Advanced echocardiography in characterization and management of patients with secondary mitral regurgitation

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Chapter four

Regurgitant Volume/Left Ventricular End-Diastolic Volume Ratio: Prognostic Value in Patients With Secondary Mitral Regurgitation

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Abstract

Objectives
The purpose of this study was to investigate the prognostic implications of the ratio of mitral regurgitant volume (RVol) to left ventricular (LV) end-diastolic volume (EDV) in patients with significant secondary mitral regurgitation (MR).

Background
Quantification of secondary MR remains challenging, and its severity can be over- or underestimated when using the proximal isovelocity surface area method, which does not take LV volume into account. This limitation can be addressed by normalizing mitral RVol to LVEDV.

Methods
A total of 379 patients (mean age 67 ± 11 years; 63% male) with significant (moderate and severe) secondary MR were divided into 2 groups according to the RVol/EDV ratio: RVol/EDV ≥20% (greater MR/smaller EDV) and <20% (smaller MR/larger EDV). The primary endpoint was all-cause mortality.

Results
During median (interquartile range) follow-up of 50 (26 to 94) months, 199 (52.5%) patients died. When considering patients receiving medical therapy only, patients with RVol/EDV ratio ≥20% tended to have higher mortality rates than those with RVol/EDV ratio <20% (5-year estimated rates 24.1% vs. 18.4%, respectively; $p = 0.077$). Conversely, when considering the entire follow-up period including mitral valve interventions, patients with a higher RVol/EDV ratio (≥20%) had lower rates of all-cause mortality compared with patients with RVol/EDV ratio <20% (5-year estimated rates 39.0% vs. 44.8%, respectively; $p = 0.018$). On multivariable analysis, higher RVol/EDV ratio (per 5% increment as a continuous variable) was independently associated with lower all-cause mortality (0.93; $p = 0.023$).

Conclusions
In patients with significant secondary MR treated medically, survival tended to be lower in those with a higher RVol/EDV ratio. Conversely, a higher RVol/EDV ratio was independently associated with reduced all-cause mortality. when mitral valve interventions were taken into consideration.

Introduction

Secondary mitral regurgitation (MR) in patients with heart failure (HF) arises from impaired left ventricular (LV) geometry and function (1,2). Although patients with secondary MR have a poor prognosis, whether the dysfunctional LV or mitral valve (MV) (i.e., MR) predominantly dictates patient outcomes may be difficult to distinguish (1,3,4). In addition, LV reverse remodeling after MR reduction has been associated with improved prognosis (5,6). However, when selecting patients with severe secondary MR for medical, surgical, or transcatheter treatments, identifying those patients who will show LV reverse remodeling and improvement in LV systolic function, HF symptoms, and prognosis may be difficult. MR quantification is challenging due to its dynamic nature and its dependence on loading conditions as well as LV size and function (2,7). The effective regurgitant orifice area (EROA) and regurgitant volume (RVol) derived using the proximal isovelocity surface area (PISA) method can over- or under-estimate the severity of MR (7), and LV volumes are not directly taken into consideration, which are important for understanding volume overload (1,7). Therefore, a multiparametric approach is recommended when assessing the severity of secondary MR. Current recommendations take the dimensions of the LV into consideration as a binary variable (i.e., dilated vs. nondilated) instead of a continuous variable (8, 9, 10). The relationship between RVol and LV dimensions can be reflected by the ratio between RVol and LV end-diastolic volume (EDV) (7,11,12). For a given RVol, a larger LVEDV will result in a smaller RVol/EDV ratio, suggesting that the degree of LV dilation is disproportionate to the severity of MR. Eliminating MR in such cases offers less potential for reduction in LVEDV than in patients with smaller LVs (11). The prognostic implications of this ratio have not been investigated. Accordingly, we sought to investigate the prognostic implications of the RVol/LVEDV ratio in a large population of patients with significant (moderate and severe) secondary MR.

Methods

Patient population

Patients with HF and at least moderate secondary MR were identified through the departmental echocardiographic database (Imagevault EchoPAC, General Electric Vingmed Ultrasound, Horten, Norway) of Leiden University Medical Center, Leiden, the Netherlands. Patients with previous MV intervention were excluded. Demographic, clinical, and echocardiographic characteristics were collected in the departmental clinical (EPD-Vision 11.8.4.0, Leiden University Medical Center, Leiden, the Netherlands) and echocardiographic databases, and were analyzed retrospectively. For this retrospective study with clinically acquired data, the institutional review board waived the need for written patient informed consent.

Clinical characteristics included New York Heart Association (NYHA) functional class, HF etiology, and medication use. Ischemic HF was defined based on previous coronary revascularization with percutaneous coronary intervention or coronary artery bypass grafting and/or coronary artery disease diagnosed on invasive coronary angiography.

Echocardiography

Transthoracic echocardiography was performed with patients in hemodynamically stable condition at rest in the left lateral decubitus position, using a commercially available system (General Electric Vingmed Ultrasound, Milwaukee, Wisconsin). Parasternal, apical, and subcostal views were acquired using 3.5-MHz or M5S transducers. Two-dimensional images and M-mode and Doppler data were digitally stored for off-line analysis (EchoPAC 201.0.0, General Electric Vingmed Ultrasound). MR severity was assessed using a multiparametric approach (7,9). EROA was measured using the PISA method, and RVol was derived by multiplying EROA times the MR velocity time integral. Severe MR was defined as EROA ≥20 mm2 and/or RVol ≥30 ml/beat (7, 8, 9). LV end-systolic volume (ESV) and LVEDV were measured in the apical 2- and 4-chamber views and calculated using the Simpson biplane method (13). Subsequently, LV ejection fraction (EF) was derived as stroke volume (SV) (calculated as EDV – ESV) divided by EDV. The regurgitant fraction (RF) was calculated by measuring the difference between SV measured at the MV annulus and SV at the LV outflow tract and dividing the difference by SV measured at the MV (10). Although the difference between SV measured at the MV annulus and SV measured at the LV outflow tract represents RVol, in the present study, RVol derived using the PISA method was used. The RVol/LVEDV index was calculated and based on previous report (11). The population was dichotomized as RVol/EDV ratio ≥20% (larger RVol and/or smaller LVEDV) and RVol/EDV ratio <20% (smaller RVol and/or larger LVEDV) (Figure 1).

Follow-up

Patients underwent follow-up for the primary endpoint of all-cause mortality after the first echocardiogram showing moderate-to-severe and severe MR. Survival data were obtained from the departmental cardiology information system (EPD-Vision 11.8.4.0, Leiden University Medical Center), which is linked to the governmental death registry database. All patients underwent complete follow-up.

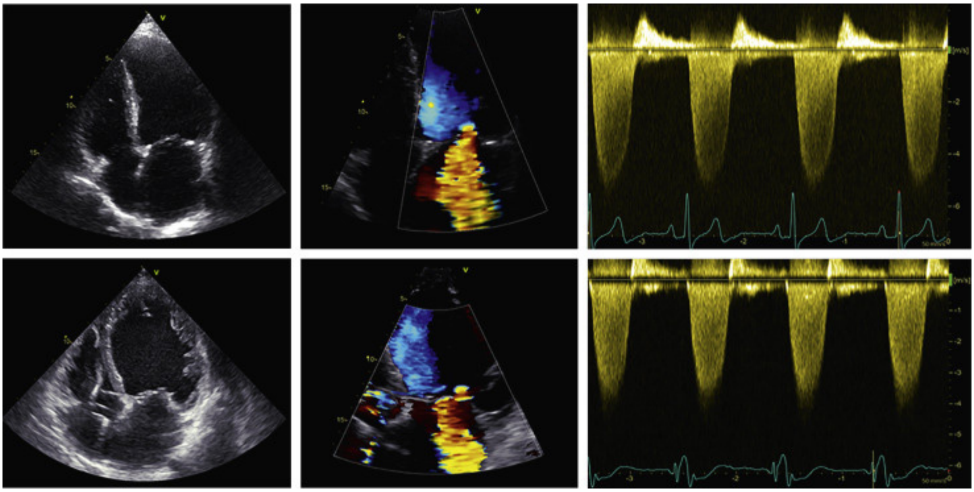


Figure 1. (Top row) Patient with severe secondary MR, LVEDV 153 ml, LVEF 38%, EROA 49.93 mm2, and RVol 88 ml/beat. This patient had RVol/EDV ratio ≥20%. (Bottom row) Patient with severe secondary MR, LVEDV 505 ml, LVEF 21%, EROA 19.46 mm2, and RVol 23 ml/beat. This patient had RVol/EDV ratio <20%. EDV = end-diastolic volume; EROA = effective regurgitant orifice area; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; PISA = proximal isovelocity area; RVol = regurgitant volume.

Statistical analysis

All statistical analyses were performed using SPSS for Windows, version 23.0 (IBM Corp., Armonk, New York). A 2-tailed $p < 0.05$ was considered statistically significant. Continuous data are presented as mean ± SD or median (interquartile range [IQR]) when not normally distributed. Categorical data are presented as absolute number (percentage). For comparison of continuous data, independent-samples Student's t-tests or Mann-Whitney U tests, as appropriate, were used. For comparison of categorical data, the chi-square test was used. To investigate the relationship between RVol/EDV ratio and all-cause mortality as a continuous variable, spline curve analyses were performed, demonstrating the changes in hazard ratio (HR) for all-cause mortality across the range of RVol/EDV ratio. Kaplan-Meier analysis was performed to estimate cumulative survival rates for all-cause mortality of patients with RVol/EDV ≥20% and patients with an RVol/EDV <20% and were compared with a log-rank test. The first set of analyses was performed with patients censored at the time of MV interventions, including surgical MV repair, surgical MV replacement, and percutaneous edge-to-edge MV repair with the MitraClip device (Abbott, Chicago, Illinois). Additional survival analyses were performed, including outcomes after MV interventions. To identify the independent predictors of all-cause mortality, a Cox proportional hazards regression analysis was performed. The proportional hazards assumption was confirmed using statistics and graphs on the basis of the Schoenfeld residuals. HR and 95% confidence interval (CI) were calculated and reported. The $p < 0.05$ in univariable analysis was considered statistically significant and included in the multivariable model.

Results

Patient population

A total of 379 patients (mean age 67 ± 11 years; 63% male) were included. Baseline clinical and echocardiographic characteristics are summarized in Tables 1 and 2. Nonischemic HF was present in 51% of the total population, and the majority of the patients were in NYHA functional class II to III. Mean LVEF was 30% ± 11%. Median LVEDV was 189 ml (IQR: 138 to 245 ml). Mean EROA and mean RVol were 24 ± 11 mm2 and 34 ± 15 ml/beat, respectively. During median follow-up of 5 months (IQR: 1 to 114 months), 234 patients received MV intervention.

Table 1. Clinical Characteristics at Baseline According to RVol/EDV Ratio

	Total Population (N = 379)	RVol/EDV Ratio <20% (n = 244)	RVol/EDV Ratio ≥20% (n = 135)	p Value
Age (yrs)	67 ± 11	66 ± 11	68 ± 11	0.070
Male	240 (63)	173 (71)	67 (50)	<0.001
BSA (m^2)	1.92 ± 0.2	1.94 ± 0.21	1.89 ± 0.22	0.023
Atrial fibrillation	164 (43)	86 (52)	78 (58)	<0.001
Hypertension	163 (43)	95 (39)	68 (50)	0.031
Diabetes mellitus	95 (25)	64 (26)	31 (23)	0.482
eGFR (ml/min/1.73 m^2)	61 ± 25	60 ± 25	63 ± 26	0.345
Heart failure etiology				
Ischemic	187 (49)	124 (51)	63 (47)	0.439
Nonischemic	192 (51)	230 (49)	72 (53)	0.439
NYHA functional class				0.041
I	28 (7)	20 (8)	8 (6)	
II	85 (22)	44 (18)	41 (30)	
III	214 (57)	147 (60)	67 (50)	
IV	52 (14)	33 (14)	19 (14)	
Medication				
Beta-blockers	265 (70)	163 (67)	102 (76)	0.075
Diuretics	321 (85)	217 (89)	104 (77)	0.002

table continues

	Total Population (N = 379)	RVol/EDV Ratio <20% (n = 244)	RVol/EDV Ratio ≥20% (n = 135)	p Value
ACE inhibitor/ ARB	297 (78)	193 (79)	104 (77)	0.641
MRA	184 (49)	124 (51)	60 (44)	0.234
ICD therapy	57 (15)	42 (17)	15 (11)	0.112

Continuous data are mean ± SD. Categorical data are n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BSA = body surface area; EDV = end-diastolic volume; eGFR = estimated glomerular filtration rate; ICD = implantable cardioverter-defibrillator; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; RVol = regurgitant volume.

Table 2. Echocardiographic Characteristics at Baseline According to RVol/EDV Ratio

	Total Population (N = 379)	RVol/EDV Ratio <20% (n = 244)	RVol/EDV Ratio ≥20% (n = 135)	p Value
LVEDV (ml)	189 (138–245)	222 (181–276)	123 (95–170)	<0.001‡
LVESV (ml)	136 (92–184)	165 (131–210)	77 (53–107)	<0.001
LVEF (%)	30 ± 11	26 ± 8	38 ± 12	<0.001
VC width (mm)	6.0 ± 0.18	6.0 ± 0.18	6.1 ± 0.18	0.557
PISA				
EROA (mm²)	24 ± 11	22 ± 11	27 ± 12	<0.001
RVol (ml)*	34 ± 15	29 ± 10	44 ± 18	<0.001‡
LAVI (ml/m²)	33 (25–44)	33 (25–41)	34 (25–48)	0.324
RVol/EDV ratio	21 ± 14	13 ± 4	35 ± 14	<0.001
RF (%)	77 (71–83)	76 (71–83)	78 (72–84)	0.226
RVol (ml)†	174 ± 79	171 ± 74	181 ± 90	0.259

Continuous data are mean ± SD or median (interquartile range). Categorical data are n (%).

EROA = effective regurgitant orifice area; LAVI = left atrial volume index; LVEF = left ventricular ejection fraction; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; PISA = proximal isovelocity surface area; RF = regurgitant fraction; VC = vena contracta; other abbreviations as in Table 1.

* RVol measured according to the PISA method; † RVol derived from RF; ‡ The p value for LVEDV and RVol demonstrating significance is indicated for illustrative purpose, due to confounding.

A total of 244 (64.4%) patients had RVol/EDV ratio <20%; the remaining 135 (35.6%) patients had RVol/EDV ratio ≥20%. Patients with a high RVol/EDV ratio (≥20%) were more frequently male and had a higher prevalence of atrial fibrillation and hypertension compared with those with a low RVol/EDV ratio (<20%). Those with a high RVol/EDV ratio (≥20%) had less severe HF symptoms and were less frequently using diuretic agents than their counterparts. In terms of echocardiographic characteristics, patients with a high RVol/EDV ratio (≥20%) had smaller LV volumes with higher LVEFs compared with those with a low RVol/EDV ratio (<20%). In addition, patients with a high RVol/EDV ratio (≥20%) had larger EROA and RVol compared with those with a low RVol/EDV ratio (<20%). Patients with a low RVol/EDV ratio (<20%) were more frequently treated with cardiac resynchronization therapy, whereas those with a high ratio (≥20%) more frequently underwent surgical MV repair (Table 3).

Table 3. Device and Mitral Valve Interventions During Follow-Up According to RVol/EDV Ratio

	Total Population (N = 379)	RVol/EDV Ratio <20% (n = 244)	RVol/EDV Ratio ≥20% (n = 135)	p Value
Device therapy				
CRT-PM	8 (2)	5 (2)	3 (2)	0.911
CRT-ICD	191 (50)	157 (64)	34 (25)	<0.001
MV interventions				
Surgical MVr	156 (41)	80 (33)	76 (56)	<0.001
Surgical MVR	2 (0.5)	1 (0.4)	1 (0.7)	0.670
MitraClip	76 (20)	43 (18)	33 (24)	0.112

Values are n (%).

CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator; MV = mitral valve; MVr = mitral valve repair; MVR = mitral valve replacement; PM = pacemaker; other abbreviations as in Table 1.

Survival analysis

During median follow-up of 50 months (IQR: 26 to 94 months) 199 (52.5%) patients of the total study population died, including 169 (44.6%) who died during medical treatment. When considering patients receiving medical therapy only, patients with a high RVol/EDV ratio (≥20%) had higher mortality rates than those with a low RVol/EDV ratio (<20%), although the difference did not reach statistical significance (5-year estimated rates 24.1% vs. 18.4% respectively; $p = 0.077$) (Figure 2A). Changes in HR across the range of RVol/EDV ratio (as a continuous variable) for all-cause mortality before any MV interventions are demonstrated with a fitted spline curve in Figure 3A. The assumption of linearity was not violated ($\chi2 = 0.849$; $p = 0.36$). When considering patients on medical therapy only, RVol/EDV ratio was significantly associated with all-cause mortality after correcting for age and renal function (HR per 5% increment: 1.08; 95% CI: 1.01 to 1.14; $p = 0.017$).

Conversely, when considering the entire follow-up period including the period after MV interventions, patients with a high RVol/EDV ratio (≥20%) had lower cumulative mortality event rates compared with those with a low RVol/EDV ratio (<20%): 5-year estimated rates 39.0% vs. 44.8% respectively; $p = 0.018$) (Figure 2B). The changes in HR across the range of RVol/EDV ratio (as a continuous variable) for all-cause mortality including MV interventions during follow-up are demonstrated as a fitted spline curve in Figure 3B. The HR for all-cause mortality gradually decreased as the RVol/EDV ratios increased. The assumption of linearity was not violated ($\chi2 = 0.695$; $p = 0.884$). In this model, a high RVol/EDV ratio was independently associated with reduced all-cause mortality (HR per 5% increment: 0.93; 95% CI: 0.87 to 0.99; $p = 0.023$) (Table 4).

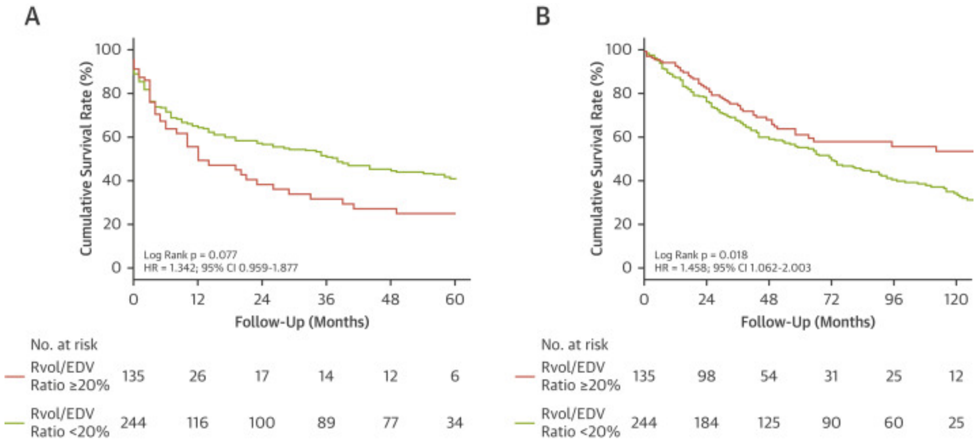


Figure 2. Kaplan-Meier Curves for All-Cause Mortality

(A) Patients were censored at the time of mitral valve interventions. (B) All follow-up data, including after mitral valve interventions. Time to all-cause mortality according to RVol/EDV ratio: ≥20% (green) and <20% (red). CI = confidence interval; EDV = end-diastolic volume; HR = hazard ratio; RVol = regurgitant volume.

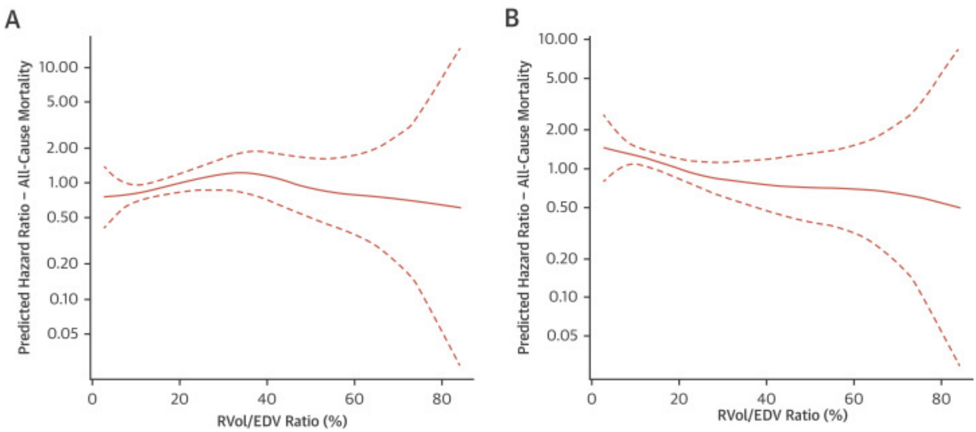


Figure 3. Spline Curve for All-Cause Mortality According to RVol/EDV Ratio

All-cause mortality across the range of RVol/EDV ratios, plotted as a cubic spline on a log-hazard scale with overlaid confidence intervals. (A) Patients were censored at the time of mitral valve interventions. (B) All follow-up data, including after mitral valve interventions. Dashed lines represent 95% confidence intervals. EDV = end-diastolic volume; RVol = regurgitant volume.

Table 4. Univariable and Multivariable Predictors of All-Cause Mortality in All Patients (Including Those Undergoing Mitral Valve Interventions)

	Unadjusted			Adjusted		
	HR	95% CI	p Value	HR	95% CI	p Value
Age (yrs)	1.02	1.01–1.04	0.001	1.01	1.00–1.03	0.077
Male	1.32	0.98–1.77	0.069	—	—	—
BSA (m^2)	1.01	0.54–1.90	0.975			
eGFR (ml/min/1.73 m^2)	0.98	0.97–0.99	<0.001	0.98	0.97–0.99	<0.001
Hypertension	1.09	0.82–1.44	0.556			
Diabetes mellitus	1.33	0.97–1.82	0.080	—	—	—
Atrial fibrillation	0.96	0.72–1.27	0.755			
Ischemic etiology	1.16	0.88–1.54	0.287	—	—	—
NYHA functional classification ≥II	1.12	0.64–1.97	0.691			
Beta-blockers	0.83	0.62–1.11	0.200	—	—	—
MV interventions*	0.87	0.65–1.15	0.310			
MV interventions†	0.99	0.99–1.00	0.084			
LAVI (ml/m^2)	1.01	0.99–1.01	0.119			
RVol/EDV ratio (per 5% increment)	0.93	0.87–0.99	0.015	0.93	0.87–0.99	0.023

BSA = body surface area; CI = confidence interval; EDV = end-diastolic volume; eGFR = estimated glomerular filtration rate; HR = hazard ratio; LAVI = left atrial volume index; MV = mitral valve; NYHA = New York Heart Association; RVol = regurgitant volume.

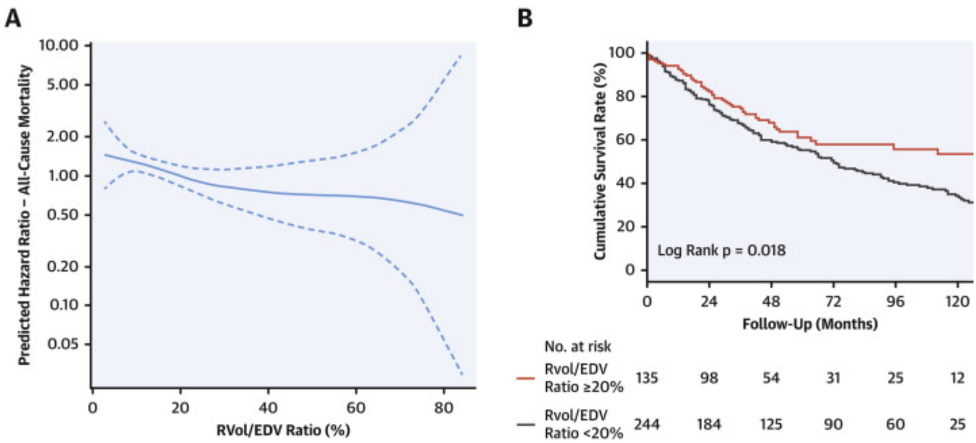
* Surgical mitral valve repair, mitral valve replacement, and percutaneous edge-to-edge mitral valve repair compared with optimal medical therapy alone.

† Mitral valve interventions introduced as a time-dependent covariate.

Discussion

In the present study, a high RVol/EDV ratio was associated with a trend toward increased all-cause mortality during medical therapy in patients with moderate and severe secondary MR. Conversely, allowing for the effects of MV interventions, a high RVol/EDV ratio was independently associated with lower all-cause mortality during follow-up.

In contrast to other Doppler echocardiographic measures of secondary MR, the RVol/EDV ratio takes into consideration the degree of LV remodeling as well as MR severity. Thus, this ratio may help identify patients who are likely to benefit from transcatheter and surgical therapies that aim to reduce MR. For the same value of RVol, a patient with low RVol/EDV ratio may not benefit as much as a patient with a high RVol/EDV ratio because the patient with a low RVol/EDV ratio has a much larger degree of LV remodeling that may not respond to MR reduction therapies. Similarly, for the same LVEDV, a patient with a high RVol/EDV ratio may benefit more from transcatheter or surgical therapies than a patient with a low RVol/EDV ratio because the volume overload caused by the MR is relatively greater in the former patient. This perspective is consistent with the concept of proportionate and disproportionate secondary MR as proposed by Packer and Grayburn (14).



Central Illustration. Association of RVol/EDV Ratio and Long-Term All-Cause Mortality in Patients With Secondary Mitral Regurgitation During Medical Treatment and After Surgical and Transcatheter Mitral Reduction Therapies

(A) All-cause mortality across a range of RVol/EDV ratios, plotted as a fitted spline model. The spline curve demonstrates a linearly increasing risk for mortality for lower RVol/EDV ratios. (B) Kaplan-Meier curves demonstrating the cumulative survival rate for all-cause mortality stratified according to a RVol/EDV ratio cutoff of 20%. EDV = end-diastolic volume; RVol = regurgitant volume.

In the present study, patients with a high RVol/EDV ratio (≥20%) tended to have worse survival during medical management than those with a low RVol/EDV ratio (<20%), suggesting that more severe MR with less LV dilation is associated with a worse prognosis. As expected, patients with a high RVol/EDV ratio (≥20%) more frequently underwent surgical correction of the MR, whereas patients with a low RVol/EDV ratio (<20%) more frequently received cardiac resynchronization therapy. After MV interventions, the relative prognosis changed such that a baseline high RVol/EDV ratio was independently associated with improved survival. For both therapies, the degree of LV remodeling has been associated with response to treatment and survival (5,6). Therefore, when evaluating patients with HF and secondary MR, assessment of the degree of LV remodeling is likely to be fundamental in estimating the potential benefit of interventional therapies. However, patients in the present analysis were not randomized to MV interventions according to RVol/EDV ratio. Thus, further investigations are warranted to assess the utility of this ratio in predicting the benefits from surgical or transcatheter interventions. Such an analysis should be possible from the recently completed COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) and MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/ Secondary Mitral Regurgitation) randomized trials (15,16).

Grading secondary MR in HF patients

Grading secondary MR remains challenging for various reasons. RVol usually is smaller than that observed in primary MR because the total LV SV is reduced. In contrast to RVol calculated according to the PISA method, RF takes into consideration the degree of LV remodeling measured either with quantitative pulsed Doppler (because the mitral annulus dimensions are included) or volumetrically (via LVEDV and LVESV). Accordingly, it has been suggested that RF provides a metric of proportionality of the secondary MR to LV dimensions and function (17). However, measurement of RF with echocardiography is prone to error. When using the quantitative pulsed Doppler method, calculation of RF can be inaccurate because of failure in tracing the modal velocity on spectral Doppler, locating the sample volume, and assuming that the mitral or aortic valve annuli are circular (leading to a squared error in the formula) (10). When the quantitative volumetric method is used, foreshortened images of the LV may lead to underestimation of SV (10). Various studies have suggested that cardiac magnetic resonance (CMR) may be a more accurate method to quantify secondary MR, although the majority of studies did not have a reference standard to resolve discrepancies between techniques (18, 19, 20). Lopez-Mattei et al. (18) showed a modest agreement between transthoracic echocardiography and CMR in quantifying RVol and RF. The discrepancy between techniques was more prominent among patients with secondary MR.

The RVol/EDV ratio proposed in the present study shares some of the limitations mentioned but provides a metric of proportionality of secondary MR and can be used in patients with concomitant aortic regurgitation (in whom RF cannot be used).

RVol/EDV ratio and outcome in secondary MR

The cutoff values of EROA ≥20 mm2 and RVol ≥30 ml/beat to define severe secondary MR included in European guidelines (8,21) are based on outcomes studies showing that patients with secondary MR and EROA or RVol values above those cutoffs have a worse prognosis (4,22, 23, 24). However, the U.S. guidelines suggest higher thresholds to define severe secondary MR (25,26). In this regard, even mild secondary MR has been associated with poor outcomes (24,27). However, MV repair in patients with moderate ischemic (secondary) MR (mean EROA ~0.20 mm2) undergoing coronary revascularization did not show improved outcomes in a randomized trial (28). Whether the association between EROA and poor outcomes relies on the severity of MR itself, the underlying LV dysfunction/remodeling, or both remains unclear (10). By adjusting RVol for LV volume in the RVol/LVEDV ratio, the extent of LV remodeling is taken into consideration, and we demonstrated that when considering surgical and transcatheter options for correction of MR, patients with a higher RVol/EDV ratio (≥20%) had improved long-term outcomes, suggesting that the long-term prognosis is determined by the lesser severity of LV dysfunction after MR reduction. Bartko et al. (29) showed in 423 HF patients with various grades of secondary MR that the measurement of RF had incremental discriminative power over RVol and EROA in identifying patients with poor prognosis. RF partially takes into consideration the severity of LV remodeling and has been proposed as a parameter that reflects the proportionality of MR. Similarly, RVol/EDV may reflect the proportionality of secondary MR and impact of available therapies. We hypothesize that for patients with a low RVol/EDV, resolving the volume overload caused by the MR, either by surgery or transcatheter techniques, may not have a major impact on outcome because the severity of MR may be less prognostically relevant than the extent of LV remodeling. In contrast, in patients with a high RVol/EDV, the volume overload caused by MR may have a major influence on LV hemodynamics and symptoms, and thus appropriate repair or replacement may improve outcomes. This hypothesis requires validation in prospective studies.

Study limitations

The present study has several limitations related to the retrospective nature of data analysis. However, to the best of our knowledge, this is the largest series evaluating the prognostic value of RVol/EDV ratio in patients with secondary MR. External validation of the present results is warranted. Symptomatic status could only be assessed based on NYHA functional class, and other quantitative measures such as 6-min walked distance or quality-of-life scores were not systematically available. In addition, patients with mild MR were excluded, and the value of RVol/EDV ratio was not assessed in this population. Assessment of EROA and RVol in secondary MR using echocardiography is limited by various previously described assumptions (30), and CMR data were not systematically available. Furthermore, a significant proportion of patients were referred for intervention, which limits the power to demonstrate the association between RVol/EDV and all-cause mortality while receiving medical therapy. Finally, the sample size limited our ability to examine which MV interventions were beneficial or hazardous according to RVol/EDV ratio.

Conclusions

In patients with significant secondary MR who were treated medically, survival tended to be lower in those with a higher RVol/EDV ratio. Conversely, a high RVol/EDV ratio was independently associated with reduced all-cause mortality if this group received therapies to correct the MR. By accounting for the relative severity of both MR and LV volume, the RVol/EDV ratio may further improve risk stratification of patients with secondary MR and identify those who may benefit from transcatheter and surgical therapies to reduce severe secondary MR.

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