Effects of surgery on ischaemic mitral regurgitation: a prospective multicentre registry (SIMRAM registry)

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Aims Functional ischaemic mitral regurgitation (IMR) is common in patients with ischaemic left ventricular dysfunction undergoing coronary artery bypass surgery. Although the presence of IMR negatively affects prognosis, the additional benefit of valve repair is debated, particularly with mild IMR at rest. Exercise echocardiography may help identify a subset of patients at higher risk of cardiovascular events by revealing the dynamic component of IMR.

Methods A large prospective, multicentre, non-randomized registry is designed to evaluate the effects of surgery on IMR at rest and on its dynamic component at exercise (z). SIMRAM will enrol approximately 550 patients with IMR in up to 17 centres with clinical and exercise follow-up for 1 year. Three sets of outcomes will be prospectively assessed and several hypotheses will be tested including determinants of adverse outcome and progressive left ventricular remodeling, efficacy of treatment and role of ischaemia on the dynamic consequences of IMR. Enrolment began in November 2006 and is expected to end by early 2008.

KEYWORDS
Mitral regurgitation; Surgery; Exercise; Echocardiography

Resting ischaemic mitral regurgitation, prognosis and treatment

Functional ischaemic mitral regurgitation (IMR) is frequently observed in heart failure patients with chronic ischaemic systolic left ventricular (LV) dysfunction.1,2 IMR develops because of unfavourable alterations in LV geometry with systolic restriction of the mitral leaflets and decreased closing forces.3–10 When present, IMR may exhibit a broad range of severity and when severe, conveys a poor outcome. The more severe the IMR, the worse the prognosis.11–13 This has led to attention focusing towards the amelioration of MR as a therapeutic target that could favourably affect outcome. However, no prospective studies have addressed this issue specifically.14 Moreover, reported results are contradictory and were derived from retrospective observational cohorts of patients with different clinical profiles with potential selection bias.15–17 Nevertheless, although undersized mitral valve annuloplasty has no clear demonstrable survival benefit, it has become the most popular surgical option, usually combined with coronary artery bypass surgery.18–21 Moreover, due to the high complexity of the mechanisms associated with IMR and according to the recurrence rate of IMR after isolated mitral ring annuloplasty, several groups have proposed complementary surgical approaches (subvalvular or ventricular).22–28 However, the effects of these new techniques also remain to be determined. In other words, a lot of questions remain unanswered and prospective large scale registries are required.

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Role of quantitative exercise echocardiography in the assessment of IMR

Stress testing has been largely validated in the setting of coronary artery disease.29 Conversely, valvular heart disease has been viewed as fairly static and management decisions have been based on resting evaluation alone.30,31 However, the evaluation of IMR only at rest underestimates the full severity of the lesion and its clinical impact.32,33 Indeed, IMR is dynamic with intermittent changes in the degree of regurgitation.34 This dynamic behaviour can be reliably quantified during exercise echocardiography using continuous imaging throughout exercise.35 Both the proximal isovelocity surface area and the Doppler methods emerged as the most accurate. During test, the magnitude of changes in IMR varies from patient to patient and does not correlate with the degree of IMR at rest.36,37 Most patients exhibit a small increase in IMR, whereas others have a large rise or a significant decrease in effective regurgitant orifice. This dynamic nature of IMR relates to changes in LV synchronicity,38–40 in mitral valve configuration (systolic tenting area, systolic expansion of the mitral annulus) and in mitral valve apparatus (papillary muscle displacement) at both ends of tethered leaflets.36,41,42 The decrease in IMR severity during exercise is observed mainly in patients with inferior infarction who have recruitable contractile reserve in the basal segments.36 Dynamic changes in IMR provide additional prognostic information over resting evaluation and unmask a subset of patients at high risk of morbidity and mortality independent from the degree of IMR at rest.43–46 The clinical management of patients with exercise-induced significant increases in IMR as well as the impact of surgery on dynamic IMR have never been examined.

The SIMRAM registry

The SIMRAM registry is a large prospective, multicentre, non-randomized study designed to evaluate the effects of surgery on IMR at rest and on its dynamic component at exercise. All participating centres will perform complete echocardiographic examinations including conventional and tissue Doppler imaging; according to the availability, select centres will also perform 3D echocardiographic studies and cardiovascular magnetic resonance imaging. Patients who satisfy all inclusion/exclusion criteria undergo exercise testing before coronary revascularization. The research protocol is approved by the locally appointed ethics committee.

Patients

Investigators at up to 17 centers in Europe and in Canada, plan to enroll approximately 550 patients with IMR in the SIMRAM registry. Enrolment started in November 2006 and will be concluded by early 2008.

Eligibility

Consecutive patients who present for elective surgical coronary revascularization with significant LV dysfunction (LV ejection fraction < 45%) and at least mild IMR (effective regurgitant orifice ≥ 10 mm²) will be prospectively enrolled in the study protocol. All patients must provide informed consent, agree to comply with the study design, and maintain scheduled follow-up visits.

Exclusion criteria

Exclusions to enrolment include the presence of unstable angina, recent myocardial infarction (< 3 months), organic mitral valve disease, atrial fibrillation or flutter before surgery, aortic regurgitation > grade 2, contra-indications to exercise test (refractory angina, ischaemia at low level on a previous stress test), New York Heart Association class IV, and echocardiographic images unsuitable for quantification. Data of patients screened but not included in the final study protocol will be also kept.

Exercise test

Beta-blockers should be withdrawn the day of the test whenever possible. A symptom-limited graded bicycle exercise test will be performed in a dedicated table. After an initial workload of 25 W maintained for 2 min, the workload will be increased every minute by 10 W. Blood pressure and a 12-lead electrocardiogram will be recorded every 2 min. Two-dimensional and Doppler echocardiographic recordings will be available throughout the test.

Echocardiographic measurements

Doppler echocardiography will be standardized to allow central reading at the core laboratory in Liège, Belgium. All 2D echocardiographic and Doppler data will be obtained in digital format and stored on optical disks for off-line analysis at rest and during exercise (Table 1). For each measurement, a minimum of three cardiac cycles will be averaged. Quantification of IMR will be performed by both the quantitative Doppler method using mitral and aortic stroke volumes and the proximal isovelocity surface area method.35,47 The results of these two methods will be averaged allowing calculation of regurgitant volume and effective regurgitant orifice. For the quantitative Doppler method, mitral and aortic stroke volumes will be calculated, and regurgitant volume refers to the difference between these two stroke volumes. Effective regurgitant orifice is the ratio of regurgitant volume to regurgitant time-velocity integral. For the proximal isovelocity surface area method, the radius of the convergence zone will be measured from at least three frames with optimal flow convergence. The largest radius, usually in mid systole, will be selected for analysis. The effective regurgitant orifice is the ratio of regurgitant flow to peak regurgitant velocity. LV end-diastolic and end-systolic volumes and ejection fraction will be measured by the biplane Simpson's rule. Global and regional LV remodelling and mitral valvular deformation will be assessed as described previously. The LV dP/dt – mitral valve closing force – will be estimated from the steepest rising segment of the mitral continuous-wave Doppler regurgitant jet. Colour-tissue Doppler will be performed in the apical views (2-, 3- and 4-chamber) to assess longitudinal myocardial regional function and cardiac synchronicity. Diastolic function and LV filling pressure will be assessed using the mitral inflow and peak velocities during early diastole obtained at the level of mitral annulus.
Data collection
Clinical information regarding age, gender, New York Heart Association class, coronary risk factors (diabetes mellitus, hypertension, cholesterol level, smoking), and medications use (beta-blockers, ACE inhibitors, angiotensin receptor blockers, nitrates, diuretics, spironolactone, anti-arrhythmic agents) will be recorded. The EuroSCORE will be automatically calculated for each patient. Plasma B-type natriuretic peptide will be measured. Laboratory findings will also include haemoglobin level, renal function and hs C-reactive protein. All echocardiographic recordings will be recorded preoperatively (<1 month before surgery) at rest and during exercise. A routine pre-discharge echocardiographic resting study will be obtained within 1 week of intervention. Follow-up visits will be obtained at rest and at exercise 3 and 12 months after surgery.

Surgical procedure
Coronary artery bypass surgery will be performed by an experienced surgical team. The cross clamp and bypass time will be notified as well as the number of vessels treated and the necessity of intra-aortic balloon pumping. The decision to perform mitral valve surgery as well as the technique used for repair will be made by the individual

Table 1  Echocardiographic parameters

<table>
<thead>
<tr>
<th>Standard echo data</th>
<th>Complex echo data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left atrial area (cm²)</td>
<td>Diastolic function</td>
</tr>
<tr>
<td>Mitral effective regurgitant orifice (mm²)</td>
<td>Mitral $E$ wave (cm/s)</td>
</tr>
<tr>
<td>Mitral regurgitant volume (mL)</td>
<td>Mitral $A$ wave (cm/s)</td>
</tr>
<tr>
<td>Transtricuspid pressure gradient (mmHg)</td>
<td>Mitral $E$ wave deceleration time (ms)</td>
</tr>
<tr>
<td>Left ventricular $dP/dt$ (mmHg/s)</td>
<td>LV filling time (ms)</td>
</tr>
<tr>
<td>Wall motion score index</td>
<td>Peak $E_s$ velocity (cm/s)</td>
</tr>
<tr>
<td></td>
<td>$E/E_s$ (average of four annuli)</td>
</tr>
<tr>
<td>Global LV remodelling</td>
<td>Dysynchrony</td>
</tr>
<tr>
<td>End diastolic volume (mL)</td>
<td>Left–right ventricular dyssynchrony (ms)</td>
</tr>
<tr>
<td>End systolic volume (mL)</td>
<td>Left ventricular systolic dispersion (ms)</td>
</tr>
<tr>
<td>Sphericity index (systolic + diastolic)</td>
<td>Mean time to peak systolic velocity (ms)</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>Systolic dyssynchrony index (ms)</td>
</tr>
<tr>
<td></td>
<td>Post-systolic shortening</td>
</tr>
<tr>
<td>Mitral valvular deformation</td>
<td></td>
</tr>
<tr>
<td>Tenting area (cm²)</td>
<td>Left ventricular diastolic dispersion (ms)</td>
</tr>
<tr>
<td>Coaptation height (cm)</td>
<td></td>
</tr>
<tr>
<td>Diastolic mitral annular area (cm²)</td>
<td></td>
</tr>
<tr>
<td>Systolic mitral annular area (cm²)</td>
<td></td>
</tr>
<tr>
<td>Mitral annular contraction (%)</td>
<td></td>
</tr>
<tr>
<td>Local LV remodelling</td>
<td>Longitudinal function (right + left)</td>
</tr>
<tr>
<td>PPM—fibrosa distance (cm)</td>
<td>Peak systolic velocity (septal, lateral, inferior, anterior, RV annulus)</td>
</tr>
<tr>
<td>Papillary muscles separation (mm)</td>
<td>Peak systolic strain (septal, lateral, inferior, anterior, RV basal + mid-segments)</td>
</tr>
<tr>
<td>Posterior displacement of PPM (mm)</td>
<td></td>
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<tr>
<td>Posterior displacement of APM (mm)</td>
<td></td>
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<tr>
<td>Lateral displacement of PPM (mm)</td>
<td></td>
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<tr>
<td>Lateral displacement of APM (mm)</td>
<td></td>
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<tr>
<td>Wall motion score index at papillary muscle level</td>
<td></td>
</tr>
</tbody>
</table>

PPM, posterior papillary muscle; APM, anterior papillary muscle; $E$ and $A$, early and late diastolic transmitral flow velocities; $E_s$, early diastolic mitral annular velocity; RV, right ventricle.

Table 2  Outcomes

<table>
<thead>
<tr>
<th>End points</th>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical (rest + exercise)</td>
<td>Cardiac death, myocardial infarction, worsening HF</td>
<td>All causes of death, myocardial infarction, worsening HF</td>
</tr>
<tr>
<td>Standard echo complex echo (rest + exercise)</td>
<td>Recurrent IMR; changes in systolic function; LV remodelling (global + regional); valvular deformation LV dyssynchrony</td>
<td>Mechanisms of recurrent IMR; changes in diastolic function; role of ischaemia on IMR Longitudinal function</td>
</tr>
<tr>
<td>Substudy</td>
<td>B-type natriuretic peptide; PR interval and QRS morphology</td>
<td>3D echocardiography; cardiac magnetic resonance</td>
</tr>
</tbody>
</table>

HF, heart failure; IMR, Ischaemic mitral regurgitation; LV, left ventricular.
surgery. Associated subvalvular approach and ventricular reconstruction will be also clearly identified.

Outcome features

The study design identifies three sets of outcome measures (Table 2). Clinical end points include all causes of death, cardiovascular death, myocardial infarction, worsening heart failure requiring hospital admission or heart transplantation and changes in New York Heart Association class. Major events will encompass cardiovascular death, myocardial infarction and worsening heart failure. Echocardiographic end points refer to recurrent IMR or persistent IMR at rest or during exercise and its mechanisms, changes in global and regional LV remodelling, changes in LV ejection fraction, and evolution of LV diastolic function. Reverse LV remodelling is defined as a reduction in LV end-systolic volume ≥ 15%. Improvement in LV ejection fraction is characterized by an increase ≥ 5%. Complex echocardiographic end points examine the effects of surgery in systolic and diastolic synchronicity and on longitudinal function. All end points will be analysed separately or combined as a composite outcome at hospital discharge and at 3 and 12 months of follow-up.

Discussion

IMR is common in patients with ischaemic LV dysfunction undergoing coronary artery bypass surgery. Although the presence of IMR negatively affects the prognosis, the benefit of treating it is debated. When IMR is severe, patients are often referred for simultaneous mitral valve surgery. The type of mitral valve intervention remains controversial and pre-operative predictors of repair failure are unknown. In moderate IMR, the clinical utility of mitral valve repair still remains unproven.48,49

Until recently, IMR has been evaluated nearly exclusively at rest. Exercise can however reveal the full severity of the lesion more accurately. Regardless of IMR degree at rest, patients with a dynamic increase in MR during exercise display a worse prognosis. This dynamic behaviour of IMR may accentuate the negative impact of pre-operative mild IMR. The management strategy of such patients has never been investigated.

The SIMRAM project will provide the largest database evaluating the effects of surgery on IMR at rest and on its dynamic component at exercise. Several hypotheses will be covered by this study protocol: the determinants of adverse outcome and progressive LV remodelling, efficacy of treatment, role of ischaemia on the dynamic behaviour of IMR.

We may postulate that pre-operative IMR, both at rest and at exercise, represents major determinants of adverse prognosis (death, worsening heart failure, heart transplantation) and ongoing LV remodelling (increase in LV volumes) following surgery. Prognosis can also be affected by the presence of LV dys synchrony, both at rest and during exercise. LV diastolic dysfunction prior to intervention may be another predictor of outcome. Post-intervention exercise test may unmask persistent impairment of diastolic function resulting in clinical worsening independently of recurrent IMR. These data will clarify the link between moderate IMR and outcome. Is poor prognosis due to altered valvular function or related to LV dysfunction?

Evaluating the dynamic behaviour of IMR during exercise prior to surgery can also help predict post-operative responses in terms of MR relief or persistent/recurrent IMR. The absence of functional recovery as assessed by longitudinal function will be associated with IMR persistence and adverse remodelling regardless of whether the mitral valve is repaired or not. Other pre-operative echocardiographic determinants of recurrent IMR will be extensively examined. Greater mitral valve deformation and severe local LV remodelling may play a crucial role and participate in the failure of mitral valve repair. Progressive LV remodelling secondary to the evolution of the ischaemic disease may also affect post-intervention IMR at rest and during exercise.

The dynamic behaviour of IMR can be positively affected or unaltered following surgery. Persistent post-intervention dynamic IMR will be observed in patients in whom IMR is already dynamic pre-operatively. Improvement of IMR may occur in the absence of mitral valve surgery in patients with recruitable contractile reserve in the basal inferior wall and exercise-induced decreases in IMR pre-operatively.

Residual dynamic IMR after intervention may also contribute to reduced post-operative exercise tolerance.

Conclusion

The SIMRAM registry is assessing multiple clinical and pathophysiologic aspects of IMR with the goal of providing further insight into the mechanism of IMR and potentially improving current management. This study will also define the place of pre- and post-operative exercise testing in the evaluation of IMR and will provide a list of predictive markers of outcome.

References

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