New insights into the surgical treatment of mitral regurgitation

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Summary

In 1513 the first drawings and descriptions of the mitral valve were made by Leonardo daVinci and in 1543 the mitral valve received its current name from Andreas Vesalius, but it wasn't until after the introduction of the heart-lung machine in the 1950s that open-heart mitral valve surgery truly came to fruition. Although the history of mitral valve surgery is relatively short, it is a rapidly evolving and exciting surgical field.

The mitral valve and mitral valve repair techniques have been subject of extensive research over the past few decades. Mitral valve repair techniques have evolved considerably and have become the gold standard for common conditions such as degenerative mitral regurgitation (MR). In less common conditions, such as ischemic mitral regurgitation (IMR) (chronic and acute), MR caused by (special forms of) endocarditis or MR in heart transplant recipients, repair techniques are still subject of much debate. Although it has become clear from different studies that mitral valve repair is generally superior to valve replacement in terms of preservation of left ventricular (LV) function, survival rates, reoperation rates, endocarditis risk, thrombo-embolic complication rates, the need for lifelong anticoagulant drugs, and costs, it is not always clear whether valve repair is indeed better or even feasible for specific, less common forms of MR. This thesis provides new insights into the surgical treatment of these specific and often complex forms of MR.

Part 1 of this thesis focuses on chronic ischemic mitral regurgitation (CIMR). IMR occurs frequently after acute myocardial infarction (MI). In many patients acute IMR (occurring in the immediate postinfarct period) is mild and it may disappear completely. In other patients, however, IMR persists or develops after a period of time (1-6 weeks), at which point IMR becomes chronic.

Chapter 1 provides a detailed overview of the present knowledge about the different aspects of CIMR, which is one of the most complex and unresolved aspects in the management of ischemic heart disease. CIMR occurs in approximately 20-25% of patients followed up after MI and in 50% of those with post-MI congestive heart failure (CHF). CIMR is defined as MR occurring as a consequence of MI or chronic myocardial ischemia in the absence of any inherent structural damage to the leaflets, chordae or papillary muscles. The presence of CIMR adversely affects prognosis, increasing mortality and the risk of CHF in a graded fashion according to CIMR severity. The primary pathofysiological mechanism of CIMR is ischemia-induced LV remodeling with papillary muscle displacement and apical

tethering of the mitral valve leaflets. Current repair techniques for CIMR (mainly restrictive mitral valve ring annuloplasty combined with coronary artery bypass grafting (CABG)) often do not target these pathophysiological mechanisms; they only provide an annular solution to a subvalvular problem. The persistence and recurrence rate (at least MR grade 3+) for CIMR repair with restrictive annuloplasty remains high (up to 30% at 6 months postoperatively), and after a 10-year follow-up there does not appear to be a survival benefit of a combined procedure compared to CABG alone (10-year survival rate for both is approximately 50%). Patients at risk of annuloplasty failure based on preoperative echocardiographic parameters (such as a tenting area ≥2.5 cm^2, a tenting height ≥10 mm, a posterior tethering angle ≥45°, an anterior tethering angle ≥39.5°, an interpapillary muscle distance >20 mm, a LV end-systolic volume ≥145 ml, a systolic sphericity index >0.7) may benefit from mitral valve replacement with preservation of the subvalvular apparatus or from annuloplasty combined with new repair techniques targeting the subvalvular apparatus including the LV. These new procedures include second-order chordal cutting, papillary muscle repositioning by a variety of techniques and ventricular approaches using external ventricular restraint devices or the Coapsys device. Although promising, at this point these new procedures still lack investigation in large patient cohorts with long-term follow-up. They will, however, be the subject of much anticipated and necessary ongoing and future research.

In *Chapter 2* CIMR repair with posterior leaflet augmentation (with bovine pericardium) combined with remodeling annuloplasty is discussed in more detail. Although it is a promising, reproducible technique with good mid-term results, it is still an annular/valvular solution to a subvalvular problem, which renders it prone to CIMR recurrence. It might be a more valuable technique when it would be combined with subvalvular techniques. Unfortunately long-term results are unknown.

Chapter 3 focuses on mechanisms of CIMR. More precisely, it focuses on the influence of papillary muscle infarction (PMI) detected by late gadolinium-enhanced cardiac magnetic resonance imaging (MRI) on CIMR and on independent predictors of PMI and CIMR. Independent predictors of PMI include infarct size, inferior myocardial infarction, and the circumflex coronary artery as the infarct-related artery. Four months after primary percutaneous intervention (PCI) for ST-elevation myocardial infarction (STEMI) CIMR rates are higher in patients with PMI, but PMI is not an independent predictor of CIMR. Instead, independent predictors of CIMR include age, infarct size, tethering height, and interpapillary muscle distance.

Due to high CIMR recurrence rates after mitral ring annuloplasty a patient-specific three-dimensional (3D) imaging-based approach to surgical treatment of CIMR is required to optimize surgical results. In *Chapter 4* we use advanced real-time 3D echocardiographic imaging models to analyze whether preoperative mitral annular geometry and regional leaflet tethering are able to predict CIMR recurrence 6 months after ring annuloplasty. Preoperative regional tethering of segment P3 is a strong independent predictor of CIMR recurrence after ring annuloplasty. In patients with a preoperative P3 tethering angle ≥29.9° chordal-sparing valve replacement or annuloplasty combined with leaflet or subvalvular repair techniques should be considered. These findings play an important role in developing a patient-specific approach to optimal surgical treatment of CIMR.

In *Chapter 5* we use a porcine CIMR model and advanced real-time 3D echocardiographic imaging models to demonstrate that saddle-shaped ring annuloplasty improves leaflet coaptation compared to flat ring annuloplasty. Undersized (flat) ring annuloplasty treats annular dilatation, but does little to improve annular saddle-shape and it does not address the main pathophysiological mechanism of CIMR, which is ischemia-induced LV remodeling with papillary muscle displacement and apical leaflet tethering. In fact, undersized (flat) ring annnuloplasty may potentiate leaflet tethering, reduce leaflet coaptation and increase leaflet and chordal strain. Strain is the main cause of limited repair durability and CIMR recurrence after repair. Saddle-shaped annuloplasty restores or maintains a more physiological annular and leaflet geometry and function, which reduces leaflet tethering and strain and improves leaflet coaptation. According to Carpentier creating a large surface of coaptation is essential to repair durability. Although compelling, long-term results are lacking and we have to keep in mind saddle annuloplasty is still an annular solution to a subvalvular problem, which renders it prone to CIMR recurrence. The ultimate objective will be to tailor the ideal combination of annular, valvular, chordal, papillary muscle and ventricular repair techniques based on preoperative clinical and echocardiographic characteristics to achieve the best result in each individual patient with CIMR. In conjunction with advancements made in real-time 3D echocardiographic mitral valve imaging this should lead to a "continuum of surgical techniques" for CIMR that can be customized to the individual patient's needs.

Part 2 of this thesis focuses on acute ischemic mitral regurgitation caused by papillary muscle rupture (PMR). After MI the posteromedian papillary muscle ruptures 3-12 times more frequently than the anterolateral papillary muscle. In the current era of early reperfusion with primary PCI following STEMI the incidence of post-MI PMR has dropped

from 1-5% in the eighties and early nineties to <0.5% in recent years. Although rare, PMR is still a devastating complication, which can lead to rapid clinical deterioration and death. Approximately 80% of ruptures occur within 7 days after MI, but a delayed rupture several weeks or months after MI is also possible.

The natural history of post-MI PMR is extremely unfavorable and under medical treatment alone mortality may be as high as 50% in the first 24 hours (especially when PMR is complete), and as high as 80% in the first week. Immediate surgical intervention is considered the optimal and most rational treatment for acute PMR. Mitral valve replacement is generally preferred in these unstable, high-risk patients, but mitral valve repair seems feasible in selected cases and may offer improved surgical outcome. *Chapter 6* analyzes the outcome of our experience with mitral valve repair for post-MI PMR and provides a systematic review of the literature on this topic. Mitral valve repair for partial or incomplete post-MI PMR is reliable and provides good short- and long-term results (freedom from grade 3+ or 4+ MR and from reoperation at 1, 5, and 10 years of 87.5±11.7%; and a 1-, 5-, and 10-year survival rate of 100%, 83.3±15.2%, and 66.7±19.2%, respectively). Established repair techniques, such as quadrangular or triangular resection of a prolapsing leaflet segment combined with annuloplasty, are efficient. If mitral valve prolapse involves a segment that is too large to resect, reimplantation of the remnant papillary muscle can be a useful technique. Due to a high risk of recurrence, the ruptured papillary muscle remnant should not be reimplanted directly at the site of rupture or into the LV wall. Ultimately PMR type and adjacent tissue quality determine the feasibility and durability of repair.

Because of the high risk some surgeons may be reluctant to operate certain patients with post-MI PMR, while others are willing to accept the high risk. At this point it is not entirely clear which patients are at highest risk. Therefore, *Chapter 7* focuses on short-term outcome after mitral valve surgery (repair and replacement) for post-MI PMR and identifies predictors of in-hospital mortality. Intraoperative mortality is 4.2% and in-hospital mortality is 25.0% for patients undergoing mitral valve surgery for post-MI PMR. The logistic EuroSCORE (optimal cut-off ≥40%), EuroSCORE II (optimal cut-off ≥25%), complete PMR, and intraoperative intra-aortic balloon pump requirement are strong independent predictors of in-hospital mortality in patients undergoing mitral valve surgery for post-MI PMR. These predictors may aid in surgical decision making and they may help improve the quality of informed consent.

Chapter 8 analyzes predictors of long-term survival after mitral valve surgery for post-MI PMR. Overall long-term survival is 49.5±7.6% after 10 years and based on the results from our cohort there is no difference in overall long-term survival between repair

and replacement. Logistic EuroSCORE ≥40%, EuroSCORE II ≥25%, preoperative inotropic drug support and mitral valve replacement without preservation of the subvalvular apparatus are strong independent predictors of a lower overall long-term survival in patients undergoing mitral valve surgery for post-MI PMR. Whenever possible, the subvalvular apparatus should be preserved in these patients to improve long-term survival.

In *Part 3* and *Chapter 9* the outcome of mitral valve surgery for mitral regurgitation caused by Libman-Sacks (LS) endocarditis is discussed. LS endocarditis is a non-bacterial (sterile) verrucous vegetative endocarditis and it is a cardiac manifestation of systemic lupus erythematosus (SLE) and the antiphospholipid syndrome (APS). LS endocarditis is usually typically mild and asymptomatic, but can lead to serious complications, such as superimposed bacterial endocarditis, thrombo-embolic events, and valvular regurgitation and/or stenosis requiring surgery. LS endocarditis should be strongly suspected when significant valve dysfunction, such as MR, develops during the course of SLE and/or APS. Differentiation from infective endocarditis and intracardiac tumors can be difficult, but is important and has different therapeutic implications. After establishing the diagnosis, periodic echocardiographic follow-up is recommended to detect deterioration of valvular function. When severe symptomatic MR requires surgery, mitral valve repair should always be considered. Chapter 7 shows that mitral valve repair is feasible and effective in young patients with relatively stable SLE and/or APS and only localized mitral valve abnormalities caused by LS endocarditis. When mitral valve abnormalities are localized, established repair techniques such as quadrangular resection and mitral valve ring annuloplasty can be used. Both clinical and echocardiographic follow-up show excellent mid- and long-term results.

In *Part 4* and *Chapter 10* several causes of MR in the tranplanted heart are discussed. These include edema and poor lymphatic drainage (early after transplantation), atrioventricular mismatch or malalignment due to the biatrial anastomotic technique, progression of natural disease in the donor heart, and accelerated graft atherosclerosis leading to ischemic mitral valve disease. *Chapter 9* shows that mitral valve repair and redo repair are feasible in a heart transplant recipient. Pushing the envelope on conventional surgical procedures in marginal donor hearts may not only improve the patient's functional status and reduce the need for retransplantation, but it may ultimately alleviate the chronic shortage of donor hearts.

Our knowledge about the mitral valve, about mitral valve disease, and about mitral valve surgery has undergone a mind-blowing development in the past few decades and it is therefore truly exciting to see what the next century of mitral valve surgery will bring.