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Percutaneous mitral valve leaflet repair: ongoing directions and future perspectives

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- coronary artery disease
- degenerative valve
- mitral regurgitation
- mitral valve repair
- other

Abstract

Percutaneous mitral valve leaflet repair has revolutionised the treatment of heart failure patients with secondary mitral regurgitation. It also offers a valuable alternative to surgery for high-risk patients with degenerative disease. More than one device is now available for leaflet repair, broadening the indications and improving outcomes, as well as complicating the decision-making algorithms. In the last two years, several trials and registries have enriched the evidence around these procedures, although many questions remain open. Two major clinical trials have provided opposing evidence, confirming that this field of cardiovascular medicine remains controversial. Probably, the challenge remains with the human factor: achieving optimal outcomes remains a challenge, highly dependent on patient selection, timing and procedural details. Operator-dependent factors are emerging as a key element, not unexpectedly, to achieve procedural excellence. Besides large randomised controlled trials, a great deal of knowledge is emerging from real-world registries. This review focuses on what we can learn from registries and single-centre experiences as a complement to the large randomised trials.

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Abbreviations

COAPT Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation

EXPAND A Contemporary, Prospective Study Evaluating Real-world Experience of Performance and Safety for the Next Generation of MitraClip Devices

MITRA-FR Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation

MR mitral regurgitation

Introduction

It took 20 years to consolidate a dream. In 1998, the group of Ottavio Alfieri, the father of edge-to-edge therapy, published a research article on the midterm follow-up data on the "Alfieri technique" in diverse mitral regurgitation (MR) settings. With a sense of innovation in mind, but without a clear idea of the details of the execution, the final paragraph of the publication predicted the future of mitral interventions[1]: "eventually, the concept introduced by this type of repair can open the perspective of percutaneous correction of MR".

The Alfieri technique has been the object of controversy in the surgical community: "it creates a stenosis", "it is not physiologic", "it restricts leaflet motion", "it does not respect the anatomy", "I do not need it".

Exactly twenty years after this publication, the controversy continues, but in the interventional field. Two seminal trials have tested the clinical value of the MitraClip® (Abbott Vascular, Santa Clara, CA, USA) in the treatment of functional (secondary) MR, COAPT[2] and MITRA-FR[3]. Now, almost two years after the presentation of the results, the world still seems to be divided into two factions – those who believe and those who remain sceptical. The two trials had very different outcomes, the COAPT trial showing a benefit from the therapy, and the MITRA-FR trial unable to identify a solid advantage from the therapy. The differences in the outcomes can be found in the study design, the issue of sponsored trials, patient selection, technical performance, periprocedural treatment, and so on.

A number of recent publications have tried to shed some light on the differences between the COAPT and MITRA-FR results[4]: the trend is to find algorithms, to set thresholds, to discover the holy number that predicts life or death. The newly introduced concept of "disproportionate MR" is intriguing but needs to be tested in a clinical setting. Adamo et al recently retrospectively analysed the outcomes of "real-world" patients undergoing MitraClip implantation for secondary MR and found that echocardiographic parameters *per se*, including the presence of disproportionate MR, did not predict outcomes.

Given the multifactorial essence of prognosis of secondary MR in heart failure, prediction of success remains a challenge. The outcomes are influenced by many factors, most of them potentially confounding. There is no doubt that the outcomes of a procedure depend on patient selection. It is also clear that the synergy of medical therapy and the support of an experienced heart failure team are key to the long-term outcomes. What should be emphasised in the discussion is the value of the operators. Edge-to-edge percutaneous mitral repair is an operator-dependent procedure. The final haemodynamic outcomes of the procedure are influenced by the operator and institutional expertise[5,6]. This is not new in the field of mitral interventions, as surgeon expertise is highly influential in terms of clinical outcomes[7].

Managing the valve opening area: the procedural details that (could) make the difference

A transcatheter edge-to-edge repair is highly dependent on the expertise of the operator, the imager and all of the team. Although any procedure starts with a plan based on baseline anatomy, the need to revise and sometimes to overturn the plan and change strategy is not uncommon. This is due to the intrinsic dynamic nature of the procedure, which is influenced by the ongoing process of leaflet approximation. The main driver of decision making derives from the underlying limitation of the Alfieri technique: it is a compromise between correction of MR and reduction of the valve opening area. In addition, during the procedure, it is not uncommon to be confronted with new mechanisms of regurgitation caused either by the implantation (iatrogenic) or by previously unrecognised lesions.

Although post-procedural gradients have been associated with clinical outcomes, there is still uncertainty regarding the relative role of MR reduction and mild mitral stenosis. Since its introduction, an arbitrary threshold of 5 mmHg has been universally set as the maximal acceptable mean diastolic gradient following MitraClip procedures. On the other hand, while residual MR is assessed as a continuous variable, there is no reason to deal with residual stenosis as if it was a categorical event. Neuss et al first reported the impact of higher diastolic gradients following MitraClip therapy in a single-centre study[8]. They found that a gradient higher than 4.4 mmHg by echo (or greater than 5 mmHg invasively) was associated with significantly worse outcomes during one-year follow-up. The presence of an elevated gradient following the procedure has a similar prognostic value for either residual moderate or severe MR. Interestingly, the authors admit that invasive left heart pressure measurements were not performed at the beginning of their experience. Later, they implemented continuous pressure measuring with a pigtail in the left atrium.

Kuwata, from our group, reported the use of continuous direct left atrial pressure measurement during MitraClip procedures as an additional predictor of clinical outcomes[9]. In a small and selected population with prevalent degenerative MR, the overall left atrial pressure was reduced significantly as the result of the procedure. Left atrial pressure was indexed to the left ventricular systolic pressure to reduce the bias of afterload variability during the procedure. In multivariate Cox regression analysis, the intraprocedural decrease of the indexed left atrial pressure was an independent predictor of persisting symptoms (hazard ratio [HR] 1.5, 95% confidence interval [CI]: 1.0-2.1, p=0.005) and of the risk

of rehospitalisation (HR 3.4, 95% CI: 3.1-3.6, p=0.005) following the procedure. Interestingly, residual MR >2+ failed to be significantly associated with the clinical outcomes in the multivariable analysis. Increase of left atrial pressures was usually not related to residual MR. This publication also suggested the importance of using continuous pressure monitoring to guide decision making prior to clip release, using the reduction of mean left atrial pressure as an indicator of successful clip implantation. In our practice, we implemented this measurement to complement the echo-guided evaluation of valve function prior to clip implantation. As mentioned in our publication, the observation of a blunted v-wave pressure tracing may induce a misleading conclusion of a good outcome, while MR has been reduced at the expense of valve area. Therefore, the reduction of mean left atrial pressure, in addition to echocardiography, is today integrated in our recipe to discriminate between a satisfactory clip implantation and one that deserves a revision, prior to clip release.

On the other hand, a sub-analysis of the COAPT trial (Halaby, personal communication, ACC 2020) reported no relationship between post-MitraClip gradients and outcomes: patients in the highest gradient quartile experienced astonishingly fewer events (even if this was not statistically significant), compared with patients in the lower quartiles. The major limitation of this study is that the gradient was only measured by echo Doppler, which could be influenced by left ventricular diastolic function. Such discrepancies highlight the need for focused investigations in this field, including invasive measurements to understand better the impact of diastolic mitral function on outcomes.

Operator experience counts

Sometimes defining quality is difficult, particularly in the field of mitral interventions, where each valve has its own fingerprint, and the details driving the final outcomes are infinite.

Institutional and operator volumes are known factors influencing outcomes in mitral valve surgery[10]. MitraClip has been able to smooth the learning curve. The data from the TRAMI registry demonstrated similar safety outcomes in low- versus high-volume centres[11]. The TVT registry data also indicated that the learning curve to achieve a reasonable outcome (less than 3+ MR) after a MitraClip procedure is quite short[6]. On the other hand, to achieve a very good result (minimal MR), the learning curve appears to be longer and there is a trend towards continuous improvement even after more than 200 procedures. This is not surprising, due to multiple factors: as experience grows, the operator tends to tackle more complex cases. On the other hand cumulative experience helps to avoid complications and apply the best tactics to achieve haemodynamic success… just as with surgery. However, acute outcomes are not everything. Durability in this field counts.

Achieving durability: towards the surgical standards

The MitraClip was introduced as an alternative to surgery for high-risk surgical candidates. However, as the experience has grown, the idea of expanding indications becomes more realistic. Nevertheless, the standard bar of surgery, particularly in the field of primary MR, is high.

Ideally, transcatheter leaflet repair should not only reduce MR, without significant gradient, but also be durable. One of the issues of durability is the absence of annuloplasty. In surgery, the absence of annuloplasty is associated with shorter durability[12]. On some occasions, leaflet repair has been associated with percutaneous annuloplasty (also called the Combo procedure[13]). Annular dimensions are also influenced by clip implantation, both as a result of immediate tension on the leaflets[14], and as a result of reverse remodelling. However, annuloplasty could be useful in selected patients with annulus-to-leaflet mismatch[15-17] in which a "surgery-like" outcome is expected.

The specific essence of durability after MitraClip procedures is the quality of the grasping, typically assessed by "leaflet insertion". Leaflet insertion is best evaluated during the grasping sequence, before the clip is closed, to avoid image artefact. Another option, recently described by Tang et al[18], involves the measurement of the leaflets before and after implantation to compare the native length of the leaflets to the residual length after the grasping. Insufficient grasping could be followed by immediate or delayed single leaflet attachment (SLA). SLA is observed in 1-2% of cases, according to the TVT and the TRAMI registries, and can be difficult to manage[5,19]. The recent introduction of the MitraClip XTR system has shown that the use of a longer clip device in short leaflets could be associated with higher risk of SLA. If a short leaflet (or rolled leaflet) does not reach the base of the clip arm, then some grippers might not be in contact with the leaflets. Therefore, it is mandatory to respect the minimal length of 6 mm for the NTR system and 9 mm for the XTR system. Another possible cause of reduced durability is leaflet lesions (tears, perforations, chordal ruptures, etc.). These can occur immediately after clip implantation or be delayed days or weeks after the implant. Distortion of the valve symmetry could increase the risk of delayed leaflet lesion, due to increased tension on the tissue; therefore, extreme attention should be applied to proper clip orientation in order to avoid any distortion.

Leaflet lesions are very difficult to treat[20-23]. In some cases a second MitraClip intervention can improve the haemodynamics (very rare circumstance), in some cases occlusion devices have been used[24], but in the end most of the patients with leaflet lesions require a surgical revision, when operable. Therefore, everything should be done to avoid this serious (although rare) complication – patient selection (careful in case of leaflet or annulus calcification), clip selection and proper handling (dive as you close the device, particularly with the XTR system).

Last but not least, early and long-term outcomes are strongly related to periprocedural care and appropriate heart failure therapy. Drug-device interaction is an important topic that requires more focus in the near future.

Two emerging indications

As new centres are starting transcatheter mitral valve programmes, as expertise grows, new indications for leaflet repair are emerging.

Recently, a number of cases of acute mitral insufficiency following acute myocardial infarction with[25] or without[26] papillary muscle rupture have been reported. Operative mortality after surgical repair/replacement is very high[27]; therefore, a catheter-based alternative, as a definitive solution or as a bridge to surgery, is very appealing. Initial results are very promising. Given the high-risk setting, percutaneous leaflet repair may become the first-line option in most patients[28].

Another interesting indication for leaflet repair is the treatment of systolic anterior motion in different settings, including the context of hypertrophic obstructive cardiomyopathy[29].

The emerging technologies

With the introduction of new models of the MitraClip and of alternative devices for leaflet approximation, operators are confronted with more options, but also with some new challenges. Recently, the MitraClip device family has been enhanced with a model with longer arms, the XTR clip[30,31], to expand indications and to improve the efficiency of clip implantation in complex anatomies. The MitraClip EXPAND Study (A Contemporary, Prospective Study Evaluating Real-world Experience of Performance and Safety for the Next Generation of MitraClip Devices) was designed to confirm the safety and performance of the MitraClip NTR system and MitraClip XTR system and to collect clinical information to guide selection strategies for clip selection (ClinicalTrials.gov Identifier: NCT03502811). Soon after the introduction in clinical use, the EXPAND Steering Committee provided clip selection recommendations based on the following anatomical considerations: the presence of longer/redundant leaflets, large flail gaps and lesions in the area of A2P2 would favour a clip with longer arms, while the presence of short/restricted leaflets, calcification of the annulus, smaller area or lesions in the commissures would favour a shorter clip version. Their initial assumptions have come face to face with "real-world" evidence from worldwide users. In general, the recommendations have been confirmed with the exclusion of the small baseline valve area. Smaller valve area was considered a relative contraindication for the XTR system with the reservation that longer arms could reduce leaflet mobility and induce stenosis. On the other hand, according to the EXPAND registry, in this subset of patients an XTR system has been used more frequently (Maisano, on behalf of the EXPAND study group, personal communication, PCR e-Course 2020). This finding, although surprising, can be related to the higher efficiency of the XTR system and the possibility of achieving greater degrees of MR reduction with single clip implantation in the setting of a small baseline valve area.

The initial results of the EXPAND registry also suggest that the greatest benefit of the XTR is to be found mainly in the primary MR setting. Both the XTR and the NTR have similar safety profiles, including the risk of SLA and leaflet lesions. Interestingly, the overall echocardiographic core lab-adjudicated outcomes are superior to previous studies, suggesting that the introduction of two sizes has improved the efficacy of the treatment platform. More recently, Abbott has introduced a new generation of the MitraClip (generation 4), including independent leaflet grasping, four sizes (long and short arms, normal and wider grasping surface), and continuous left atrial pressure monitoring capability. Safety and effectiveness studies are ongoing to analyse further the value of these novelties.

However, leaflet repair is possible not only with a clip device. In 2017, Edwards Lifesciences (Irvine, CA, USA) introduced the PASCAL system[32], a nitinol-based leaflet approximation device that allows independent clasping of leaflets, induces reduced stress on leaflets, is simple to reposition and retrieve, and includes a unique central spacer designed to block more jet and to minimise residual MR. The CLASP study demonstrated a very promising performance of the system: a large majority of patients had no or minimal MR at 30 days from the implant.

Other leaflet approximation platforms are under evaluation or in the early clinical trial phase.

Conclusion

A long road connects the initial intuition of Professor Alfieri and the current use and future perspective of mitral valve repair. Randomised trials and several real-world registries have been instrumental in supporting further indications for percutaneous edge-to-edge repair in different clinical scenarios. Further implementation of technological advances and operator expertise will surely improve outcomes and determine the role of these procedures in the future.

Conflict of interest statement

F. Maisano has received grant and/or research support from Abbott, Medtronic, Edwards Lifesciences, Biotronik, Boston Scientific Corporation, NVT, and Terumo, consulting fees and honoraria from Abbott, Medtronic, Edwards Lifesciences, SwissVortex, Perifect, Xeltis, Transseptal Solutions, Cardiovalve, and Magenta, has royalty income/IP rights with Edwards Lifesciences, and is a shareholder (including share options) of CardioGard, Magenta, SwissVortex, Transseptal Solutions, Occlufit, 4Tech, and Perifect. M. Taramasso has received consulting fees or honoraria from Abbott, Boston Scientific, 4Tech, Edwards Lifesciences, CoreMedic, Mitraltech, and SwissVortex, and is a shareholder in 4Tech.

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