Personalised surgical treatment of functional mitral regurgitation

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Chapter 9

Summary, discussion, clinical implications and future perspectives

Summary

Functional mitral regurgitation (MR) – also referred to as secondary MR – is a disease condition which results from a combination of annular dilatation, papillary muscle displacement with increased systolic leaflet tethering, and reduced closing forces, due to regional or global left ventricular (LV) remodelling. Functional MR is a common phenomenon and can be classified as either ischaemic or non-ischaemic, based on aetiology of LV remodelling. Regardless of aetiology, functional MR carries a poor prognosis.

The primary step in the treatment of patients with functional MR consists of optimal medical and device therapy. In patients with persistence of MR despite optimal medical and device therapy, surgical treatment options can be considered. Over the past decades, many surgical treatment options have been developed, of which mitral valve repair by implantation of a restrictive mitral annuloplasty (RMA) ring forms the mainstay.

In this thesis an integrated medico-surgical approach for patients with functional MR was examined, consisting of optimal medical and device therapy combined with RMA, and additional surgical interventions when indicated. The indication for each surgical intervention was determined after careful balancing of treatment options by the multidisciplinary Heart Team – consisting of heart failure specialists, interventional cardiologists, arrhythmia cardiologists and cardiac surgeons. Focus of this thesis was to determine (long-term) clinical and echocardiographic outcomes after this approach and to identify which patients are (un)likely to benefit from it.

Chapter 2 provides an overview of the surgical and interventional treatment options that have been developed for patients with functional MR over the past decades. Mitral valve repair by restrictive mitral annuloplasty forms the cornerstone in the surgical treatment of functional MR. Additional (sub)valvular procedures – such as an edge-to-edge repair, RING + STRING or papillary muscle approximation – have been introduced to reduce the risk of recurrence of MR after mitral valve repair and can be useful for patients who meet criteria for an increased failure rate after RMA alone. For these patients, mitral valve replacement may also be considered instead. Furthermore, transcatheter edge-to-edge repair (MitraClip implantation) has gained ground for the treatment of functional MR in patients who are ineligible for mitral valve surgery and meet specific criteria. Finally, left ventricular assist device implantation (LVAD) may be considered in patients with functional MR in whom LV dysfunction is too advanced, and who most likely will not benefit from any mitral valve procedure. For each of these treatment options, the rationale, indication, surgical technique, results and limitations are discussed by experts in the field.

Chapter 3 comments on the two-year results of the Cardio-Thoracic Surgery Network (CTSN) trial. This randomized controlled trial compared mitral valve repair versus mitral valve replacement for severe ischaemic MR, and demonstrated no between-group differences with regard to LV reverse remodelling (primary end-point) or survival, but recurrent MR was more frequently observed after mitral valve repair. These findings may lead to the conclusion that mitral valve replacement is better than mitral valve repair. However, recurrence of MR was observed in 30% of patientswho underwent repair only 30 days after surgery, which should be regarded as residual MR due to inadequate surgical technique rather than true recurrent MR. Furthermore, patients with a successful mitral valve repair (i.e. without recurrent MR) had a 30% reduction in LV end-systolic volume, whereas reverse remodelling was absent after mitral valve replacement. These points should be taken into account when translating the results of this trial into conclusions for clinical practice.

The results of the CTSN trial described in Chapter 3 (i.e. no difference in LV reverse remodelling or survival between mitral valve repair and mitral valve replacement, despite a 59% recurrent MR rate 2 years after mitral valve repair versus 4% after replacement), raised the question: does recurrent MR, in terms of clinical outcome, matter at all?

Chapter 4 evaluates long-term clinical and echocardiographic outcomes in 261 patients who underwent RMA and revascularization for moderate to severe ischaemic MR according to a structured surgical protocol, focusing on the mortality-adjusted incidence, clinical impact, and determinants of recurrent MR. The cumulative incidence of recurrent MR ≥ grade 2, assessed by competing risk analysis, was low, with 9.6 ± 1.8 at 1-year, 20.3 ± 2.5% at 5-year, and 27.6 ± 2.9% at 10-year follow-up. Cumulative survival was favourable with 86% [81 – 90] at 1-year, 67% [61 – 73] at 5-year and 46% [39 – 53] at 10-year follow-up. Age, preoperative New York Heart Association Class III or IV, a history of renal failure, and recurrence of MR expressed as a time-dependent variable [HR 3.28 (1.87 – 5.75), p <0.001], were independently associated with an increased mortality risk. These findings indicate that RMA with revascularization for ischaemic MR results in a low incidence of recurrent MR with favourable clinical outcome up to 10 years after surgery. However, development of recurrent MR at any moment after surgery is independently associated with an increased risk for mortality. Female gender, a history of ST-elevation myocardial infarction, a preoperative QRS duration ≥120 ms, a higher preoperative MR grade, and a higher preoperative indexed LV end-systolic volume were in-dependently associated with an increased likelihood of recurrent MR.

In non-ischaemic MR – as opposed to ischaemic MR – the underlying ventricular disease itself cannot be addressed. Consequently, treatment options for patients with MR due to non-

ischaemic cardiomyopathy who remain symptomatic despite optimal medical and device therapy, are limited and consist of mitral valve repair, LVAD implantation or heart transplantation (HTx).

In chapter 5 long-term outcomes are described of 77 patients with non-ischaemic MR and symptomatic heart failure, who underwent an integrated approach of mitral valve repair with concomitant procedures – tricuspid valve repair, implantation of a cardiac support device (CSD) and arrhythmia surgery – when indicated by the Heart Team. Left ventricular reverse remodelling was observed in 38% of patients and recurrent MR in 20% of patients at mid-term follow-up. The absence of reverse remodelling and presence of recurrent MR – which were highly related – were significantly associated with worse HTx-free survival. HTx-free survival 1 and 3 years after mid-term follow-up was favourable in patients with LV reverse remodelling (100% and 88 ± 6%), significantly worse but still acceptable in patients without LV reverse remodelling and without recurrent MR (83 ± 7% and 68 ± 8%), and extremely poor in patients without LV reverse remodelling and with recurrent MR (49 ± 14% and 33 ± 13%). None of the baseline variables in this study was predictive of LV reverse remodelling and a history of ventricular tachyarrhythmia was the only independent predictor of recurrent MR. These findings emphasize the need for close echocardiographic monitoring after surgery, to timely identify the subgroup of patients who do not show LV reverse remodelling and develop recurrence of MR, in order to re-evaluate additional treatment options and improve their prognosis.

Long-term effects of advanced surgery for patients with refractory heart failure due to a post-infarction anteroseptal aneurysm were evaluated in chapter 6. In this chapter, outcomes of 159 patients who underwent left ventricular reconstruction (LVR) with concomitant procedures – mitral valve repair, tricuspid valve repair, coronary revascularization and arrhythmia surgery – when indicated, were described. Mid-term echocardiography demonstrated decreased indexed LV end-systolic volumes (89 ± 42 ml/m^2 preoperatively to 51 ± 18 mL/m^2 at mid-term, p <0.001) and absence of MR ≥ grade 2 in all patients. Event-free survival was 83 ± 3% at 1-year, 68 ± 4% at 5-year and 46 ± 4% at 10-year follow-up. Preoperative wall motion score index (WMSI, a measure of LV systolic function), presence of MR ≥ grade 2, age and a longer time interval after myocardial infarction, proved to be independently associated with adverse event-free survival. Event-free survival was favourable in patients with WMSI <2.5 and significantly worse in patients with WMSI ≥2.5. In both groups, the presence of preoperative MR ≥ grade 2 negatively affects event-free survival, despite successful correction of MR. These results

demonstrate that preoperative risk stratification by WMSI and MR can support the Heart Team in choosing the optimal surgical strategy for these patients.

Restrictive mitral annuloplasty has raised concerns, in that extensive reduction of the mitral annular dimension could result in obstruction to antegrade mitral flow and might induce a functional mitral stenosis at rest, that may become even more pronounced during exercise.

Chapter 7 assesses mitral valve exercise haemodynamics in 32 patients after RMA for functional MR. In this study population, mitral valve area (MVA) was found to be dynamic during exercise, and to differ between individual patients: MVA increased in 25 patients and decreased in 7 patients. Change in MVA in response to exercise proved to be related to the extent of LV geometrical and functional changes after surgery. The group of patients with an increased MVA in response to exercise showed LV reverse remodelling and a significant myocardial contractile reserve, whereas the group of patients with a decreased MVA during exercise was characterized by absence of LV reverse remodelling and limited myocardial contractile reserve. Furthermore, a decreased MVA proved to be strongly associated with a disproportionally higher increase in mean PAP with respect to cardiac output – suggesting that a decreased MVA during exercise has significant haemodynamic impact – and worse (event-free) survival, compared to patients with an increased MVA during exercise.

Each cardiac operation carries peri-operative risks, which should be taken into account when considering an intervention. Vasoplegia – defined as a state of low systemic vascular resistance despite normal or high cardiac output and the need for vasopressor therapy, due to an imbalance of vasodilator and vasopressor mechanisms – is an important determinant for adverse postoperative outcome in patients undergoing cardiac surgery.

In chapter 8, the incidence, clinical impact and preoperative predictors of vasoplegia after RMA are determined. Vasoplegia was observed in 19% of patients after RMA and its incidence was independent of the aetiology of functional MR. Patients who developed vasoplegia had significantly longer intensive care unit admissions and a significantly increased 30- and 90-day mortality. Several preoperative patient characteristics, which seem mainly related to the severity of heart failure – no beta-blocker use, no hypertension, a lower creatinine clearance and anaemia – proved to be associated with an increased risk of postoperative vasoplegia, as was a prolonged cardiopulmonary bypass time. These findings indicate that the likelihood of developing vasoplegia after surgery should be taken into account by the Heart Team when deciding on whether or not to perform surgery. Furthermore, preoperative optimisation of haemodynamic and renal function could potentially reduce the risk of vasoplegia.

Discussion

Over the past decades, major advances have been made in the treatment of functional MR, and several surgical and interventional treatment options have been developed. Despite these developments, the optimal treatment strategy for patients with functional MR remains a topic of debate, since randomized controlled trials are limited in number and have contradictory outcomes. These conflicting results are most likely explained by the fact that functional MR comprises a highly heterogeneous disease for which a "one-size-fits-all" approach does not suffice. Thus, a patient-tailored approach seems crucial for improving the outcomes of patients with functional MR.

Mitral valve repair by RMA forms the cornerstone of the surgical treatment of functional MR. The studies in the present thesis examined (long-term) clinical and echocardiographic outcomes after restrictive mitral annuloplasty – with concomitant procedures when indicated. The goal of this thesis was to identify patients likely or unlikely to benefit from this approach, in order to personalise the treatment strategy and optimise outcomes for each patient with functional MR.

To accomplish this goal, we aimed at:
1) unravelling the mechanisms attributing to outcomes after RMA surgery;
2) identifying preoperative predictors for outcomes after RMA surgery.

Mechanisms attributing to outcomes after restrictive mitral annuloplasty

Early outcomes after RMA surgery have proven to be favourable. The addition of mitral valve repair to CABG in patients with ischaemic MR did not increase the rate of perioperative complications compared to CABG alone in randomized controlled trials.[1, 2] Adverse early outcomes after RMA surgery may be affected by development of postoperative vasoplegia.

Adverse long-term outcomes may be associated with failure to restore mitral valve competence and/or failure to initiate and sustain LV reverse remodelling – the two major aims of the treatment of patients with functional MR. In addition, implantation of an undersized ring reduces mitral annular dimension and might lead to induction of a (functional) mitral valve stenosis after RMA, which may affect long-term clinical outcomes as well.

In this thesis, the role of each of these mechanisms in determining clinical outcomes after RMA surgery was assessed.

Vasoplegia

Postoperative vasoplegia is associated with adverse early outcomes after cardiac surgery, especially in patients with heart failure and in patients undergoing valvular procedures.[3-5] Adverse early outcomes after RMA surgery may therefore be partially related to vasoplegia as well.

In this thesis, the incidence of vasoplegia after RMA surgery was 19%. Patients who developed vasoplegia after surgery had a significantly longer duration of intensive care unit stay and a higher 30-day mortality rate (22% in vasoplegic patients versus 2% in non-vasoplegica patients, $p < 0.001$).

These findings demonstrate that vasoplegia is an important determinant of adverse early outcomes after RMA surgery. The risk for postoperative vasoplegia should therefore be one of the factors for the Heart Team to consider when deciding on whether or not to refer the patient for surgery. For these patients, potential adjustable risk factors (as described) should be modified, although in general preventive and therapeutic treatment options for vasoplegia (apart from symptomatic treatment) are limited. These results stress the need for developing such direct treatment options in order to improve early outcome after RMA surgery.

Recurrence of mitral regurgitation and left ventricular (reverse) remodelling

Restoration of mitral valve competence resolves the volume overload that ensues with MR and may break the cycle of progressive LV remodelling and worsening MR. Recurrence of MR after RMA leads right back to this vicious cycle and is therefore thought to negatively affect clinical outcome.

Studies in this thesis demonstrated that RMA following a structured surgical approach results in a low incidence of recurrent MR in both patients with ischaemic MR (Chapter 4 and Chapter 6) and non-ischaemic MR (Chapter 5). The incidence of recurrent MR observed in this thesis was far lower than that observed in many other studies.[6-9] However, recurrence of MR 18 months after RMA in non-ischaemic MR patients proved to be independently associated with absence of LV reverse remodelling (Chapter 5), while recurrence of MR in ischaemic MR patients occurring at any moment during the course of follow-up was related to poor long-term clinical outcome, including an increased risk of reoperation, heart failure readmissions, and death (Chapter 4).

These studies emphasize the need for durable correction of MR and demonstrate that RMA can result in such durable correction in a majority of patients when performed by a structured surgical approach, consisting of implantation of a complete semi-rigid annuloplasty ring,

stringent downsizing by two ring sizes, and aiming at absence of MR and a mitral leaflet coaptation length of at least 8 mm on intra-operative echocardiography. Residual MR was observed in only 3-4% of patients at discharge in this thesis (Chapter 4 and Chapter 5), whereas others reported considerable incidences of MR early after surgery (e.g. 30% within 30-days after surgery in the CTSN trial, where the mean number of repairs per centre was 5.2).[8, 9] MR in the early phase after surgery cannot be explained by disease progression (LV dilatation with increased mitral leaflet tethering) and should be considered residual MR due to suboptimal repair rather than true recurrent MR. Therefore, RMA surgery should only be performed in specialized centres with expertise in valvular heart disease and heart failure.

Left ventricular remodelling is the primary cause of functional MR. Initiating sustained LV reverse remodelling is therefore a key element in the treatment of functional MR.

In the present thesis, the clinical impact of LV reverse remodelling after RMA surgery was assessed (Chapter 5). Patients with LV reverse remodelling (defined as ≥15% decrease in indexed left ventricular end-systolic volume) proved to have beneficial clinical outcome, including a low risk of heart failure readmissions and beneficial long-term HTx-free survival. However, patients in whom LV reverse remodelling was absent, had an increased risk of recurrent MR and heart failure readmissions, and poor HTx-free survival.

These findings confirm that the LV plays a crucial role, not only in the development, but also as a target in the treatment of functional MR, and underline that LV reverse remodelling is of major importance for obtaining beneficial clinical outcomes after surgery.

The studies in this thesis clearly demonstrate that absence of LV reverse remodelling and recurrence of MR are both important mechanisms leading to adverse clinical outcome after RMA surgery. In line with literature[10], recurrence of MR and absence of LV reverse remodelling proved to be highly associated (Chapter 5). The simultaneous observation of recurrent MR and absence of LV reverse remodelling does not elucidate the causality between the two, since they are interrelated in a complex way. Residual or recurrent MR may lead to absence of LV reverse remodelling, whereas the absence of LV reverse remodelling may lead to recurrence of MR – with both scenarios leading to adverse clinical outcome. It is important to appreciate that the patients who developed MR after surgery in this thesis had true recurrent MR (developed in the course of follow-up), rather than residual MR due to improper correction of MR during surgery. As such, it is most likely that progression of LV disease is the primary determinant of recurrent MR, which develops when ongoing LV remodelling causes further papillary muscle displacement with progressive mitral leaflet tethering. Once recurrent MR is present, the

ensuing volume overload poses additional strain on an already fragile LV, further exacerbating the remodelling process and consequently deteriorating clinical outcome.

The hypothesis that the extent of LV dysfunction (in other words, the inability for LV reverse remodelling to occur) rather than recurrence of MR is the primary determinant of adverse clinical outcome after RMA surgery is supported by the results of the CTSN trial. In this trial there was no difference in LV reverse remodelling or survival between patients who underwent mitral valve repair versus mitral valve replacement, despite a significantly higher incidence of recurrent MR after mitral valve repair.[8, 9] These results indicate that completely resolving functional MR – which is obtained by replacing the mitral valve – does not always lead to LV reverse remodelling. This may be explained by considering that a subgroup of patients may already be at a stage of LV disease where simply resolving the volume overload that ensues with MR is insufficient to halt or reverse LV remodelling – and better clinical outcome is no longer attainable at the time of surgery. The fact that in this trail the patients after mitral valve replacement were not showing more LV reverse remodelling than patients after mitral valve repair, who had in 60% recurrence of MR, also poses the question whether the replacement itself may have a negative impact on LV reverse remodelling.

Functional mitral stenosis

Restrictive mitral annuloplasty enforces mitral leaflet coaptation by reducing the mitral annular dimension. However, such reduction might obstruct antegrade mitral flow, resulting in a mitral stenosis with potential clinical consequences.[11] Such (functional) stenosis would be even more pronounced during exercise.

In this thesis (Chapter 7), MVA during exercise after RMA proved to be dynamic: MVA increased in the majority of patients but decreased in a subgroup of patients. A decreased MVA in response to exercise was associated with LV geometry (absence of LV reverse remodelling) and function (limited myocardial contractile reserve) after surgery. Furthermore, a decreased MVA during exercise was strongly related to a disproportionate increase in mean PAP with respect to the rise in cardiac output and to significantly worse event-free survival.

The fact that MVA is dynamic during exercise – despite implantation of a semi-rigid annuloplasty ring with a fixed orifice area – suggests that MVA is determined at level of the leaflet tips and contradicts that a functional mitral stenosis simply results from implantation of a downsized annuloplasty ring. Indeed, earlier studies demonstrated that MVA during exercise after RMA surgery is associated with diastolic anterior leaflet tethering, with increased tethering leading to decreased MVA and vice versa.[12, 13] Furthermore, the association of a decreased MVA with adverse LV geometry and function implies that progressive mitral leaflet

tethering due to ongoing LV remodelling may not only lead to incomplete mitral closure during systole (i.e. recurrence of MR), but also to incomplete mitral leaflet opening during diastole (i.e. functional mitral stenosis). Once again, these findings emphasize the importance of LV reverse remodelling for beneficial outcomes after RMA surgery. The role of a functional mitral stenosis after RMA surgery, independently of LV geometry and function, should be further investigated in larger studies to draw any definitive conclusions regarding its clinical implications.

Preoperative predictors for outcomes after restrictive mitral annuloplasty

Ideally, patients who are (un)likely to benefit from RMA surgery are selected preoperatively. Given the clinical impact of vasoplegia, recurrence of MR and absence of LV reverse remodelling, we aimed to identify preoperative predictors for each of these factors and for mortality throughout this thesis (Chapters 4, 5, 6 and 8).

Several preoperative predictors (no prior hypertension, a lower creatinine clearance, no beta-blocker use and anaemia), and longer cardiopulmonary bypass time, were associated with an increased risk for vasoplegia and adverse early outcomes (Chapter 8). These predictors seem to be primarily markers of patients with a fragile balance of the vascular systems, making them less able to compensate for haemodynamic disturbances associated with the systemic inflammatory response following cardiopulmonary bypass and major surgery. This thesis presents a first step in preoperative identification of patients at risk for vasoplegia after RMA surgery. However, further research is needed to unravel the pathophysiologic mechanisms causing vasoplegia and to identify more specific preoperative predictors for patients at risk for vasoplegia, and possible preventive strategies and/or treatment options.

Female gender, a history of STEMI, a preoperative QRS duration ≥120 ms, a higher preoperative MR grade and higher indexed LV end-systolic volume were predictors for recurrent ischaemic MR after RMA surgery (Chapter 4). A history of ventricular tachyarrhythmias was the only predictor of recurrent MR after RMA surgery in patients with non-ischaemic MR. For this subset of patients no preoperative predictors – including preoperative parameters reflecting the extent of LV remodelling – could be identified to predict LV reverse remodelling (Chapter 5). This may be due to the limited study population. However, the personalised use of a CSD in patients with more advanced LV remodelling (i.e. preoperative LV end-diastolic diameter ≥65 mm or indexed LV end-diastolic diameter ≥30 mm/m^2) could also explain this, since implantation of a CSD has additional beneficial effect on LV reverse remodelling and may consequently mitigate the deleterious effect of advanced LV remodelling in this subgroup of patients. Predictors for poor survival after RMA for ischaemic MR were age, preoperative New

York Heart Association class III or IV, renal failure and recurrence of MR at any time during follow-up (Chapter 4). A preoperative WMSI ≥2.5, preoperative MR ≥ grade 2 and a longer time interval after myocardial infarction were predictors for adverse event-free survival after LVR – and concomitant RMA when indicated – for patients with heart failure due to an anteroseptal LV aneurysm (Chapter 6).

In line with literature, most predictors for recurrent MR and adverse clinical outcome in this thesis are related to the degree of MR, extent of LV remodelling (LV size, geometry and function) or severity and duration of heart failure symptoms. These parameters provide useful information and may help the Heart Team in their decision making process. However, prediction of the potential to reverse LV remodelling – which seems crucial for recovery after RMA surgery – remains difficult. In the absence of such predictors, close echocardiographic monitoring after surgery is warranted – focusing on absence of LV reverse remodelling and recurrence of MR – to allow early identification of patients at risk for adverse clinical outcomes. These patients should periodically be re-evaluated by the Heart Team to assess the possibilities and appropriateness of additional procedures (such as LVAD or HTx).

Clinical implications and future perspectives

In this thesis we have demonstrated that a personalised medico-surgical approach – consisting of optimal medical and device therapy, RMA surgery, and concomitant surgical procedures when indicated – results in beneficial (long-term) clinical and echocardiographic outcomes in the vast majority of patients with functional MR. The subgroup of patients for which this approach does not offer a definitive solution proved to be characterized by the occurrence of perioperative vasoplegia (which increases the risk of adverse early outcome after surgery), and by the development of recurrence of MR and/or absence of LV reverse remodelling (both leading to adverse long-term outcome after surgery). Several preoperative predictors for patients at increased risk for vasoplegia, recurrent MR and adverse clinical outcome after RMA surgery have been identified in this thesis. These findings should be translated into clinical practice and be incorporated into the decision-making process in the Heart Team in order to further improve outcomes of patients with functional MR.

The overall favourable long-term clinical and echocardiographic outcomes observed in this thesis underline that care for patients with persistent functional MR despite optimal medical and device therapy should be concentrated in specialized centres with expertise in valvular heart disease and heart failure. In these centres a dedicated multidisciplinary Heart Team should carefully balance the treatment options for each patient, taking into account the risk for

vasoplegia, recurrence of MR and absence of LV reverse remodelling. The preoperative risk factors identified both in this thesis and in earlier reports may help the Heart Team in this decision-making process. RMA – performed according to a structured surgical approach – should form the cornerstone in the surgical treatment of patients with functional MR. In patients with a high risk of recurrent MR, additional subvalvular procedures or replacement of the mitral valve may be considered to minimize the risk of MR recurrence – keeping in mind that this does not always lead to LV reverse remodelling. In patients accepted for mitral valve surgery, the indication for concomitant surgical procedures – coronary artery revascularization, tricuspid valve repair, left ventricular reconstruction and arrhythmia surgery – should be considered on a case-by-case basis as well. In patients who are unable to undergo mitral valve surgery due to comorbidities and in whom symptoms of heart failure are predominantly related to valvular dysfunction rather than LV dysfunction (i.e. severe MR but not so dilated LV), a percutaneous edge-to-edge mitral valve repair can be considered. Finally, the subgroup of patients with functional MR in whom LV disease is too advanced to such an extent that LV reverse remodelling is unlikely – although, as said, hard to identify – will not benefit from any mitral valve intervention but should be considered for HTx or LVAD implantation.

The results of this thesis contribute to further personalisation and optimisation of the treatment for patients with functional MR. Still, there are some major challenges to be addressed.

First, it remains difficult to identify preoperatively whether an individual patient with functional MR will or will not benefit from a mitral valve procedure, and consequently to select the appropriate procedure for each individual. This difficulty is due to the fact that functional MR comprises a highly heterogeneous disease in which the mitral valve and LV are interrelated in a complex way. Evolving imaging techniques may play a role in identifying new predictors for outcome after mitral valve procedures. 3D echocardiography may provide more advanced information regarding mitral valve geometry, LV geometry and function, and the interrelation between mitral valve and LV. Furthermore, cardiac magnetic resonance imaging focusing on fibrosis and scar, and stress echocardiography focusing on viability, may provide additional information regarding the (extent of the) underlying LV disease and the expected potential for LV reverse remodelling after surgery. In addition to these imaging techniques, technological advances may offer a solution as well. Machine learning algorithms are able to combine a vast amount of information and take the multi-dimensional correlations between different variables into account as well. Consequently, a machine learning algorithm may be able to predict outcomes after RMA surgery more accurately compared to prediction models developed by statistical analysis methods. Indeed, a recent study demonstrated that a risk score developed

using machine learning could accurately – and more accurately than existing risk scores – predict the risk of mortality in heart failure patients.[14]

Second, most current treatment options for functional MR are directed at the mitral valve and sometimes local LV geometry, whereas the underlying problem – the intrinsic myocardial disease – is largely left untouched, except for coronary revascularization in patients with ischaemic MR. Since the LV seems to play a crucial role in determining outcomes after mitral valve procedures, the underlying LV disease should become the focus of future treatment strategies. External cardiac restraining devices may be useful to break the vicious cycle of LV remodelling and worsening MR by reducing both MR and LV wall stress. However, such a device is currently not on the market, and the results of two devices which are currently being investigated – the BACE (Basal Annuloplasty of the Cardia Externally) and VenTouch device – are to be determined.[15] Ultimately, the intrinsic myocardial disease itself should be addressed, for both patients with ischaemic and non-ischaemic MR. Regenerative medicine may provide such a treatment option by restoring normal myocardial cell function, but at the moment it seems still a long way before such therapies can be used in everyday clinical practice.

Future studies should therefore focus on improving preoperative prediction of patients who are (un)likely to benefit from a mitral valve procedure and on the treatment of the underlying myocardial disease, in order to genuinely personalise the treatment strategy and optimise outcomes for all patients with functional mitral regurgitation.

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