Right Ventricular Systolic Function in Organic Mitral Regurgitation:

Impact of Biventricular Impairment

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Abstract:

**Background**—To assess the prevalence, determinants and prognosis value of right ventricular (RV) ejection fraction (EF) impairment in organic mitral regurgitation (MR).

**Methods and Results**—Two-hundred-eight patients (62±12 years, 138 males) with chronic organic MR referred to surgery underwent an echocardiography and bi-ventricular radionuclide angiography with regional function assessment. Mean RV EF was 40.4±10.2%, ranging from 10 to 65%. RV EF was severely impaired (≤35%) in 63 patients (30%), and biventricular impairment (LV EF<60% and RV EF≤35%) was found in 34 patients (16%). Pathophysiologic correlates of RV EF were LV septal function (\(\hat{\beta} =0.42, P<0.0001\)), LV end diastolic diameter index (\(\hat{\beta} =0.22, P=0.002\)) and PASP (\(\hat{\beta} =0.14, P=0.047\)). Mitral effective regurgitant orifice size (n=84) influenced RV EF (\(\hat{\beta} =-0.28, P=0.012\)). In 68 patients examined after surgery, RV EF increased strongly (27.5±4.3 to 37.9±7.3, P<0.0001) in patients with depressed RV EF while it did not change in others (P=0.91). RV EF≤35% impaired 10-year cardiovascular survival (71.6±8.4% versus 89.8±3.7%, P=0.037). Biventricular impairment dramatically reduced 10-year cardiovascular survival (51.9±14.3% versus 90.3±3.2%, P<0.0001, HR: 5.2, P<0.0001) even after adjustment for known predictors (HR: 4.6, P=0.004). Biventricular impairment reduced also 10-year overall survival (34.8±13.0% versus 72.6±4.5%, P=0.003; HR: 2.5, P=0.005) even after adjustment for known predictors (P=0.048).

**Conclusion**—In patients with organic MR referred to surgery RV function impairment is frequent (30%) and depends weakly on PASP but mainly on LV remodelling and septal function. RV function is a predictor of postoperative cardiovascular survival while biventricular impairment is a powerful predictor of both cardiovascular and overall survival.

**Key words:** mitral regurgitation, right ventricular function, radionuclide imaging, echocardiography, surgery
Ventricular function is an important determinant of preoperative and postoperative outcome of mitral regurgitation (MR). This is well known in regard to left ventricular (LV) function, which figures prominently in the clinical guidelines for surgical indications\textsuperscript{1,2} but it is less well known in regard to right ventricular (RV) function, which is currently not a clear part of the management of patients with MR. Pilot studies suggested that RV ejection fraction (EF) is depressed in patients with chronic organic MR\textsuperscript{3-6}. Right ventricular (RV) systolic performance is influenced by pulmonary artery systolic pressure (PASP)\textsuperscript{7,8}. In organic MR, elevated PASP increases RV afterload and is thought to elicit progressive RV failure, particularly in patients with disproportionate PH\textsuperscript{9}. Right ventricular alterations are thus perceived as secondary to the frequent pulmonary hypertension (PH) observed in patients with organic MR,\textsuperscript{9-12} even in those with normal LV systolic function\textsuperscript{9}.

Right ventricular systolic function is a well known predictor of mortality after acute myocardial infarction or CABG, in chronic heart failure or primary PH\textsuperscript{13-16}. Limited data raised the question of whether RV function influences the prognosis of patients with chronic organic MR\textsuperscript{3,4,17,18} but these small series could not be fully conclusive.

By contrast, PH is a predictor of outcome under medical treatment\textsuperscript{11} or after surgery\textsuperscript{10,11} in patients with organic MR. In addition, exercise-induced PH has been lately identified as a predictor of symptom onset in organic MR\textsuperscript{19}. Pulmonary hypertension is therefore an indication for surgery in patients with severe organic MR\textsuperscript{1,2} but whether RV alterations and implications for outcome are purely linked to PH or influenced by other factors is uncertain.

Therefore, in a cohort of patients referred to surgery for chronic organic MR, we sought to assess the prevalence of RV EF impairment, the pathophysiologic determinants of RV systolic function, and its actual impact on postoperative outcome, particularly in patients with depressed...
LV function.

Materials and Methods

Study Population

Two-hundred eight patients with chronic organic MR referred to surgery who underwent a preoperative LV and RV radionuclide angiography between January 1994 and December 2006 were included in this study. Patients with non organic MR, other significant valve disease (excepted tricuspid regurgitation), previous myocardial infarction or mitral valve surgery, or at least moderate pulmonary disease or pericardial disease were excluded from this study. The study was approved by the local ethics committee.

Echocardiography

All echocardiograms were performed by experienced investigators (T.L.T., A.S.P) using a commercially available echocardiograph. All values were obtained from the mean of 3 beats and from the mean of 5 to 10 beats in patients with atrial fibrillation (AF). All data were prospectively recorded and were transferred without alteration for the purpose of the study.

Left ventricular end-diastolic and end-systolic diameter (LVEDD and LV ESD) were measured in the parasternal long axis view by using M-mode or 2D images. Right ventricular diameter was measured in the parasternal long-axis view. Left atrial diameter (LAD) was measured at ventricular end-systole in the parasternal long-axis view. Mitral regurgitation degree was assessed either by a quantitated or semi-quantitated method according to guidelines. The mitral flow profile was recorded in the four-chamber apical view, with the sample positioned at the tips of the leaflets. The peak Doppler velocities of early (E) and late diastolic mitral flow (A), the mitral E-wave deceleration time (mitral DT), and the E/A ratio were measured. The tricuspid regurgitant velocity was recorded from any view with continuous-wave Doppler and was used to
determine PASP using the modified Bernoulli equation.

Tissue Doppler profiles were recorded in 98 patients at the medial and lateral mitral annulus from the apical 4-chamber view. Systolic tissue velocity (S), early diastolic (E’) and late diastolic (A’) tissue velocities were recorded, and the medial and lateral E/E’ ratio were calculated. Systolic tissue S wave velocity of tricuspid annulus was recorded at the free wall of the right ventricle in most of these patients (n=91).

Radionuclide angiography

All patients underwent baseline radionuclide angiography during preoperative hospital workup. Radionuclide angiography was performed at rest in the supine position using red blood cells labeled in vivo with 20mCi of technetium-99m. Data were acquired in the left anterior oblique view at 45°. All studies were formatted at 16 frames per cardiac cycle. RR intervals and heart rate (beats/min) were recorded. Cardiac cycles with RR intervals that were not within 20% of the average value were discarded. LV and RV ejection fraction (EF) were determined using the equilibrium technique by automated detection of end diastolic and end systolic contours, with manual correction if necessary. Both LV and RV were divided into nine regions to analyze regional EF in the left anterior oblique view at 45° (Figure 1). The LV was divided into regions 1 and 9 for the base, regions 2-4 for the posterolateral region, 5 and 6 for the antero-apical region, 7 and 8 for the septal region. Regions 1, 6, 7, 8, 9 are considered to explore the medial part of the LV, and regions 2, 3, 4, 5 the lateral part of the LV. The RV was also divided into nine regions: regions 1 and 2 for the base, regions 3 and 4 for the septal region, 5 and 6 for the antero-apical region, 7, 8 and 9 for the free wall of the RV. Regions 2, 3, 4, 5 are considered to explore the medial part of the RV, and regions 1, 6, 7, 8, 9 the lateral part of the RV. The inter-ventricular septum function (Figure 1) was defined as the mean value of regional LV EF 7 and 8 for the LV
(LV septal function), and as the mean value of regional RV EF 3 and 4 for the RV (RV septal function). All radionuclide angiography were performed by the same experienced investigator (C.F.) and analyzed at the time of preoperative hospital workup.

**Surgery**

The decision regarding the type of corrective surgery was made by the cardiovascular surgeon on the basis of preoperative data and after assessment of the anatomic status of the mitral valve during surgery. All patients were postoperatively anticoagulated for 3 months. After 3 months oral anticoagulation was continued in patients with AF, flutter and mechanical valves, but discontinued in other patients.

**Follow-up**

Sixty-eight patients underwent a second radionuclide angiography in our institution within 1 year (216±80 days) after surgery. Last follow-up was achieved by phone contacts with patients, general practitioner and cardiologists in 2010. Mean follow-up time was 7.1±4.3 years after surgery, giving a total follow-up of 1448 years. The main endpoint was cardiovascular mortality.

**Statistical analysis**

Results are expressed as mean ± SD or number (percent). Comparisons between groups were performed with Student’s t tests or with $\chi^2$ tests as appropriate. Comparisons of changes from pre-op to post-op were based on paired Student’s t tests. Correlations between variables were assessed by linear regression for continuous variables and Spearman correlation for categorical variables. To identify pathophysiological correlates of RV EF we restricted the explanatory variables to age and gender, rhythm (atrial fibrillation), echocardiographic (LV end diastolic and end systolic diameters, LV fractional shortening, LV mass, LA diameter, PASP, MR grade/quantification, tricuspid regurgitation grade) and isotopic variables (LV EF, LV septal...
function, LV regional EF 1 to 6 and 9). Candidate variables were entered into a stepwise multivariate regression analysis. Long-term survival and cardiovascular survival rates were calculated by the Kaplan-Meier method. The Log-rank test was used to compare event rates. The association of LV and RV EF to endpoints (cardiovascular mortality and overall mortality) used the Cox proportional-hazards method without and with adjustment for known predictors of outcome. Adjustment variables were age, gender, NYHA class 3-4, atrial fibrillation, LV end-systolic diameter, PASP, type of surgery performed (mitral valve repair/replacement) and CABG. A P value ≤0.05 was considered statistically significant.

Results

Baseline Characteristics

Baseline clinical and surgical characteristics of the entire patient population are shown in the left part of table 1 and baseline echocardiographic and isotopic data are shown in table 2. Mean age was 62±12 and 138 (66%) patients were male. Atrial fibrillation was present in 57 (27%) patients at the time of surgery, 75 (36%) patients were in NYHA class 3-4. The main etiology of MR was degenerative (prolapse or flail leaflet) in 183 (88%) patients. Mitral regurgitation was grade 3 or grade 4 in all patients. In patients with MR quantitation (n=84) effective regurgitant orifice averaged 0.48±0.19 cm² and regurgitant volume 74±27 mL.

Right Ventricular Systolic Function

Right ventricular (RV) EF averaged 40.7 ± 10.1% ranging from 10 to 65%. Right ventricle S wave velocity (measured in 91 patients) correlated weakly with RV EF (r=0.28, P=0.006). Patients were stratified into 2 groups (RV EF ≤ or > 35%) according to previous studies⁴,²¹. Sixty-three patients (30%) had a RV EF ≤ 35% before surgery. Baseline clinical and surgical
characteristics of patients with RV EF ≤ or > 35% are shown in the right part of table 1 and baseline echocardiographic and isotopic data in the right part of table 2. Patients with RV EF ≤ 35% had more severe MR, a larger LV and RV, lower LV EF and higher PASP (Table 2). Biventricular impairment, defined as LVEF < 60% and RVEF ≤ 35%, was found in 34 patients (16% of the entire patient population but 54% of patients with RVEF ≤ 35%).

**Regional Right and Left Ventricular Function**

Regional RV EF 2, 5-6 and RV septal function were decreased (P<0.001 for all) in patients with RV EF ≤ 35% compared with those with RV EF > 35% (**Figure 2A**). By contrast, regional RV EF 7-9 did not differ significantly between the 2 groups. Regional RV EF 1, 2, 5, 6 correlated significantly with RV EF in the entire patient population (r=0.42 to 0.60, all P<0.0001). Septal function of the RV correlated tightly with RV EF (r=0.57, P<0.0001) suggesting that RV septal function is an important component of RV EF in these patients. Regional RV EF 7-9 did not correlate or correlated only weakly with RV EF (r=0.13 to 0.22, P=0.04 to 0.17).

Regional LV EF 1, 6, 9 and LV septal function were decreased (P<0.001 for all) in patients with RV EF ≤ 35% compared with those with RV EF > 35%. By contrast, regional LV EF 2-5 were not significantly decreased (**Figure 2B**).

**Pathophysiologic Correlates of Right Ventricular Ejection Fraction**

In univariate analysis, predictors of RV EF were LV end-diastolic diameter indexed to body surface area (EDD index, r=-0.27, P<0.0001), LV end-systolic diameter index (ESV index, r=-0.25, P<0.0001), LA diameter (r=-0.25, P<0.0001), radionuclide LV EF (r=0.32, P<0.0001), regional LV EF 1, 6, 9 (r=0.29 to 0.37, all P<0.0001) and LV septal function (r=0.49, P<0.0001). The relation of RV EF to PASP (r=-0.24, P<0.0001) was relatively weak (**Figure 3**). Moreover, PASP was ≥ 50 mmHg in 28 (44%) patients with impaired RV EF but also in 37 (26%) patients.
with preserved RV EF (P=0.01). Age and gender did not influence RV EF in these patients with MR referred to surgery.

By multivariate analysis (Table 3), pathophysiologic correlates of RV EF were LV septal function (\( \hat{\beta} = 0.42, P<0.0001 \)), LV EDD index (\( \hat{\beta} = -0.22, P=0.002 \)) and PASP (\( \hat{\beta} = -0.14, P=0.047 \)).

In the subgroup with MR quantitation (n=84) RV EF correlated inversely with mitral effective regurgitant orifice (ERO, \( r=-0.28, P=0.012 \)), regurgitant volume (\( r=-0.25, P=0.021 \)) or regurgitant fraction (\( r=-0.28, P=0.015 \)). Left ventricular diameters and PASP (\( P=0.05 \) to 0.10) correlated marginally with RV EF. In a stepwise multivariate analysis the only predictor of RV EF was mitral ERO or regurgitant volume (Table 3).

**Surgery and Operative mortality**

After in-hospital assessment 4 out of 208 patients were not operated for very high operative risk (n=3) and overestimation of MR degree (n=1). Among these patients 2 had a RV EF \( \leq 35\% \). One hundred forty-eight patients (73%) underwent mitral valve repair and 56 (27%) mitral valve replacement with either mechanical (n=38, 19%) or bioprosthetic valves (n=18, 9%). Associated procedures included left atrial radiofrequency ablation in 35 patients (17%), tricuspid annuloplasty in 11 (5.3%), and coronary artery bypass (CABG) in 7 (3.4%).

Four (1.96%) out of 204 operated patients died within 30 days of surgery. Early postoperative mortality was 1.6% (1 patient) in those with RV EF \( \leq 35\% \) and 2.1% (3 patients) in those with RV EF \( > 35\% \) (\( P=0.69 \)).

**Changes in RV function after surgery**

Sixty-eight patients underwent LV and RV radionuclide angiography within 1 year (on average 215±92 days) after surgery. Baseline characteristics of this subgroup of patients are shown Table
4 and did no differ significantly compared with the rest of the patient population in terms of age, gender, comorbidities, LV remodelling, global and regional LV and RV EF. After surgery LV EF did not change significantly (62.2±10.3 to 60.4±10.4, P=0.13) while RV EF increased (40.3±10.6 to 43.6±8.7, P<0.0001) in these patients. Right ventricular EF increased strongly (27.5±4.3 to 37.9±7.3, P<0.0001) in the 21 patients with preoperative RV EF ≤35% while it did not change (46.0±6.9 to 46.1±8.2, P=0.91) in those (n=47) with preoperative RV EF >35% (Figure 4). However, the difference in RV EF after surgery (8.2 points of EF) remained highly significant (P=0.0002) between the 2 groups. In the same time, LV EF did not change significantly in patients with preoperative RV ≤35% (56.1±11.3 to 58.6±10.7, P=0.20) but decreased slightly in those with preserved RV EF before surgery (64.9±8.7 to 61.3±10.2, P=0.008). LV EF did not differ between the 2 groups after surgery (P=0.37). Despite RV translation due to surgery⁶, changes in regional RV EF 2, 5 (P=0.005 and P=0.02) and RV septal EF (P=0.0025) as well as in LV septal function (P=0.039) were significantly better in patients with preoperative RV EF ≤35% compared with those with RV EF > 35% (Figure 5A and B).

Long-term follow-up

Among the 204 patients who underwent surgery 57 patients died during the post-operative follow-up of 7.1±4.3 years. Cause of death was cardiovascular in 23 patients.

Patients with impaired (≤ 35%) compared with preserved (>35 %) preoperative RV EF had a lower cardiovascular survival rate (Figure 6A) at 10 years (71.6±8.4% versus 89.8±3.7%, P=0.037) with a HR of 2.3 (95% CI 1.1-5.3, P=0.042). Irrespective of RV EF patients with LV EF ≥ 60% had an excellent cardiovascular survival rate 10 years after surgery (on average 92.8±2.7%). An isolated alteration of LV EF <60% (and RV EF >35%) was associated with a moderate decrease in cardiovascular survival rate at 10-year (83.2±9.1%). By contrast, patients
with biventricular systolic function impairment (RV EF \leq 35\% and LV EF < 60\%) had a dramatic
decrease in cardiovascular survival rate (Figure 6B) at 10 years (51.9\pm14.3\%, P<0.0001) with a
HR of 5.2 (95\% CI 2.2-12.1, P<0.0001). After adjustment for age and gender, preoperative
NYHA class 3-4, LV end-systolic diameter, PASP, atrial fibrillation, CABG and mitral valve
repair/replacement, preoperative bi-ventricular impairment (HR=4.62 [95\% CI 1.62-12.9],
P=0.004) remained an independent predictive factor of cardiovascular mortality.

Although impaired RV EF per se did not influence overall survival rate at 10 years
(64.6\pm8.6\% versus 68.5\pm5.3\%, P=0.79), 10-year survival was dramatically reduced in patients
with biventricular impairment (34.8\pm13.0\% versus 72.6\pm4.5\%, P=0.003) with a HR of 2.5 (95\% 
CI 1.3-4.6, P=0.005). After adjustment for age and gender, preoperative NYHA class, LV end-
systolic diameter, PASP, atrial fibrillation, CABG, and mitral valve repair/replacement,
biventricular impairment remained an independent predictive factor of 10-year overall mortality
(HR=2.1 [95\% CI 1.1-4.4], P=0.048).

Discussion
The objectives of the present study were to assess the prevalence and the determinants of RV EF
impairment in chronic organic MR, and to evaluate the influence of preoperative RV EF on
postoperative outcome. Right ventricular systolic function alteration is a frequent finding in
chronic organic MR as 30\% of patients referred to surgery had a RV EF \leq 35\%. The severity of
MR is an important determinant of RV EF only partially acting through an increased PASP.
Volume overload owing to MR also influences RV function through other interactions as
demonstrated by the association of LV enlargement with RV EF and by the link to LV septal
function alteration. Furthermore, the improvement of RV EF after suppression of volume
overload also supports such a link emphasizing the impact of LV remodelling and septal function on RV function as a sign of ventricular interdependence in organic MR in the relatively inextensible pericardial envelop. The prompt but incomplete RV improvement after surgery in patients with baseline RV impairment suggests a greater and direct beneficial effect of MR suppression on the RV as compared with the LV.

Regarding prognosis influence of RV function, preoperative RV EF was associated with long-term postoperative cardiovascular survival but was not a predictor of overall survival. While isolated LV or RV alteration influences moderately postoperative prognosis, biventricular impairment (RV EF ≤ 35% and LV EF < 60%, 16% of patients) emerged as a strong predictive factor of both long term cardiovascular and overall survival in organic MR, even after adjustment to known predictive factors of postoperative outcome.

Thus, RV systolic function impairment in organic MR particularly as part of biventricular impairment should be taken into account in the clinical decision making process.

Prevalence of RV function impairment

Right ventricular EF impairment is a consequence of left sided valve heart disease but has been studied in small series of patients with chronic organic MR \(^4\,^5\,^6\,^12\). Thus, its prevalence in patients with chronic organic MR referred to surgery was unknown. The present study shows for the first time that RV EF impairment is a frequent finding in the setting of chronic organic MR. Indeed, RV EF was strongly depressed (≤35%) in up to 30% of patients referred to surgery. Right ventricular EF impairment is frequently associated with LV EF alteration (54%) but is also encountered in patients with preserved LV function.

Magnitude of mitral regurgitation and RV EF

In chronic organic MR volume overload is associated with left atrial dilatation, LV remodeling,
PASP elevation\textsuperscript{10, 22-24} but also with RV function impairment. Although objective quantification of MR was available in only 40\% of patients in the present study, the magnitude of MR, assessed by the effective regurgitant orifice area or the regurgitant volume measurement, is a clear determinant of RV EF. A negative association between the amount of regurgitation and RV EF has been previously reported in a small series of patients with organic MR\textsuperscript{25}. The prompt rescue of RV function after mitral valve surgery, in agreement with previous studies\textsuperscript{3, 4}, further confirms that RV impairment is a consequence of the magnitude of MR and can be reversed, at least in part, by MR suppression.

**Pulmonary systolic pressure and RV EF**

As demonstrated in the present study, the strongest determinants of RV EF alteration in patients with chronic organic MR are LV septal function impairment, LV enlargement and increased PASP as a consequence of MR. Right ventricular load, myocardial function and ventricular interaction are known as the three main determinants of RV function\textsuperscript{7, 26}. Compared with the LV the RV is a thin-walled structure. Since pulmonary resistance level is low in normal subjects the RV is accustomed to low afterload and functions with low cavity pressure and high chamber compliance. Hence, the RV is a very sensitive chamber to changes in load conditions but is much more sensitive to pressure overload than to volume overload\textsuperscript{7}.

Right ventricular systolic function is reduced in PH related to primary or secondary pulmonary disease as well as to left heart failure\textsuperscript{7, 27}. Increase in LV filling pressure and/or left atrial pressure elicits a backward rise in pulmonary venous pressure, pulmonary capillary wedge and artery pressure. As a consequence, PASP is usually proportionate to left atrial pressure and pulmonary capillary wedge pressure\textsuperscript{10, 28}. The backward rise in PASP is particularly marked in severe organic MR. Beyond the direct effect of backward pressure, pulmonary vascular
remodeling or abnormal vasoconstriction contributes to the elevation of PASP. RV performance is influenced by PASP in organic MR with an inverse relation of RVEF to the level of PASP. Acute pharmacologic PASP reduction in patients with organic MR reduces RV afterload and elicits partial RV EF improvement. Although the present study confirms an independent relation of PASP to RV EF, this relation is weak (β = -0.14), clearly suggesting that PASP is not the main determinant of RV function in chronic organic MR. Indeed, scarce data have previously suggested that RV function in organic MR is not a simple function of PASP which accounted for less than one quarter of RV EF alteration. Finally, preserved RV EF did not exclude PH in the present study in agreement with a previous work further highlighting that PASP is only a weak determinant of RV EF in chronic organic MR.

**Left ventricular septal function and RV EF**

Left ventricle function and size influence RV function. First, the LV acts on RV function through the interventricular septum. The septum transmits systolic and diastolic pressure between right and left cavities. Although pressure interaction through the interventricular septum is considered less important than interaction through the pulmonary circulation LV pressure can also influence RV function while RV pressure is well known to influence LV function. Septal contraction contributes to both RV and LV functions, and is regarded a major determinant of RV performance. Interventricular septum contraction is able to maintain RV function and cardiac output despite RV free wall impairment. The contribution of septal contraction to RV systolic function ranges from 24% in a normal RV to 35% in pathology. In our series of patients with organic MR global RV systolic performance was linked to the systolic performance of the RV septal region but not or weakly to the RV lateral or free wall systolic function. Moreover, the alteration of RV systolic performance was clearly associated with the systolic impairment of LV
septal region, and RV EF improvement after surgery was also associated with an improvement in LV septal function. Thus, LV septal function appears a key determinant of RV EF in organic MR.

**Left ventricular remodeling and RV EF**

Second, the right and left ventricles are enclosed within the pericardium, a relatively inextensible envelop, leading to strong interactions when intrapericardial pressure and pericardial constraint rise\(^3\). Chronic organic MR results in an eccentric hypertrophy with geometric changes of the LV cavity as an adaptative mechanism to volume overload. The LV enlarges and its shape evolves into a more spherical pattern increasing the constraint on and the interaction with the RV, particularly but not only at the septal level. The pericardial and LV constraint rise likely contributes to RV function alteration in chronic organic MR.

Third, RV EF impairment was frequently associated with LV EF alteration (54%) suggesting that RV impairment reflects also the intrinsic myocardial consequences\(^{35}\) of long-standing MR. In chronic organic MR LV EF is preserved for a long period despite progressive alteration of myocardial function\(^{36}\). Mitral valve surgery suppresses LV volume overload and ejection toward the left atrium, a low impedance pathway, unmasking in the same time the true or intrinsic LV myocardial function. As well, suppression of LV volume overload, reduction of LV and pericardial constraint on the RV, and the drop of PASP unmask RV intrinsic myocardial function. The persistent difference in RV EF (37.9 versus 46.1%, 8.2 points) after surgery between patients with preoperative depressed versus preserved RV EF likely corresponds to the intrinsic myocardial function alteration in the first group. Thus, myocardial function of the LV influences directly or indirectly RV performance\(^{35}\).

Right ventricular systolic function in chronic organic MR results therefore of complex interactions of RV to LV remodelling, LV septal function, LV myocardial function and to a less
extent to PASP.

**Post-operative Outcome**

Age\(^{37,38}\), symptoms\(^{37,39}\), LV function and size\(^{22,23,37,38,40,41}\), PASP\(^{10,11,19}\), atrial fibrillation\(^{42}\) and the type of valve surgery\(^{38,43-45}\) are predictors of postoperative outcome in organic MR.

Right ventricular EF impairment has been associated with increased mortality risk in unoperated patients with severe MR\(^4\), particularly in the decompensated stage. Among asymptomatic patients with subnormal LV EF and RV EF before mitral valve surgery RV EF was thought to be a predictor of late postoperative survival\(^{18}\), but these data were obtained in small series of patients. In addition, the prognosis value of RV EF seemed mitigated after surgery compared to its predictive value in unoperated patients with severe MR\(^3,4\). In the present study, the largest one evaluating RV function in organic MR, RV EF was associated with long-term post-operative cardiovascular mortality but was not predictive of overall mortality. As demonstrated RV systolic impairment reflects direct and indirect ventricular, myocardial and pulmonary consequences of volume overload. Due to this complex interplay isolated RV function impairment (with normal LV EF) is not a harmful condition per se in organic MR and improves promptly after surgery. In the same way an isolated alteration of LV EF (and RV EF >35%) was only associated with a moderate decrease in cardiovascular survival rate at 10-year. By contrast, biventricular impairment defined by the conjunction of both LV and RV systolic function alteration (LV EF <60% and RV EF ≤ 35%) emerged as a strong predictor of cardiovascular outcome with a 4-fold increase in the risk of cardiovascular mortality after adjustment on other known predictive factors including age, functional status, LV remodeling, PASP, atrial fibrillation, type of surgery and CABG. Biventricular impairment is a well recognized pejorative prognostic factor in heart failure related to ischemic or non-ischemic cardiomyopathy\(^{16,21,35,46}\). It
is noteworthy that the strong effect of biventricular impairment on cardiovascular survival translated into a strong impact on overall survival with a dramatic 10-year survival reduction in patients with chronic organic MR. Multiple factors may be involved in this reduction of overall survival in patients with biventricular impairment. Heart failure is a well known predictor of poor outcome particularly in patients with biventricular impairment\textsuperscript{16, 35, 47}. Biventricular impairment may testify of an advanced stage of the disease with long-standing MR and deep intrinsic myocardial function depression\textsuperscript{35}, long-term exposure of the RV to elevated atrial and pulmonary pressure, systolic and diastolic ventricular alterations, infra-clinic ischemic lesions and other sub-clinical pulmonary parenchymal or vascular diseases not evidenced by conventional clinical work-up. Biventricular impairment should therefore be taken into account in the clinical decision making process of severe MR. Although LV systolic function is a useful indicator for referring patients to surgery, further stratification based on RV EF should be helpful in distinguishing patients with severe myocardial function alteration requiring urgent surgery and close follow-up after discharge.

**Limitations**

In the present study, RV systolic function was assessed by radionuclide angiography, the reference method for the measurement of RV EF\textsuperscript{5, 6, 21} before the development of cardiac magnetic resonance (CMR) imaging capabilities. An important advantage of radionuclide angiography is the absence of geometric assumption in assessing RV EF. Cardiac magnetic resonance imaging or emerging techniques such as real-time 3D echocardiography or 2D-strain\textsuperscript{48, 49} would be used to assess RV function in future studies to confirm and extend our findings, as well as to monitor patients in daily clinical practice. Another limitation of the present study is the absence of RV remodeling parameters such as RV length and width in the apical 4 chamber view,
or other parameters of RV systolic function. However, this study was a part of current practice
and most echocardiography examinations were not recorded precluding measurement of new
parameters to further evaluate RV remodeling and function. On the other hand, recent study in
heart failure demonstrated that echocardiographic parameters of RV systolic function are less
effective in predicting outcome than radionuclide angiography of the RV.\textsuperscript{16}

The 35\% cutoff value for depressed RV EF was derived from the literature. A recent
study in heart failure identified a cutoff value of 37\%\textsuperscript{16}. By using ROC curve analysis the RV EF
cutoff value that best predicts cardiovascular survival in organic MR was around 40\%. However,
our results remained broadly unchanged after stratification of patients according to this cutoff
value. Patients with RV EF \( \leq 40\% \) had a lower 10-year cardiovascular survival (77.8\%+6.1 vs
90.1\%+4.5, \( P=0.019 \)). Patients with biventricular impairment (LV EF <60\% and RV EF \( \leq 40\% \))
had a strong decrease in 10-year cardiovascular survival rate (59.8\%+11.8\% vs 94.9\%+3.0\% in those
with no ventricular impairment, \( P<0.0001 \)) and overall survival (\( P<0.0001 \)).

Objective quantification of MR was performed in only 40\% of patients limiting the
analysis of the influence of the magnitude of volume overload on RV alteration, but such
quantification was not widespread used at the early stage of the study.

The last limitation relies on the relative small number of events after surgery in this low
risk patient population. Although further studies are therefore needed to confirm and extend our
results regarding the influence of RV function on postoperative outcome, biventricular
impairment emerged as a powerful prognostic factor of outcome and should be henceforth
integrated in the clinical evaluation of patients with chronic organic MR. Further studies should
also explore the influence of surgery on outcome of patients with organic MR and biventricular
impairment.
Conclusion

Right ventricular systolic function alteration is a frequent finding in patients with chronic organic MR referred to surgery. Right ventricular systolic dysfunction is a direct and indirect consequence of chronic volume overload. Beyond the classical but weak effect of pulmonary pressure, RV systolic function is the result of a complex interaction with the remodelled and enlarged LV. As a sign of ventricular interdependence in the relatively inextensible pericardial envelop LV septal function alteration emerges as an important contributor to RV performance in organic MR. The prompt but incomplete RV improvement after surgery in patients with severe RV dysfunction before surgery suggests a greater and direct beneficial effect of MR suppression on the RV as compared with the LV.

Right ventricular systolic function conveys important prognosis information in patients with chronic organic MR. While isolated RV dysfunction before surgery is not a harmful condition per se in chronic organic MR and should not be used to deny surgery, biventricular impairment portends a dramatic 10-year decrease in cardiovascular and overall survival. In patients with chronic organic MR RV function assessment should therefore be integrated in the clinical-decision making process. In clinical practice, RV EF might be assessed by using 3D echo or CMR imaging and considered as a part of the clinical workup of organic MR. Finally, more than isolated LV or RV dysfunction, biventricular impairment as a high risk condition in chronic organic MR should be incentive to refer promptly patients to surgery and to propose a close follow-up after discharge.

Conflict of Interest Disclosures: None.
References:


Table 1. Baseline Clinical and Surgical Characteristics of the Entire Patient Population and after Stratification According to RV EF.

<table>
<thead>
<tr>
<th></th>
<th>All Patients n=208</th>
<th>RV EF ≤ 35%, n=63</th>
<th>RV EF &gt; 35%, n=145</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>62±12</td>
<td>62±13</td>
<td>62±12</td>
<td>0.88</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>138 (66)</td>
<td>39 (62)</td>
<td>99 (68)</td>
<td>0.46</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>76.4±16.4</td>
<td>78.9±17.6</td>
<td>75.3±15.7</td>
<td>0.16</td>
</tr>
<tr>
<td>Sytolic Blood Pressure, mmHg</td>
<td>129±18</td>
<td>124±18</td>
<td>130±18</td>
<td>0.047</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>57 (27)</td>
<td>25 (40)</td>
<td>32 (22)</td>
<td>0.006</td>
</tr>
<tr>
<td>NYHA class 3-4</td>
<td>75 (36)</td>
<td>23 (36)</td>
<td>52 (36)</td>
<td>0.95</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>50 (24)</td>
<td>12 (19)</td>
<td>38 (26)</td>
<td>0.35</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>24 (12)</td>
<td>4 (7)</td>
<td>20 (14)</td>
<td>0.19</td>
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<tr>
<td>MR mechanism</td>
<td></td>
<td></td>
<td></td>
<td>0.37</td>
</tr>
<tr>
<td>- Degenerative, n (%)</td>
<td>183 (88)</td>
<td>53 (84)</td>
<td>130 (90)</td>
<td></td>
</tr>
<tr>
<td>- Rheumatic or endocarditis, n (%)</td>
<td>25 (12)</td>
<td>10 (16)</td>
<td>15 (10)</td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>103 (49)</td>
<td>30 (48)</td>
<td>73 (50)</td>
<td>0.83</td>
</tr>
<tr>
<td>Digoxin</td>
<td>51 (25)</td>
<td>20 (32)</td>
<td>31 (21)</td>
<td>0.093</td>
</tr>
<tr>
<td>Diuretics</td>
<td>96 (46)</td>
<td>37 (59)</td>
<td>59 (41)</td>
<td>0.025</td>
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<tr>
<td>Additive Euroscore</td>
<td>4.5±2.1</td>
<td>4.5±2.4</td>
<td>4.5±2.1</td>
<td>0.93</td>
</tr>
<tr>
<td>Charlson Index</td>
<td>2.1±1.4</td>
<td>2.0±1.4</td>
<td>2.1±1.4</td>
<td>0.61</td>
</tr>
<tr>
<td>Mitral Valve repair, n (%)</td>
<td>148 (71.1)</td>
<td>41 (65)</td>
<td>107 (74)</td>
<td>0.27</td>
</tr>
<tr>
<td>CABG, n (%)</td>
<td>7 (3.4)</td>
<td>1 (2)</td>
<td>6 (4)</td>
<td>0.61</td>
</tr>
<tr>
<td>Radiofrequency ablation, n (%)</td>
<td>35 (17.1)</td>
<td>14 (22)</td>
<td>21 (15)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

CABG: coronary artery bypass grafting, MR: mitral regurgitation, NYHA: New York Heart Association
Table 2. Baseline Echocardiography and Isotopic Characteristics of the Entire Patient Population and after Stratification According to RV EF.

<table>
<thead>
<tr>
<th></th>
<th>All Patients n=208</th>
<th>RV EF ≤ 35%, n=63</th>
<th>RV EF &gt; 35%, n=145</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Echocardiography</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV EDD index, mm/m²</td>
<td>31.4±4.4</td>
<td>33.0±4.5</td>
<td>30.8±4.2</td>
<td>0.001</td>
</tr>
<tr>
<td>LV ESD index, mm/m²</td>
<td>19.8±3.7</td>
<td>20.9±3.7</td>
<td>19.3±3.6</td>
<td>0.004</td>
</tr>
<tr>
<td>LV EDVol, mL/m²</td>
<td>71.1±23.2</td>
<td>80.1±30.5</td>
<td>68.2±19.6</td>
<td>0.008</td>
</tr>
<tr>
<td>LV ESVol, mL/m²</td>
<td>27.2±12.2</td>
<td>30.9±13.1</td>
<td>26.0±11.7</td>
<td>0.04</td>
</tr>
<tr>
<td>Mitral E wave, m/s</td>
<td>1.43±0.37</td>
<td>1.57±0.39</td>
<td>1.38±0.35</td>
<td>0.001</td>
</tr>
<tr>
<td>Mitral E/A</td>
<td>2.09±0.96</td>
<td>2.43±0.79</td>
<td>2.01±0.98</td>
<td>0.07</td>
</tr>
<tr>
<td>Mitral deceleration time, ms</td>
<td>183±40</td>
<td>177±35</td>
<td>184±42</td>
<td>0.36</td>
</tr>
<tr>
<td>Mitral Medial E/E’</td>
<td>16.6±6.1</td>
<td>17.0±6.6</td>
<td>16.6±6.0</td>
<td>0.96</td>
</tr>
<tr>
<td>Mitral Lateral E/E’</td>
<td>11.4±4.1</td>
<td>12.0±4.9</td>
<td>11.2±3.8</td>
<td>0.49</td>
</tr>
<tr>
<td>LAD, mm</td>
<td>47.6±8.2</td>
<td>49.9±10.1</td>
<td>46.6±7.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Mitral ERO, cm²</td>
<td>0.48±0.19</td>
<td>0.58±0.26</td>
<td>0.45±0.16</td>
<td>0.01</td>
</tr>
<tr>
<td>Regurgitant Volume, mL</td>
<td>73.9±27.1</td>
<td>86.9±31.3</td>
<td>69.7±24.3</td>
<td>0.01</td>
</tr>
<tr>
<td>RV diameter, mm</td>
<td>29.1±4.3</td>
<td>30.8±4.3</td>
<td>28.4±4.1</td>
<td>0.005</td>
</tr>
<tr>
<td>Tissue Doppler RV S velocity, cm/s</td>
<td>14.5±3.9</td>
<td>13.2±3.0</td>
<td>14.9±4.1</td>
<td>0.053</td>
</tr>
<tr>
<td>RA area, cm²</td>
<td>19.3±6.9</td>
<td>22.3±7.7</td>
<td>18.2±6.2</td>
<td>0.007</td>
</tr>
<tr>
<td>PASP, mmHg</td>
<td>45.4±13.0</td>
<td>48.4±13.7</td>
<td>44.1±12.5</td>
<td>0.027</td>
</tr>
<tr>
<td>PASP ≥ 50 mmHg</td>
<td>65 (31)</td>
<td>28 (44)</td>
<td>37 (26)</td>
<td>0.011</td>
</tr>
<tr>
<td>Tricuspid Regurgitation grade ≥ 2</td>
<td>18 (9)</td>
<td>9 (14)</td>
<td>9 (6)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

**Radionuclide angiography**

| LV EF, %                     | 62.5±9.8           | 58.6±10.1         | 64.2±9.1           | <0.0001|
| LV EF < 60%                  | 76 (37)            | 34 (54)           | 43 (30)            | 0.002 |
| RV EF, %                     | 40.4±10.2          | 28.2±5.7          | 45.8±6.4           | -     |

Table 3. Echocardiographic and Isotopic predictors of RV EF in multivariate analysis.

<table>
<thead>
<tr>
<th></th>
<th>R</th>
<th>$\hat{\beta}$</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall group (n=208)</td>
<td>0.55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV septal function</td>
<td></td>
<td>0.42</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV EDD index</td>
<td></td>
<td>-0.22</td>
<td>0.002</td>
</tr>
<tr>
<td>PASP</td>
<td></td>
<td>-0.14</td>
<td>0.047</td>
</tr>
<tr>
<td>With MR quantitation (n=84)</td>
<td>0.35</td>
<td>-0.28</td>
<td>0.012</td>
</tr>
</tbody>
</table>

EDD index: end-diastolic diameter indexed to body surface area, ERO: effective regurgitant orifice area, LV: left ventricle, PASP: pulmonary artery systolic pressure.

Table 4. Baseline Characteristics of the 68 patients with preoperative and postoperative radionuclide angiography

<table>
<thead>
<tr>
<th></th>
<th>All Patients n=68</th>
<th>RV EF $\leq 35%$ n=21</th>
<th>RV EF $&gt;35%$, n=47</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>61.3±11.3</td>
<td>61.7±12.8</td>
<td>61.1±10.7</td>
<td>0.83</td>
</tr>
<tr>
<td>Males, n (%)</td>
<td>41 (60)</td>
<td>11 (52)</td>
<td>30 (64)</td>
<td>0.53</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.80±0.17</td>
<td>1.81±0.20</td>
<td>1.80±0.15</td>
<td>0.69</td>
</tr>
<tr>
<td>Rest Heart rate, bpm</td>
<td>80±17</td>
<td>82±16</td>
<td>77±17</td>
<td>0.26</td>
</tr>
<tr>
<td>Atrial Fibrillation, n (%)</td>
<td>21 (31)</td>
<td>10 (48)</td>
<td>11 (23)</td>
<td>0.09</td>
</tr>
<tr>
<td>NYHA 3-4, n (%)</td>
<td>29 (43)</td>
<td>10 (48)</td>
<td>19 (40)</td>
<td>0.77</td>
</tr>
<tr>
<td>LV EDD index, mm/m²</td>
<td>31.9±4.6</td>
<td>33.1±5.1</td>
<td>31.4±4.4</td>
<td>0.21</td>
</tr>
<tr>
<td>LV ESD index, mm/m²</td>
<td>19.1±3.7</td>
<td>20.7±3.7</td>
<td>18.4±3.5</td>
<td>0.03</td>
</tr>
<tr>
<td>LAD, mm</td>
<td>46.9±7.2</td>
<td>50.3±9.3</td>
<td>45.5±5.7</td>
<td>0.02</td>
</tr>
<tr>
<td>PASP, mmHg</td>
<td>47.3±11.5</td>
<td>50.4±12.5</td>
<td>45.8±10.9</td>
<td>0.13</td>
</tr>
<tr>
<td>Tricuspid Regurgitation grade ≥2</td>
<td>5 (7.3)</td>
<td>4 (19)</td>
<td>1 (2)</td>
<td>0.049</td>
</tr>
<tr>
<td>LV EF, %</td>
<td>62.2±10.3</td>
<td>56.0±11.3</td>
<td>64.9±8.7</td>
<td>0.0008</td>
</tr>
<tr>
<td>RV EF, %</td>
<td>40.3±10.6</td>
<td>27.5±4.3</td>
<td>50.0±6.9</td>
<td>-</td>
</tr>
<tr>
<td>Diuretics, n (%)</td>
<td>44 (65)</td>
<td>15 (71)</td>
<td>29 (62)</td>
<td>0.62</td>
</tr>
<tr>
<td>Mitral Valve Repair, n (%)</td>
<td>39 (57)</td>
<td>10 (48)</td>
<td>29 (62)</td>
<td>0.41</td>
</tr>
</tbody>
</table>
Figure Legends:

**Figure 1.** Radionuclide angiography of right and left ventricle in 45° left oblique anterior view. Regional segmentation of RV (left) and LV (right). The inter-ventricular septum function is defined as the mean value of regional LV EF 7 and 8 for the LV (LV septal function), and as the mean value of regional RV EF 3 and 4 for the RV (RV septal function).

**Figure 2.** A) Comparison of regional RV EF 1 to 9 in patients with RV EF ≤ 35% (black) or > 35% (white). In patients with RV EF ≤ 35% regional RV impairment comprises mainly the septal region (3 and 4) and antero-apical region (5 to 6), while there is no significant impairment of the RV free wall (region 7, 8 and 9). B) Comparison of regional LV EF 1 to 9 in patients with RV EF ≤ 35% (black) or > 35% (white). In patients with RV EF ≤ 35% regional LV impairment comprises mainly the septal region of the LV (LV EF 6 to 9) while there is no significant impairment of the lateral part of the LV (LV EF 1 to 5).

**Figure 3.** Relation of RV EF to PASP in patients with chronic organic MR

**Figure 4.** Changes in RV EF from the preoperative (Preop) to the postoperative (Postop) stage in patients with A) preserved RV EF before surgery or B) reduced RV EF before surgery. Note that RV EF improved in almost all patients with depressed RV.

**Figure 5.** Comparison from baseline to 6 months after surgery of A) changes of regional RV EF 1 to 9 in patients with RV EF ≤ 35% (black round and dotted line) or > 35% (black square and
continuous line) and B) changes of regional LV EF 1 to 9 in patients with RV EF ≤ 35% (black round and dotted line) or > 35% (black square and continuous line). This graph illustrates both antero-medial translation of the heart after cardiac surgery and the regional improvement after surgery for both RV and LV.

**Figure 6.** A) Ten years cardiovascular survival rate after mitral valve surgery in patients with preserved (>35%) versus depressed (≤35%) RV EF (P=0.037). B) Ten years cardiovascular survival rate after mitral valve surgery in patients with normal RV and LV systolic function (continuous line), isolated depression of RV EF (dotted line), isolated depression of LV EF (dashed line) and biventricular impairment (dashed and dotted line). Note the dramatic decrease in 10-year cardiovascular survival in patients with biventricular impairment compared with the remaining patients (P<0.0001).
Figure 1
Figure 2A

- **RV EF ≤ 35%**
- **RV EF > 35%**

![Graph showing regional RV EF and associated P-values](http://circ.ahajournals.org/)

- **Regional RV EF**
  - 1: P<0.001
  - 2: P<0.001
  - 3: P<0.001
  - 4: P<0.001
  - 5: P<0.001
  - 6: P<0.001
  - 7: P=0.11
  - 8: P=0.13
  - 9: P=0.06

**RV septal function**
Figure 2B
Figure 3

$\text{RV EF, } \%$

$\text{PASP, mm Hg}$

$r = -0.24, P = 0.001$
Figure 5A

Preop to Postop Changes in Regional RV EF, %

RV septal function
P = 0.0025

P = 0.009  P = 0.002

P = 0.005

P = 0.02

RV EF ≤ 35%

RV EF > 35%

Regional RV EF

Medial part  Lateral part
Figure 5B

Preop to Postop Changes in Regional LV EF, %

- RV EF ≤ 35%
- RV EF > 35%

LV septal function
P = 0.039

Regional LV EF

Lateral part
Medial part
Figure 6A
Figure 6B

Cardiovascular survival rate, %

- RV EF > 35% and LV EF ≥ 60%
- RV EF ≤ 35% and LV EF ≥ 60%
- RV EF > 35% and LV EF < 60%
- RV EF ≤ 35% and LV EF < 60%

P < 0.0001

<table>
<thead>
<tr>
<th>Years</th>
<th>100</th>
<th>92</th>
<th>79</th>
<th>50</th>
<th>29</th>
<th>23</th>
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<td>22</td>
<td>19</td>
<td>10</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

93.2 ± 3.1%
91.1 ± 6.2%
83.2 ± 9.1%
51.9 ± 15.3%
Right Ventricular Systolic Function in Organic Mitral Regurgitation: Impact of Biventricular Impairment

Thierry Le Tourneau, Guillaume Deswarte, Nicolas Lamblin, Claude Foucher-Hossein, Georges Fayad, Marjorie Richardson, Anne-Sophie Polge, Claire Vannesson, Yan Topilsky, Francis Juthier, Jean-Noel Trochu, Maurice Enriquez-Sarano and Christophe Bauters

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