients undergoing surgical or transcatheter valve

repair. Further prospective studies are needed to determine if earlier intervention improves clinical outcomes and whether TMVr is associated with better outcomes than surgery in patients with PH.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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