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Long-term outcome of patients with heart failure and dynamic functional mitral regurgitation

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Aims In patients with heart failure and chronic ischaemic mitral regurgitation (MR), the mortality risk is related to the quantified severity of MR at rest and its dynamic changes during exercise. The impact of dynamic MR on long-term mortality, hospital admission for heart failure, and major adverse cardiac events has never been investigated.

Methods and results We prospectively studied 161 patients with chronic ischaemic left ventricular (LV) dysfunction and at least mild MR who underwent quantitative measurement of the effective regurgitant orifice (ERO) of MR at rest and during semi-supine exercise test and who were followed up for 35 ± 11 months. The 20 patients who underwent surgery were censored at the time of operation. Of the 141 patients who were treated medically, 23 died, 22 required hospitalization for heart failure, 4 had non-fatal myocardial infarction, and 11 developed unstable angina. By multivariate analysis, an exercise-induced increase in ERO by $\geq 13\,mm^2$ and a greater increase in transtricuspid pressure gradient during exercise emerged as predictors of mortality and of hospital admission for heart failure. MR severity under basal conditions (ERO $\geq 20\,mm^2$) was an independent predictor of only cardiac death. Greater LV volumes at rest and lack of contractile reserve during exercise were additional independent markers of poor outcome.

Conclusion In patients with ischaemic heart disease and LV dysfunction, large exercise-induced increases in MR identify patients at high risk of morbidity and of death.

Introduction

Functional mitral regurgitation (MR) is a common complication of ischaemic heart disease.[1] Its incidence and clinical importance are, however, largely underestimated, partly because physical examination is rather insensitive.[2] It results from distortion of left ventricular (LV) geometry tethering the structurally normal mitral leaflets and from decreased LV force to close them.[3] Ischaemic MR can be accurately quantitated by Doppler echocardiography. The effective regurgitant orifice (ERO) area of MR is the most useful measurement.[4] Quantified severity of MR (ERO $\geq 20\,mm^2$) is a marker of increased mortality.[5] Ischaemic MR is characteristically dynamic.[6] The dynamic component can be reliably quantitated during exercise.[7] Large exercise-induced increases in ERO ($\geq 13\,mm^2$) unmask patients at high risk of short-term mortality.[8]

We aimed to evaluate whether the dynamic component of ischaemic MR is also an independent predictor of long-term mortality, hospital admission for cardiac decompensation, and major adverse cardiac events.

Methods

Patients

Between May 1998 and December 2003, 161 consecutive patients with chronic ischaemic LV dysfunction (ejection fraction $\leq 45\%$) and at least mild functional MR underwent quantitative exercise Doppler echocardiography. All of them were stable since at least 2 months and none had the following exclusion criteria: technically inadequate echocardiogram, more than trivial aortic regurgitation, intraventricular conduction abnormality, functional class IV, history of myocardial infarction <6 months, and atrial fibrillation or flutter or evidence of inducible ischaemia on upright exercise test. Successful prospective follow-up for future cardiac events was obtained in all patients. The protocol was approved by the ethics committee of the Liège University Hospital and all patients gave their informed consent.

Procedures

Beta-blockers were stopped 24 h before the test. A symptom-limited graded bicycle exercise test was performed in semi-supine position on a tilting exercise table. After an initial workload of 25 W maintained for 6 min, the workload was increased every 2 min by 25 W. Blood pressure and a 12-lead electrocardiogram were recorded every 2 min. Two-dimensional and Doppler echocardiographic recordings were available throughout the test. Echocardiographic examinations were performed using a phased

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array Acuson Sequoia imaging device. All echocardiographic and Doppler data were obtained in digital format and stored on optical disks for off-line analysis. Quantitation of MR was performed by both the quantitative Doppler method using mitral and aortic stroke volumes and the proximal isovelocity surface area (PISA) method as previously described.[4,7] The results of these two methods were averaged for calculation of the ERO. LV volumes and ejection fraction were measured by the biapical Simpson disk method. Systolic pulmonary arterial pressure was estimated from the systolic transtricuspid pressure gradient (in mmHg) using the simplified Bernoulli equation ($\Delta P = 4V^2$, where V = maximal tricuspid regurgitant velocity in m/s). The deceleration time (in ms) of the E-wave velocity obtained by pulsed wave Doppler was also measured.

Statistical analysis

Continuous variables are expressed as mean ± SD. Student's *t*-test was used to assess differences between mean values, and categorical variables were compared with χ^2 test. The endpoints were cardiac mortality, hospital admission for worsening heart failure, and a combined endpoint of major adverse cardiac events (cardiac death, admission for heart failure, nonfatal myocardial infarction, and unstable angina). Analysis was performed by censoring follow-up at the time of cardiac surgery if eventually performed. The individual effects of clinical, rest, and exercise Doppler echocardiographic variables on event-free survival were evaluated with the use of the Cox proportional hazard regression model. To select the factors most predictive of cardiac events, an unmodified forward-selection stepwise analysis was performed (STATISTICA version 5). The variable that had the most significant relation with dependent outcome was included first in the model. At the second and subsequent steps, the set of remaining variables were evaluated, and the most significant was included if it significantly improved the prediction of outcome. The algorithm ceased to select variables when there was no further significant improvement in the prediction of the whole model. MR was used in the model as continuous or categorical variables. The Kaplan–Meier method was used for cumulative survival analysis with the log-rank test for assessing statistical differences between curves. $P < 0.05$ was considered significant.

Results

Clinical characteristics

The study population comprised 107 men and 54 women, aged 65 ± 11 years. Patients were in New York Heart Association functional class I ($n = 18$), II ($n = 104$), or III ($n = 39$). The site of previous myocardial infarction was anterior in 68 patients, inferior in 72 and both anterior and inferior in 21. Medications included an angiotensin-converting enzyme inhibitor in 125 patients, diuretic in 70, beta-blocker in 99, nitrate in 58, and spironolactone in 38. A history of systemic arterial hypertension was noted in 71 patients, and 39 patients were diabetic. Twenty-nine patients had previously been submitted to surgical revascularization.

Baseline and exercise characteristics

During the exercise test, no patient developed ischaemia. The ERO of MR increased from 17 ± 9 mm^2 (range: 3.5–50 mm^2) at rest to 25 ± 13 mm^2 (range: 0.5–66 mm^2) at peak exercise ($P < 0.0001$) (*Table 1*). The ERO increased by ≥13 mm^2 in 48 patients. Of the 51 patients with severe MR (ERO ≥ 20 mm^2) at rest, ERO increased by ≥13 mm^2 in only 20 patients (39%). Of the 48 patients with increases in ERO by ≥13 mm^2, 28 (58%) had mild MR at rest. The ERO decreased in 18 patients.

Table 1 Haemodynamic and Doppler echocardiographic parameters at rest and their exercise induced changes ($n = 161$ patients)

Rest	
Heart rate (beats/min)	74 ± 12
Systolic arterial pressure (mmHg)	128 ± 15
LV end-diastolic volume (mL/m^2)	144 ± 30
LV end-systolic volume (mL/m^2)	93 ± 25
LV ejection fraction (%)	36 ± 7
Mitral deceleration time (ms)	178 ± 51
ERO (mm^2)	17 ± 9
ERO ≥ 20 mm^2 *n* (%)	51 (32)
Transtricuspid pressure gradient (mmHg)	27 ± 10
Difference between exercise and rest	
Heart rate (beats/min)	39 ± 14*
Systolic arterial pressure (mmHg)	27 ± 17*
LV end-diastolic volume (mL)	0.51 ± 18
LV end-systolic volume (mL)	−8.3 ± 17*
LV ejection fraction (%)	8 ± 7*
ERO (mm^2)	8 ± 10*
ERO ≥ 13 mm^2 *n* (%)	48 (30)
Transtricuspid pressure gradient (mmHg)	19 ± 13*

*Significant difference ($P < 0.05$).

Cardiac events

The patients were followed for 35 ± 11 months (range: 2–53). The median was 36 months and the interquartile range 30–42. Twenty patients were treated by surgery: 4 underwent cardiac transplantation and 16 patients were treated by mitral annuloplasty ($n = 14$) and/or by bypass surgery ($n = 12$). In this subgroup, three patients died: one during the perioperative period, and two 1 year later (one from fatal myocardial infarction and one from acute pulmonary oedema). These 20 patients were censored at the time of cardiac surgery. Of the 141 patients treated medically, 23 died (7 from sudden death, 9 from refractory heart failure, and 7 from fatal myocardial infarction), 22 patients were admitted in the hospital for worsening heart failure, 4 had nonfatal myocardial infarction, 11 developed unstable angina, 7 were treated by cardiac resynchronization therapy ($n = 4$) and/or implantable defibrillator ($n = 4$), and 1 had permanent right ventricular stimulation for high degree AV-block. Among the 23 patients who died, 4 had been admitted and discharged from the hospital for heart failure before their death.

Predictors of cardiac death

In univariate analysis, patients who died had, more often, arterial hypertension (15/23 vs. 56/138, $P = 0.028$) and displayed in baseline conditions higher LV end-diastolic volume (155 ± 21 vs. 141 ± 30 mL/m^2, $P = 0.03$) and ERO (24 ± 11 vs. 16 ± 8 mm^2, $P < 0.0001$). Patients with ERO ≥20 mm^2 at rest had a high mortality rate (16/23 vs. 35/138, $P < 0.0001$). During exercise, increases in ERO and in transtricuspid pressure gradient were larger in patients who died: 18 ± 11 vs. 7 ± 4 mm^2, $P < 0.0001$ and 29 ± 12 vs. 17 ± 5 mmHg, $P < 0.0001$, respectively. Patients with exercise-induced increases in ERO by ≥13 mm^2 displayed a

higher mortality (17/23 vs. 31/138, $P < 0.0001$). One of the 18 patients with a decrease in ERO during exercise died during follow-up. In multivariate analysis, ERO at rest ($P = 0.0003$), and larger exercise-induced increases in transtricuspid pressure gradient ($P = 0.01$) and in ERO ($P < 0.0001$) emerged as independent predictors of cardiac death. With MR as a categorical variable, an increase in ERO by ≥ 13 mm^2 during exercise and an ERO > 20 mm^2 at rest were selected in the final model (*Table 2*; *Figure 1*).

Determinants of hospital admission for heart failure

During follow-up, a total of 26 patients were hospitalized for cardiac decompensation. These patients had higher LV end-diastolic (158 ± 35 vs. 140 ± 28 mL/m^2, $P = 0.0002$) and end-systolic volume (106 ± 31 vs. 90 ± 22 mL/m^2, $P < 0.0001$) in baseline conditions. Their LV ejection fraction was lower (33 ± 8 vs. $36 \pm 7\%$, $P = 0.029$). During exercise, increases in ERO (16 ± 10 vs. 7 ± 10 mm^2, $P < 0.0001$) and in transtricuspid pressure gradient (28 ± 15 vs. 17 ± 12 mmHg, $P < 0.0001$) were larger in patients who were admitted for heart failure. In contrast to patients with severe MR at rest (11/26 vs. 40/135, $P = 0.1$), patients with exercise-induced increases in ERO by ≥ 13 mm^2 (18/26 vs. 30/135, $P < 0.0001$) presented a higher incidence of worsening heart failure. In multivariate analysis, a larger increase in ERO ($P = 0.0003$) and in transtricuspid pressure gradient during exercise ($P = 0.004$) and a higher LV end-systolic volume ($P = 0.03$) emerged as independent predictors of hospital admission for heart failure. With MR as a categorical variable, an increase in ERO by ≥ 13 mm^2 during exercise was selected in the multivariate model (*Table 3*; *Figure 2A*).

Predictors of major adverse cardiac events

During follow-up, a total of 60 adverse cardiac events was noted. In univariate analysis, higher LV end-diastolic ($P = 0.0008$) and end-systolic volumes ($P = 0.0041$) were associated with the occurrence of cardiac events. During exercise, increases in ERO ($P = 0.004$) and in transtricuspid pressure gradient ($P < 0.0001$) were larger in patients who experienced events, whereas LV ejection fraction was lower at peak exercise ($P = 0.0002$). In multivariate analysis, an increase in ERO by ≥ 13 mm^2 (categorical variable) during exercise, an exercise-induced decrease or small increase in LV ejection fraction and high LV end-diastolic volume were independent predictors of major adverse cardiac events (*Table 4*; *Figure 2B*).

Discussion

We have confirmed by a long follow-up of a large cohort of patients with ischaemic LV dysfunction that both quantified severity of MR and a large increase in the degree of MR during exercise are associated with increased mortality risk. In addition, we have shown the strong prognostic importance of the dynamic component of ischaemic MR which best predicted hospital admission for worsening heart failure and the occurrence of major adverse cardiac events. In contrast, the degree of MR at baseline was not an independent predictor of morbidity. The risk of hospital admission for heart failure was also independently determined by exercise-induced increase in pulmonary vascular pressure and more severe LV remodelling, as indicated by large LV end-systolic volume. A large increase in ERO during exercise had again

Table 2 Multivariate predictors of time to cardiac death

	HR (95% CI)	*P*-value
ERO diff ≥ 13 mm^2	5.0 (1.9–13)	0.0009
ERO ≥ 20 mm^2	4.5 (1.8–11)	0.001
Transtricuspid pressure gradient diff	1.03 (1.00–1.09)	0.02

diff, difference between exercise and rest; HR, hazard ratio; CI, confidence interval.

Table 3 Factors predictive of hospital admission for heart failure as obtained by stepwise Cox proportional hazard regression analysis ($n = 161$ patients)

	HR (95% CI)	*P*-value
ERO diff ≥ 13 mm^2	3.6 (1.4–9.2)	0.0082
Transtricuspid pressure gradient diff	1.05 (1.01–1.08)	0.009
LV end-systolic volume	1.02 (1.01–1.04)	0.016

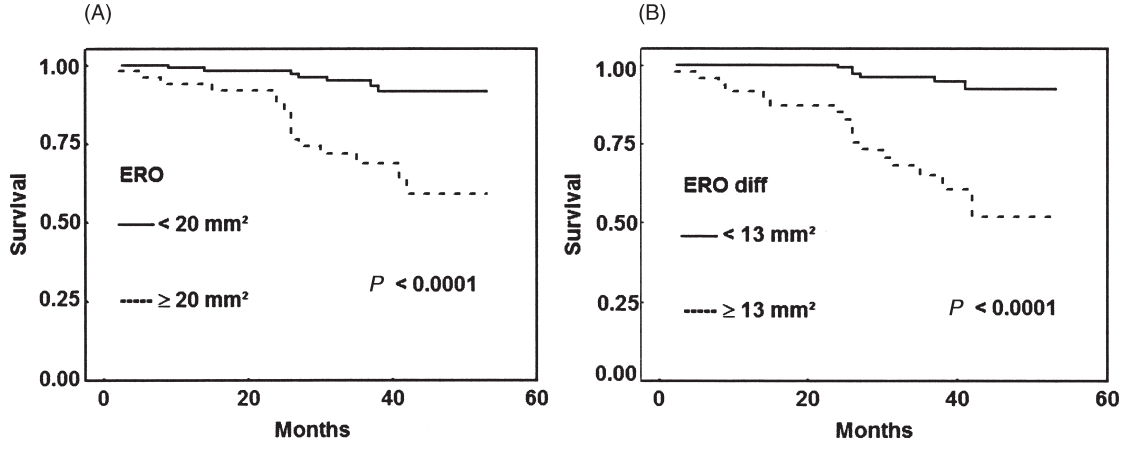

Figure 1 Survival curves according to the severity of MR. (*A*) at rest and (*B*) during exercise.

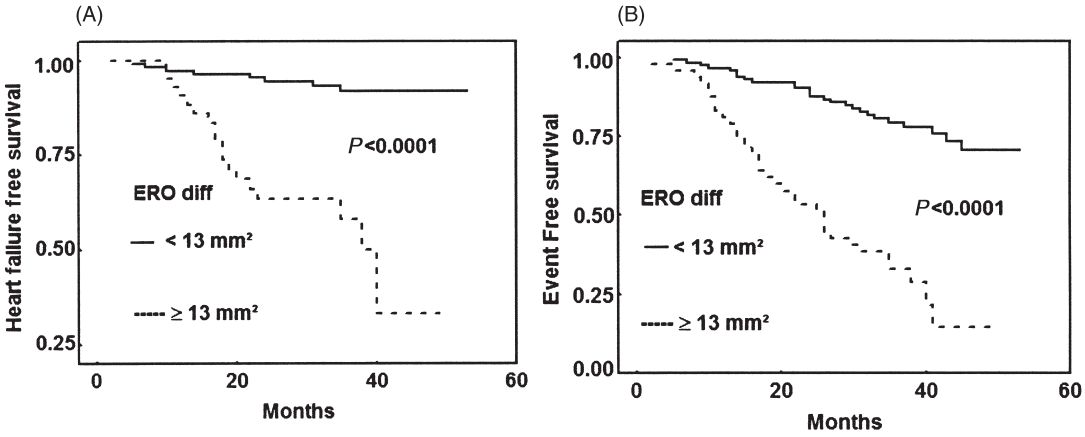

Figure 2 (*A*) Proportion of patients without admission for heart failure and (*B*) without major adverse cardiac events, according to exercise-induced differences in effective regurgitant orifice area of mitral regurgitation.

Table 4 Factors predictive of major adverse cardiac events as obtained by stepwise Cox proportional hazard regression analysis ($n = 161$ patients)

	HR (95% CI)	*P*-value
ERO diff $\geq$ 13 mm^2	4.42 (2.61–7.53)	0.0001
LV ejection fraction diff	1.04 (1.00–1.09)	0.023
LV end-diastolic volume	1.01 (1.00–1.02)	0.032

the highest prognostic value for predicting major adverse cardiac events, including mortality, admission for heart failure, nonfatal myocardial infarction, and unstable angina. Additional independent predictors of this combined end-point were larger LV end-diastolic volume and lack of contractile reserve.

Our observations emphasize the importance of exercise Doppler echocardiography in the setting of ischaemic heart failure. Indeed, one-third of the patients with a large exercise-induced increase in MR who died had moderate MR at rest. In addition, only one of the 18 patients who exibited a decrease in MR during exercise died during follow-up.

The rates of admission for heart failure and major adverse cardiac events were similar in patients with either mild or severe MR at rest. Although 70% of the patients with no or small exercise-induced increases in MR had an uneventful clinical course, 81% of the patients with significant dynamic changes in MR during exercise experienced an event during follow-up.

The link between a significant increase in MR during exercise and cardiac events could involve several mechanisms. Intermittent increases in MR severity during everyday life activities or during night can acutely rise left atrial and pulmonary vascular pressures contributing to worsening of dyspnoea and flash pulmonary oedema.[7,9,10] Acute increase in pulmonary systolic artery pressure as estimated by the exercise-induced changes in transtricuspid pressure gradient was also an independent predictor of cardiac death and of admission for heart failure. Such increases result at least in part from the dynamic changes in MR.[7] Other haemodynamic factors can play a role, such as pulmonary vascular compliance. Repetitive transient increase in MR may also worsen LV volume overload and contribute to myocardial disease progression.[11] Impaired LV contractile reserve, a marker of more severe disease, leads to inadequate cardiac adaptation to exercise. Dynamic MR is also a determinant of rapid increase in QRS duration at short-term follow-up; this may subsequently induce permanent electromechanical dyssynchronization.[12] LV asynchrony further deteriorates LV systolic function which in turn reduces mitral valve closing force and accelerates the progression to refractory heart failure.[13,14]

Limitations

Our results pertain only for patients who are not in New York Heart Association (NYHA) class IV and who are capable of exercising in a semi-supine position. None of the patients had an evidence of exercise-induced myocardial ischaemia which obviously might influence the prognosis. The absence of exercise-induced ischaemia was mainly based on clinical and electrocardiographic evaluation which are known to be less sensitive in patients with previous myocardial infarction. For technical reasons, rest and exercise images were not recorded side-by-side or in a quad-screen format to specifically evaluate ischaemia. The Doppler methods performed to quantify MR have some pitfalls.[4] The values of the ERO are low but this is consistent with previous reports concerning patients with functional MR.[5] Moreover, the two quantitative methods used in this study have been validated at rest and during exercise in our institution.[7] Treatment was not standardized and specific management was given by the cardiologist in charge of the patients. The potential benefit of surgical treatment was not assessable.

Conclusion

This study showed that in chronic heart failure patients, the evaluation of ischaemic MR only at rest underestimates the full severity of the lesion and its prognostic impact. Quantitative measurement of MR by Doppler echocardiography during exercise has strong prognostic importance.

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