Summary

In this thesis the surgical options for treatment of functional mitral regurgitation (MR) are described. In functional MR, the mitral valve has a normal anatomy, which distinguishes this type of insufficiency from organic MR. Regurgitation in functional MR is related to an abnormal geometry of the left ventricle, which can be the result of an infarction or ischaemia, or may be caused by another—intrinsic—disease of the myocardium. Based on aetiology, we can distinguish ischaemic and non-ischaemic functional MR. Patients with functional MR often present with signs and symptoms of heart failure. Current guidelines do not offer clear treatment algorithms for these patients, and an intervention on the mitral valve is often discouraged, mainly because of contradictory results from studies on surgical interventions on the valve.
In this thesis, the role of surgery in the multidisciplinary treatment of patients with functional MR, typically associated with heart failure, is evaluated with regard to clinical and echocardiographic outcomes. The ultimate goal is to establish an individualised medico-surgical approach to this pathology. As such, this thesis results from close collaboration between the departments of Cardiothoracic Surgery and Cardiology of the Leiden University Medical Center.

Chapter 1 reviews and comments the currently available literature on the subject of functional MR, starting with a definition. A historical overview of the pathophysiologic thoughts and considerations regarding this condition is presented. Normal anatomy and function of the mitral valve are discussed, followed by the pathophysiologic changes that occur in functional MR – in clinical and experimental settings. The consequent surgical interventional options are discussed and analysed. The clinical relevance of functional MR is illustrated by publications on incidence and prevalence, on its natural course, and on predictors for mortality. Different imaging techniques to identify and quantify functional MR are discussed. Outcomes of surgery for both ischaemic and non-ischaemic functional MR are presented and reviewed.
The surgical basis for functional MR is a restrictive mitral annuloplasty (RMA). This concerns implantation of a so-called undersized ring—a complete, non-flexible (i.e., rigid or semi-rigid) ring that is 2 sizes smaller than would be chosen if organic pathology were present. Considerations that determine ring choice are discussed based on available research on this topic. Next, the problem of recurrent MR following surgery is discussed. The chapter ends with an overview of the available additional surgical techniques—at the level of the mitral valve, but also directed at the left ventricle and the tricuspid valve. Finally, the role of current non-surgical interventions (cardiac resynchronization) in this pathology is mentioned.

In **chapter 2**, the initial experience with RMA combined with coronary revascularization (CABG) is described in 51 patients with ischaemic functional MR and left ventricular dysfunction (mean ejection fraction, 31%). In these patients, a 2-year survival of 84% is

described (including 6% early mortality), as well as a significant improvement of functional status and improvement of left ventricular dimensions. The latter phenomenon is referred to as reverse remodelling.

Chapter 3 further explores this reverse remodelling, which is the ultimate goal of the (surgical) treatment of functional MR. The occurrence of reverse remodelling is the most important demonstrable manifestation of breaking the vicious cycle that consists of MR, ongoing left ventricular remodelling and consequent progression of MR. In a study with 87 patients with ischaemic functional MR it is demonstrated that treatment with RMA and CABG (median ring size, 26, mean number of distal anastomoses 3.3 ± 1.3) in most cases leads to reverse remodelling in patients with limited left ventricular dilatation preoperatively. Using ROC (receiver-operating characteristic) curve analysis, a cut-off value of 65 mm left ventricular end-diastolic dimension (LVEDD) on pre-operative transthoracic echocardiography is found to be the most important predictor for the occurrence of reverse remodelling after surgery, with a sensitivity and specificity of 89%.

In **chapter 4**, mid-term follow-up results are described for 100 patients with ischaemic functional MR treated with RMA and CABG. After a mean follow-up of 4.3 years, survival of patients with a preoperative left ventricular end-diastolic dimension exceeding 65 mm is demonstrated to be significantly lower than that of patients with a less dilated left ventricle. Five-year survival for the whole patient group was 71 ± 5.1%; for patients with LVEDD of 65 mm or less, survival was 80 ± 5.2%, compared to 49 ± 11% for patients with a higher preoperative LVEDD. In addition, it is demonstrated that patients with a preoperative LVEDD >65 mm also after longer follow-up have a very limited chance of left ventricular reverse remodelling. The percentage of recurrent MR exceeding grade 2 is 15% after 4 years' follow-up.

Chapter 5 features 2 patients with refractory cardiogenic shock resulting from acute ischaemic MR, without papillary muscle rupture. Both patients underwent uneventful implantation of a restrictive mitral annuloplasty ring and CABG with good short-term results. Acute ischaemic MR without papillary muscle rupture is a rare phenomenon that can be treated with RMA and CABG in acute settings.

In **chapter 6**, the application of MRI (magnetic resonance imaging) to assess left ventricular reverse remodelling is described in patients with mild to moderate heart failure with functional MR and non-ischaemic cardiomyopathy (NYHA class 2.2 ± 0.4; LVEDD 61 ± 5 mm, forward LV ejection fraction 37 ± 5%, LV end-diastolic volume 215 ± 34 mL). MRI is a technique that can provide insight into changes in LV dimension, shape and volumes in a more accurate fashion compared to echocardiography. The technique as yet however has a limitation in that it cannot be used in patients with an internal defibrillator (ICD). This implies that MRI to assess postoperative reverse

remodelling can only be used in patients without an ICD, thereby excluding patients with more advanced stages of heart failure. Using MRI, in 22 patients sustained reverse remodelling and increase of forward ejection fraction of the left ventricle are described up to 3.5 years after surgery (isolated RMA). When the technique can be expanded to patients with an ICD, MRI will become an important modality in the follow-up of heart failure patients.

In **chapter 7**, the experience with RMA in non-ischaemic functional MR is described. The most important difference with patients with ischaemic MR lies in the fact that in those patients the ventricular component of the disease can be addressed by coronary revascularization. In non-ischaemic cardiomyopathy the underlying left ventricular problem has no clear substrate that can be addressed. Possible treatments are cardiac transplantation or a left ventricular assist device, with their inherent limitations.
In this patient group, changes in the (surgical) treatment strategy are implemented based on ongoing research. This is reflected in the application of additional interventions, which may include techniques directed at the level of the ventricle (e.g., external cardiac restraint by implantation of a CorCap cardiac support device in patient with an LVEDD >65 mm), but also a more 'aggressive' approach to tricuspid valve repair. In addition, these patients also undergo cardiac resynchronization therapy often combined with ICD placement. In this chapter, the experience with 69 patients with a 3.1 year follow-up is described. After 3 years, survival is more favourable compared to the natural history, combined with a low rate of recurrent MR and sustained LV reverse remodelling. This has led to a structured and individualised approach to patients in the Mission! Heart Failure programme.

Chapter 8 reflects the results from studying echocardiographic parameters that can predict recurrence of functional MR following RMA. This is a fairly detailed analysis aimed at geometric ultrasound parameters of the mitral valve that express the degree of left ventricular remodelling. The most important predictors are the angle made between the tip of the anterior mitral leaflet and the line perpendicular to the annulus (distal anterior mitral leaflet angle), and the angle made between the tip of the posterior mitral leaflet and the line perpendicular to the annulus (posterior mitral leaflet angle). Ultimately, these angles are determined by the degree of geometric changes in the sub-valvular apparatus as a result of left ventricular remodelling.

Functional tricuspid regurgitation is the subject of **chapter 9**. This condition results from left-sided valve dysfunction (often mitral regurgitation) and is often not well recognized in the surgical and cardiology communities. For a long time it was thought that a limited tricuspid valve insufficiency would cure from successful treatment of the mitral valve. Long-term studies have shown, however, that this thought is not true. Other studies have demonstrated that the degree of tricuspid valve regurgitation is an unreliable parameter for treatment decision making, because regurgitation is highly

dependent on preload and afterload. Instead, the degree of tricuspid annular dilatation (which is independent of the previously mentioned parameters and is easily and reliably measured by transthoracic echocardiography) should be leading. Since the latter approach has been adopted at the LUMC since 2003, in this chapter two patient groups are compared: one group of patients who underwent tricuspid valve repair in the earlier era—during which the decision to perform valve surgery was only based on severity of tricuspid regurgitation—and another group of patients treated according to the new algorithm (which included surgery with annular dilatation >40 mm, even in the absence of tricuspid regurgitation). It was demonstrated that patients who were treated in the more recent era had significantly better echocardiographic outcome regarding severity of tricuspid regurgitation, right ventricular dimensions, and right ventricular function, after 2 years' follow-up.

Chapter 10 is an overview and analysis of the most relevant literature on the subject of ischaemic MR published between 2008 and 2011. During this time frame, treatment of functional MR with RMA has gradually gained more support. In addition, new techniques have been developed to reduce MR recurrence rate, especially in patients with advanced stages of remodelling. New imaging techniques aimed at functional MR are discussed, with a focus on integration of mitral valve geometry and LV characteristics—geometry, dimensions, function and potential functional recovery. For the future, it will be important to further develop these techniques in order to further individualise and optimise the medico-surgical treatment of patients with functional MR.

Final considerations

Functional MR has tremendous impact on functional status and survival of heart failure patients. Following myocardial infarction, functional MR frequently develops, with percentages varying between 20 and 60 percent. In ischaemic MR, left ventricular function may still be relatively preserved with MR resulting from local LV wall motion abnormalities. In non-ischaemic cardiomyopathy, global LV dilatation is invariably present. Regardless of aetiology, functional MR carries an increased risk of death, which is approximately two-fold and is related to the severity of MR

Functional MR is a dynamic phenomenon, which has specific implications for MR assessment: this should preferably be performed prior to surgery and the induction of anaesthesia, and should incorporate several techniques in order to assess severity. Exercise echocardiography should be performed in patients with heart failure symptoms and non-significant MR at rest.

Ischaemic MR treated by revascularization only does not improve in two-thirds of patients and leads to ongoing LV remodelling. There are no criteria to identify patients with ischaemic MR who may benefit from revascularization only. Series reporting on the results of mitral valve repair in functional MR are difficult to compare because of different patient populations and different surgical techniques.

For ischaemic MR, good and durable results with regard to recovery of functional status, absence of recurrent MR, and reverse LV remodelling have been described in this thesis following complete revascularization and restrictive mitral valve annuloplasty (RMA). In our institution, RMA needs to fulfill three criteria: (1) stringent downsizing of the ring by 2 ring sizes, using a semi-rigid or rigid ring, and (2) verifying absence of residual MR with (3) sufficient coaptation length: 8 mm at the A2-P2 level. This technique seems insufficient in patients with too advanced LV remodelling, which can be assumed in severe LV dilatation (more than 65 mm end-diastolic dimension and/or severe mitral valve tethering). For functional MR in non-ischaemic cardiomyopathy, a similar approach to the mitral valve applies, although the ventricular component of the disease cannot be addressed in a straightforward manner. In this thesis, external cardiac restraint has been shown to lead to more extensive LV reverse remodelling in these patients.

MR recurrence should be distinguished from residual MR; regurgitation within 6 months after surgery should be considered to result from insufficient repair and not be regarded as secondary to progress of the underlying ventricular disease. True MR recurrence may occur in patients without LV reverse remodelling but also in patients with reverse remodelling. Specific indicators to predict MR recurrence are not available, but the extent of preoperative LV remodelling—partially reflected by mitral valve leaflet geometry on echocardographic examination—might identify patients in whom adjunctive measures are necessary to prevent recurrence. Patients with an estimated increased risk of MR recurrence might benefit from adjunctive measures; these can be directed at the mitral valve leaflets, at the subvalvular apparatus, or at the left ventricle.

Patients with heart failure and functional MR should benefit from a practical medico–surgical approach in a heart failure team, in which knowledge of and experience with both interventional and non-interventional treatment strategies are incorporated. A tailored surgical approach to functional MR also involves assessment of the left ventricle, the tricuspid valve and cardiac resynchronisation therapy.

One of the major challenges in the field of functional MR remains patient selection: who will benefit from an individualized surgical strategy, and who will not. Imaging techniques are rapidly improving and a further integration of techniques will provide better answers to the question which patients have already too extensive remodelling and thus will not benefit from current techniques.

With the advent of percutaneous techniques to address MR, it seems that an increasing number of patients with functional MR is being treated. Although this technology has the advantage of avoiding major surgery, results have not yet been evaluated in large cohort studies. At this moment, it is our opinion that this new technology might be useful for extremely high-risk patients, but for all other patients a proven surgical concept exists and as such should be the therapy of choice. Moreover, it is our strong believe that the same principles as described in this thesis apply to patients treated with percutanous devices, and that the indication for treatment—which should be discussed in a heart failure team—should not be expanded before further evidence has been obtained.

Functional MR has tremendous impacts on functional status and survival of heart failure patients. Surgical techniques have developed over more than 15 years, and our current knowledge indicates that—when properly applied and evaluated—these techniques have an important place in the treatment of heart failure patients with functional MR.