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An observational, prospective study on surgical treatment of secondary mitral regurgitation: The SMR study. Rationale, purposes, and protocol

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Abstract

The natural history of secondary mitral regurgitation (MR) is unfavorable. Nevertheless, there are no evidence that its correction can improve the outcome. If from one side the original cause of secondary MR can be such to limit the possibilities of improvement, from the other side it is possible that the surgical technique widely applied to repair, restrictive mitral annuloplasty, is not adequate to correct the regurgitation. The addition of valvular and/or subvalvular techniques has been considered a possible technical solution. However, we do not know the prevalence of each technique, how many times mitral replacement is used to correct secondary MR. This aspect is of particular importance, as we know that a successful mitral repair causes a better left ventricular systolic

remodeling than a unsuccessful repair or replacement. This study is a prospective, observational registry, conceived to understand what is done in the real world. Any surgeon will use the technique he thinks the most suitable for the patient. Every year, for 5 years, patients will have a clinical and echocardiographic follow-up, to evaluate the risk factors for a worse result (death, rehospitalization for heart failure, reoperation for MR return, moderate, or more MR return). This knowledge will give us the possibility to understand which is the technique, or the strategy, more efficient to treat this disease and the real efficacy of the surgical treatment.

KEYWORDS

coronary artery disease, mitral regurgitation, valve repair/replacement

1 | INTRODUCTION

Surgical treatment of secondary mitral regurgitation (MR), in particular, if ischemic or secondary to idiopathic dilated cardiomyopathy, is still not standardized. Secondary MR represents a unique situation in cardiac surgery. There are clear evidence that patients outcome is affected negatively by the disease,[1,2] but there is no evidence that the natural history of the disease is improved by its correction.[3,4]

Longitudinal studies in patients with previous myocardial infarction (MI) and ischemic MR (IMR) or idiopathic dilated cardiomyopathy showed reduced survival and lower freedom from congestive heart failure in patients with any grade of MR,[1,2,5-7] even if mild.[8] The presence of IMR immediately after the onset of acute MI has been demonstrated to be a predictor of reverse LV remodeling and heart failure in the follow-up after treatment with primary angioplasty.[9] Even mild IMR detected 2 days after admission for acute MI is a factor of reduced 1-year survival.[10] These findings were confirmed even in the drug-eluting stents era.[11-13] Medical treatment has suboptimal results, as the presence of IMR is a risk factor for heart failure and death.[6,14,15] Percutaneous or surgical revascularization alone are only partially successful in eliminating or reducing IMR. IMR at the moment of percutaneous revascularization is a risk factor for lower survival[16,17] and improvement of IMR grade happens not frequently after percutaneous revascularization.[18,19] Surgical myocardial revascularization reduces IMR grade only in a minority of patients.[20] In a recent meta-analysis[21] in patients with moderate IMR with or without mitral valve (MV) repair or replacement the incidence of moderate-to-severe MR at follow-up was higher in the coronary artery bypass grafting alone group (risk ratio, 3.24; 95% confidence interval, 1.79-5.89; $P < .001$). The same findings were confirmed by other studies on moderate IMR.[3,22-24]

Similar studies on MR secondary to aortic valvulopathies showed that, after aortic valve replacement, both transfemoral and surgical, preoperative MR was a risk factor for higher mortality[25-31] or heart failure[28,29,32] during the follow-up, in particular, if ejection fraction was less than 50%[33] or, in general, low.[32] Other studies found that the patients at risk were those where MR did not reduce but persisted or worsened after either procedure.[26,27,34-37] MR grade improvement after transfemoral or surgical aortic valve replacement was variable.[25,26,29,34]

The evaluation of MR secondary to atrial fibrillation is not yet well evaluated as the other etiologies. A study from Abe et al[38] showed that patients with chronic AF, ejection fraction more than 50% and moderate or more MR had lower freedom from cardiac death and hospitalization due to worsening heart failure than patients with less than moderate MR ($P < .0001$). The outcome was even worse in association with moderate or more tricuspid regurgitation. Restrictive mitral annuloplasty (RMA) provided favorable results,[39,40] but not in all the patients.[41]

Comparison between treated and untreated patients has been done mostly for patients with moderate IMR. Review papers did not find any difference in survival[21,42,43] and results in changes in functional status were mixed.[43] In a subanalysis of a randomized study in patients with ejection fraction ≤35%, adding MV repair to coronary artery bypass grafting (CABG) improved survival compared to CABG alone or medical therapy.[44] Results of three randomized trials were not uniform. Fattouch et al[23] and Chan et al[22] showed that, in patients with moderate IMR who needed CABG, MV repair was related to a better functional status and a reduced amount of IMR. Moderate or more IMR at follow-up, in patients where the MV was treated, was 0% and 4%, respectively. When isolated CABG was performed, the prevalence rose to 60% and 50%, respectively. The third randomized study, from CTS network, had a great impact on the scientific world.[3,45] It was demonstrated that adding MV repair did not influence survival or functional status or LV reverse remodeling, but it was associated to higher early hazard of increased neurologic events and supraventricular arrhythmias. After 2 years, moderate or severe IMR return was 54.8% in the CABG alone group compared to 28.3% of the patients who had MV repair.[3]

In general, the surgical technique used to correct secondary MR is RMA. In patients with IMR, other adjunctive valvular or subvalvular techniques have been proposed, such as papillary muscles approximation[46,47] or relocation of papillary muscle(s),[48,49] augmentation of the anterior leaflet[50] or of the posterior leaflet,[51,52] chordal

cutting,[53-55] and edge-to-edge[56] or surgical mitral plasticity[57] (augmentation of the anterior leaflet together with chordal cutting and RMA). In selected cases, MV replacement has been proposed, in particular when IMR was severe. Different observational studies, mostly including a small number of patients, reported that adding adjunctive techniques (isolated or in combination) to RMA reduced significantly the prevalence of moderate or more IMR at follow-up compared to cases where RMA alone was used.[46,54,55,58-61] A randomized controlled trial from CTS network compared RMA to MV replacement in case of severe IMR.[4,62] Results showed similar survival and LV remodeling, but patients with RMA had higher moderate or more IMR return (58.8% vs 3.8%) and higher heart failure-related events after a 2-year follow-up.

The two randomized controlled trials from CTS network demonstrated that results of RMA were poor due to high moderate or more IMR return at 2-year follow-up. However, when patients had a good result (no or mild IMR at follow-up) LV remodeling was by far better if compared to patients who had a poor result, in particular in patients with preoperative severe IMR.[63] When the MV was replaced, LV remodeling was not as important as in patients with a successful MV repair.[63] Then, the failure is not in the "repair" concept, but in the technique used for repair. In other words, RMA alone seems not to be sufficient in many cases.

2 | STUDY DESIGN

If it is true that RMA can be not sufficient to correct secondary MR, it is true as well that we do not know what is daily performed in the real world and what really works at least in the midterm. In particular, we do not know if the MV is repaired with annuloplasty alone, if valvular or subvalvular techniques are added or not, and when the MV is replaced. Even if the case load is not high, grouping many centers can allow us to have a high number of procedures, a strength that no study has.

The Secondary Mitral Regurgitation Surgical Treatment (SMR study) is a multicenter, prospective, observational study, where surgeons report the cases as performed. They will use RMA, alone or with some valvular or subvalvular technique, or MV replacement. What is important is that the surgical procedure will be the best choice for the patients according to the surgeon's experience.

Patients will be grouped into three arms, which are as follows:

1. isolated RMA;
2. RMA + valvular and/or subvalvular procedures, such as papillary muscles approximation[46,47] or relocation of papillary muscle (s),[48,49] augmentation of the anterior leaflet[50] or of the posterior leaflet,[51,52] chordal cutting,[53-55] and edge-to-edge[56] or surgical mitral plasticity[57];
3. MV replacement.

For each group, there will be subgroups according to the different secondary MR etiologies.

2.1 | Objective

1. The primary aim is to test the hypothesis that adding a valvular or subvalvular technique to RMA can improve the clinical outcome (survival and rehospitalization for heart failure-free survival) compared with RMA alone and MV replacement. Risk factors for clinical events will be evaluated.
2. The secondary aim is to test the hypothesis that adding a valvular or subvalvular technique to RMA can improve the echocardiographic result (reduction of moderate or more secondary MR at follow-up, and/or improved LV remodeling) compared with RMA alone or MV replacement. Risk factors for moderate or more secondary MR return and LV remodeling will be evaluated.
3. The third aim is to see which valvular or subvalvular technique is the most efficient.

2.2 | Inclusion criteria

1. First time surgery in patients with secondary MR (ischemic, idiopathic, associated to aortic valvulopathy, secondary to atrial fibrillation, and others) treated with repair or replacement.
2. MV has to be repaired with RMA, with/out valvular or subvalvular techniques, or replaced.

The surgical team will choose the technique considered the most suitable for the patient.

2.3 | Exclusion criteria

1. Previous cardiac surgery.
2. Age ≤18 years.

2.4 | Patient enrollment

All patients with secondary MR can be included, any etiology and any status (elective, urgent, or emergent). Patients who sign the consent form and agree to be followed up yearly for 5 years will be enrolled. Clinical history, list of comorbidities (if any) and transthoracic echocardiographic evaluation with the necessary data on MV indicated in the database, will be recorded. Transesophageal echocardiography would be optimal, but not indispensable.

2.5 | Surgical procedure

Median sternotomy or other surgical approach can be used. RMA can be performed with a ring or a band. Valvular and/or subvalvular procedures can be performed according to the surgeon's preference. MV replacement with a mechanical or biologic prosthetic valve. Any other added procedure will be performed at surgeon's discretion.

2.6 | Outcome measures

1. The early outcome includes all the major events (death, stroke, prolonged ventilation, low cardiac output, reoperation for bleeding or hemodynamic reasons or necessity to reoperate on the MV, transfusion, new atrial fibrillation, ventricular sustained arrhythmias, and pacemaker insertion) happened during the first 30 days from surgery or during the hospitalization. The last echocardiographic data before discharge (or death) will be recorded for comparison. Details on medications will be recorded.
2. The late outcome includes all the events that happened during a specific time frame (from 1 to 5 years) and includes death, stroke, reoperation on the MV, hospital readmission for heart failure, the presence of moderate or more secondary MR, and pacemaker insertion. The outcome of hospital readmission will be recorded. NYHA Class will be recorded and grouped in I/II and III/IV. A transthoracic (or transesophageal) echocardiogram has to be performed yearly for 5 years to evaluate the outcome of mitral surgery. Details on medications will be recorded.

2.7 | Sample size calculation and statistical analysis

Number of patients has been calculated having as a target moderate or more secondary MR return, estimated more or less in 50% after 5 years, at least for IMR. Object of the study is to see if adding valvular or subvalvular procedures to annuloplasty could be able to reduce moderate or more secondary MR return of at least 15%. Then the number of patients in the repair arm has been calculated in 1756. Assuming a 5-year survival of 60% in patients who undergo MV replacement and of 70% in patients who undergo MV repair, the number has been calculated in 2106, with 350 patients who undergo replacement (software G*Power 3.1). However, as we do not know exactly, in such a heterogenic population, the real survival, we are aware that the number of patients can change. An increase of survival of 10% will reduce the sample size to 2076, with 311 patients undergoing replacement. Then, we can estimate the need of at least 2000 patients with 300 undergoing replacement.

Data collection will start in 2020. If participating centers will be 50, assuming 15 cases per year (750 cases per year), recruitment will last 3 years. As it is not possible to know how many cases per center and how many centers will be participating, it is prudent to assume that recruitment can last 5 years.

Continuous variables will be reported as mean and standard deviation in case of normal distribution, otherwise as median and quartiles. Categorical data will be reported as count and percentage. Univariate analysis will be performed to identify risk factors for early outcome (in-hospital mortality, presence of residual moderate or more SMR, need of reintervention, perioperative and postoperative complications, etc), then multivariable analysis with logistic regression will be used to confirm independent risk factors. The accuracy of the final model will be tested with c-statistics and Hosmer-Lemeshow test. Survival will be evaluated using the Kaplan-Meier curves (univariate) and Cox regression (multivariable). Moderate-to-severe secondary MR return will be evaluated as cumulative incidence and compared using the Gray method. The predictive model will be built using the method of semiparametric regression of Fine and Gray to avoid competing risk. Independent *t* test or the Mann-Whitney *U* test will be used for comparison between groups; in case of repeated measures, comparison will be obtained using a paired *t* test or Wilcoxon test. Finally, risk factors for change between preoperative and late echocardiographic controls will be identified using linear mixed model for repeated measures. Analyses will be done using Development Core Team (2008); R: A language and environment for statistical computing; R Foundation for Statistical Computing, Vienna, Austria (http://www.R-project.org).

2.8 | Ethics

This study will conform to the Medical Research Council (MRC) Guidelines for Good Clinical Practice in Clinical Trials and the Declaration of Helsinki. The study protocol will be approved by the local ethics committee in each participating Center before the study commences.

2.9 | Publications

Publications of study data will take place at the following time points.

1. Study protocol.
2. In-hospital results (descriptive analysis).
3. One-year, 3-year, and 5-year clinical and echocardiographic outcomes and analysis of the related risk factors.
4. One-year, 3-year, and 5-year subgroups analyses.

3 | CONCLUSIONS

The purpose of the SMR-study is to evaluate is there still room for MV repair in secondary MR, in particular of ischemic origin. The possibility that isolated RMA could be not efficient to obtain a result stable overtime does not mean that either MV has to be always replaced (if MR is severe) or has to be left untreated (if MR is moderate). Repair can be more complex, as the disease can be more complex than usually perceived. Knowing what is done in the real world and evaluating clinical and echocardiographic results, and the related risk factors, will be crucial to understand the limits, if any, of what is done, and which are the surgical techniques that can improve the surgical results.

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