Congestive heart failure complicating aortic regurgitation with medical and surgical management: A prospective study of traditional and quantitative echocardiographic markers

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Objective: Congestive heart failure complicating aortic regurgitation is poorly described, and predictive roles of quantitative versus traditional (symptoms or low ejection fraction) surgical markers are unclear.

Methods: We prospectively enrolled 287 patients with aortic regurgitation (age, 61 ± 17 years; 68% male) in whom we performed quantitative Doppler echocardiographic analysis and personal physicians conducted management.

Results: After diagnosis, 40 congestive heart failure episodes occurred under medical management (10-year, $23\% \pm 4\%$) causing high subsequent mortality (hazard ratio [HR], 2.8; 95% confidence interval [CI], 1.2–6.8; $P = .02$). Patients with traditional surgical markers (symptoms or ejection fraction $<50\%$) were surprisingly followed 1.4 ± 3.3 years under medical management with frequent congestive heart failure (adjusted risk, 4.9; 95% CI, 2.1–11.0; $P < .001$) and excess postoperative mortality (HR, 3.0; 95% CI, 1.3–7.1; $P = .01$). Quantitative American Society of Echocardiography aortic regurgitation grading and left ventricular end-systolic volume index independently predicted congestive heart failure (quantitative American Society of Echocardiography severe aortic regurgitation: HR, 3.6; 95% CI, 1.3–13.0; $P = .015$; end-systolic volume index ≥ 45 mL/m²: HR, 2.1; 95% CI, 1.03–4.4; $P = .04$) or death—congestive heart failure with incremental predictive value ($P < .001$). Higher congestive heart failure rates occurred with quantitative American Society of Echocardiography severe aortic regurgitation (regurgitant volume of ≥ 60 mL/beat or orifice of ≥ 30 mm²) versus quantitative American Society of Echocardiography mild aortic regurgitation (10-year: $44\% \pm 10\%$ vs $15\% \pm 7\%$, $P < .001$) and end-systolic volume index of 45 mL/m² or greater versus less than 45 mL/m² ($33\% \pm 7\%$ vs $9\% \pm 2\%$, $P < .001$). Traditional markers (symptoms and ejection fraction $<50\%$) had lower sensitivity for congestive heart failure than quantitative echocardiography (all $P < .001$). Cardiac surgery for aortic regurgitation markedly reduced congestive heart failure in quantitative American Society of Echocardiography severe aortic regurgitation (HR, 0.23; 95% CI, 0.08–0.68; $P = .008$) without excess mortality ($P = .10$).

Conclusion: This prospective study of aortic regurgitation shows frequent congestive heart failure under conservative management. Traditional surgical markers (symptoms and ejection fraction $<50\%$) predict subsequent congestive heart failure but are insensitive, and rescue operations are often delayed and associated with excess mortality. Quantitative echocardiography provides congestive heart failure predictors that are independent, incremental, and more sensitive than traditional markers. Cardiac surgery for aortic regurgitation markedly reduces congestive heart failure rates in high-risk patients with aortic regurgitation.

Congestive heart failure (CHF) is a dreaded complication of cardiac disease, which remains challenging in valvular heart disease despite the availability of valvular surgery.¹ In patients with aortic regurgitation (AR), data regarding CHF are sketchy and discordant, leaving doubts regarding its rates

and determinants.^{2–5} Uncertainties were amplified by a lack of specific AR severity measures.⁶ Limited data suggest poor outcome after CHF in patients with AR.^{7,8} Thus defining patients' subsets at high CHF risk is crucial to the risk-stratification process.

In clinical guidelines risk stratification in AR is essentially based on symptoms or reduced ventricular function.^{1,9} These traditional surgical markers play a central role because they are considered the strongest predictors of outcome.² However, when surgical intervention is performed with these traditional markers, symptoms usually improve, but surgical series suggest that survival might remain suboptimal.^{10,11} These dubious outcomes warrant new risk-stratification tools to provide better outcomes.

Quantitative echocardiography codified by the American Society of Echocardiography (quantitative American Society of Echocardiography [QASE] grading)⁶ might play an

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Abbreviations and Acronyms

AR	= aortic regurgitation
CHF	= congestive heart failure
CI	= confidence interval
EF	= ejection fraction
ERO	= effective regurgitant orifice
ESVI	= end-systolic volume index
HR	= hazard ratio
LV	= left ventricular
QASE	= quantitative American Society of Echocardiography
RVol	= regurgitant volume

important role in AR. For this purpose, we conducted a prospective study in patients with quantified AR and ventricular volumes using Doppler echocardiography. Pilot data from the asymptomatic segment of this study were encouraging by showing a link between these novel variables and the combined end point of cardiac events.¹² However, clinically relevant issues are whether these quantitative echocardiographic variables specifically predict CHF occurrence and have an incremental role over symptoms and ejection fraction (EF) and whether these various types of predictors affect not only medical but also surgical outcome.¹³ Thus we hypothesized that CHF is frequent in AR treated medically and that quantitative echocardiography independently and incrementally (over symptoms and EF) predicts CHF and defines high-risk groups. We also hypothesized that surgical intervention for AR reduces the risk of CHF, with excellent survival in the quantitatively defined high-risk subsets.

MATERIALS AND METHODS**Study Population**

The study was approved by the institutional review board, and patients were consecutively and prospectively enrolled after oral consent between 1990 and 2003 (1) if they had AR that was at least mild, as determined by means of standard color flow imaging¹⁴; (2) if they had AR that was pure (no stenosis) and isolated (no other valve disease); and (3) if they underwent quantitative echocardiography performed by the investigators with measurement of AR degree and left ventricular (LV) volumes. Exclusion criteria were (1) aortic dissection or ongoing endocarditis; (2) functional AR caused by hypertension; (3) associated aortic systolic gradient of 20 mm Hg or greater; (4) concomitant mitral, congenital (other than bicuspid valve), or pericardial disease; or (5) previous valve repair or replacement.

Clinical Evaluation and Management

Patients were evaluated and treated by their independent personal physicians who assessed symptoms, were informed of all results, and made all management decisions (without interference from investigators). Follow-up, collected after closure of enrollment and of all baseline data-collection procedures, was complete up to death or 2006 in 95% of patients and was less than 1 year in only 1.7% of patients. CHF ascertainment used Framingham criteria,¹⁵ and documentation of patients' clinical events was reviewed to assess these criteria. Symptoms alone were not sufficient for CHF diag-

nosis, and congestive manifestations were required. Comorbidity assessment used the Charlson index.¹⁶

Doppler Echocardiographic Analysis

Quantitation of AR. Comprehensive AR quantitation used 3 validated methods that were eventually averaged to calculate both regurgitant volume (RVol) and effective regurgitant orifice (ERO) area (85% of patients had 2 or 3 methods). These were quantitative Doppler scanning based on aortic and mitral stroke volume measurement,^{17,18} quantitative 2-dimensional echocardiography based on LV and mitral stroke volume,^{18,19} and a proximal isovelocity surface area method analyzing proximal flow convergence.²⁰ QASE guidelines regarding AR grading⁶ define QASE severe AR as an RVol of 60 mL/beat or greater or an ERO area of 30 mm² or greater, QASE mild AR as both an RVol of less than 30 mL/beat and an ERO area of less than 10 mm², and QASE moderate AR as greater than mild criteria (RVol $\geq$ 30 mL/beat or ERO area $\geq$ 10 mm²) but not reaching QASE severe criteria. Color flow imaging jet width/LV outflow tract width ratio¹⁴ was also prospectively measured from parasternal long-axis views.⁶

LV assessment. LV end-diastolic and end-systolic volume indexes (ESVIs) and EF determined by using the Simpson disk method and LV mass were measured as recommended by the American Society of Echocardiography.¹⁹ LV diameters using M-mode echocardiography were measured as absolute values and normalized to body surface area.

Statistical Analysis

Data are presented as mean values $\pm$ standard deviations or percentages. Group comparisons used analysis of variance or the χ^2 test, as appropriate. The main outcome end point was CHF occurrence under medical management (censored at surgical intervention), and the entire follow-up after diagnosis was used to assess the effect of surgical intervention as a time-dependent variable. Survival after surgical intervention was also analyzed. A secondary end point was combined CHF or death event. Event rates (estimated $\pm$ standard error) with the Kaplan-Meier method were compared by using the log-rank test. Time to CHF (or CHF death) was analyzed by means of the Cox proportional hazard method, with calculation of risk ratio unadjusted and adjusted for age, sex, and comorbidity score. The main variables of interest in predicting CHF were baseline symptoms, EF, ESVI, and QASE AR grading.

RESULTS**Baseline Characteristics**

The 287 patients enrolled in the cohort were followed for 7.7 ± 4.0 years. Their baseline characteristics are presented in Table 1. Some data on the asymptomatic segment of this population were previously presented.¹² Symptoms at presentation were observed in 25 (9%) patients, and LV dysfunction (EF $< 50\%$) was observed in 17 (6%) patients. These 2 patient subsets had greater LV volume and mass and lower EF (all $P < .001$) but showed no difference in age (both $P > .22$), sex (both $P > .34$), or comorbidity (both $P > .49$) compared with the cohort remainder. Causes of AR were degenerative in 53%, congenital in 22%, aortic root dilatation in 12%, chronic endocarditic lesions in 4%, rheumatic in 3%, and miscellaneous in 6%. QASE grading¹ was 18% QASE mild, 40% QASE moderate, and 42% QASE severe AR (Table 1). With higher grade, there were more symptoms, lower EF, and greater LV dilatation and hypertrophy and jet size (Table 1). Vasodilator therapies during medical follow-up were angiotensin-converting enzyme

TABLE 1. Baseline characteristics of patients according to quantitative assessment of AR and their association with CHF under conservative management

	Overall population (n = 287)	AR grading*			P value	Association with time to CHF, P value
		QASE mild (n = 52)	QASE moderate (n = 114)	QASE severe (n = 121)		
Clinical characteristics						
Age, y	61 ± 17	63 ± 15	62 ± 18	59 ± 18	.25	.003
Male sex, no. (%)	194 (68)	23 (44)	69 (60)	102 (84)	<.001	.12
Atrial fibrillation, no. (%)	18 (6)	1 (2)	8 (7)	9 (7)	.24	.03
History of hypertension, no. (%)	123 (46)	27 (59)	53 (49)	43 (39)	.06	.54
History of coronary artery disease, no. (%)	44 (16)	8 (15)	17 (15)	19 (16)	.99	.02
Charlson comorbidity index, arbitrary units	1.9 ± 2.3	1.4 ± 2.0	2.2 ± 2.5	1.9 ± 2.3	.08	.001
Symptoms, no. (%)	25 (9)	0 (0)	2 (2)	23 (19)	<.001	<.001
Echocardiographic characteristics						
Ejection fraction, %	66 ± 11	70 ± 9	67 ± 10	64 ± 11	.002	<.001
End-systolic diameter index, mm/m ²	19 ± 4	17 ± 3	19 ± 4	21 ± 5	<.001	<.001
End-diastolic volume index, mL/m ²	109 ± 29	74 ± 17	114 ± 22	136 ± 38	<.001	<.001
End-systolic volume index, mL/m ²	39 ± 22	22 ± 11	33 ± 18	50 ± 27	<.001	<.001
Left ventricular mass, g	257 ± 80	188 ± 58	235 ± 73	307 ± 97	<.001	<.001
AR parameters						
Jet to outflow tract width ratio, %	40 ± 14	27 ± 12	36 ± 13	50 ± 16	<.001	.13
Regurgitant volume, mL/beat	57 ± 22	17 ± 5	41 ± 12	89 ± 31	<.001	<.001
Effective regurgitant orifice, mm ²	26 ± 12	7 ± 2	18 ± 6	42 ± 18	<.001	<.001

AR, Aortic regurgitation; CHF, congestive heart failure; QASE, quantitative American Society of Echocardiography. *QASE severe AR is defined as a regurgitant volume of 60 mL/beat or greater or an effective regurgitant orifice area of 30 mm² or greater, QASE mild AR is defined as a regurgitant volume of less than 30 mL/beat and an effective regurgitant orifice area of less than 10 mm², and QASE moderate AR is defined as regurgitation greater than QASE mild (regurgitant volume ≥ 30 mL/beat or effective regurgitant orifice ≥ 10 mm²) but not reaching QASE severe criteria.

inhibitors in 116 patients, calcium-channel blockers in 58 patients, and angiotensin receptor blockers in 37 patients.

CHF Rates and Determinants Under Medical Management

Follow-up under conservative management was 1492 patient-years, with survival of 91% ± 2% and 77% ± 4% at 5 and 10 years, respectively. Remarkably, patients with symptoms or EF of less than 50% were followed for 1.4 ± 3.3 years under medical management. Reasons for deferral of surgical intervention were multiple but essentially reflected that patients were considered well or improved with medical treatment while patient preference and comorbidity seldom justified surgical delay. Under conservative management, 40 episodes of CHF occurred with 5- and 10-year rates of 15% ± 2% and 23% ± 4%, respectively. CHF occurrence was associated with almost tripling of subsequent mortality (adjusted hazard ratio [HR], 2.8; 95% confidence interval [CI], 1.2–6.8; *P* = .02).

Univariate baseline predictors of CHF under conservative management are listed in Table 1. Traditional surgical markers (symptoms and EF) were linked to CHF. Quantitative variables, ESVI (HR, 1.04; 95% CI, 1.02–1.05 [per milliliter per square meter]; *P* < .001), RVol (HR, 1.19; 95% CI, 1.10–1.29 [per 10 mL/beat]; *P* < .001), and ERO area (HR, 1.49; 95% CI, 1.25–1.72 [per 10 mm²]; *P* < .001) were also powerful univariate CHF predictors. Table 2

shows that AR quantitation predicted CHF (with or without adjustment) and that QASE severe versus QASE mild grading implied quadrupling of CHF risk. QASE moderate grading was not independently associated with CHF. Prediction of CHF by means of QASE grading was not affected by vasodilator therapy (*P* < .004). The other independent determinants of CHF adjusting for age, sex, and comorbidity were symptoms (*P* < .01) and LV dysfunction assessment based on either an EF of less than 50% (*P* < .001) or an ESVI of 45 mL/m² or greater (*P* < .01).

Table 3 shows that adjusting for age, sex, and comorbidity and grouping traditional surgical indicators (symptoms or EF < 50%), quantitative variables, ESVI of 45 mL/m² or greater (*P* = .04), and QASE severe AR (*P* = .015) independently predicted CHF under conservative management and provided incremental predictive power (overall χ^2 increment = 17, *P* < .001).

Five-year CHF rates under medical management were 65% ± 17% with and 12% ± 2% without traditional surgical indicators (symptoms or EF < 50%, *P* < .001); were 2% ± 2%, 12% ± 3%, and 28% ± 6% for QASE mild, moderate, or severe AR (*P* < .001, Figure 1); and were 33% ± 7% with an ESVI of 45 mL/m² or greater and 9% ± 2% with an ESVI of less than 45 mL/m² (*P* < .001, Figure 2).

History of clinical coronary disease and baseline atrial fibrillation were univariate CHF predictors but lost

TABLE 2. CHF risk under conservative management associated with baseline regurgitant volume, effective regurgitant orifice area, and QASE severe AR*

Models	Regurgitant volume		Effective regurgitant orifice		QASE severe AR*	
	Hazard ratio (95% CI)†	P value	Hazard ratio (95% CI)‡	P value	Hazard ratio (95% CI)§	P value
Unadjusted	1.19 (1.1–1.3)	<.001	1.49 (1.3–1.7)	<.001	5.7 (2.2–19.8)	<.001
Adjusted for age, sex, ESVI, NYHA, comorbidity	1.18 (1.1–1.3)	.0015	1.35 (1.1–1.3)	.004	4.3 (1.4–16.4)	.009
Adjusted for age, sex, EF, NYHA, comorbidity	1.24 (1.1–1.4)	<.001	1.4 (1.2–1.7)	<.001	5.9 (2.1–21.4)	<.001

CHF, Congestive heart failure; QASE, quantitative American Society of Echocardiography; AR, aortic regurgitation; 95% CI, 95% confidence interval; ESVI, end-systolic volume index; NYHA, New York Heart Association; EF, ejection fraction. *QASE severe AR is defined as a regurgitant volume of 30 mL/beat or greater or an effective regurgitant orifice area of 20 mm² or greater, QASE mild AR is defined as a regurgitant volume of less than 30 mL/beat and an effective regurgitant orifice area of less than 10 mm². †Per 10-mL/beat increment. ‡Per 10-mm² increment. §Using QASE mild AR grading as comparison.

significance in multivariate analysis and did not affect RVol, ERO area, QASE severe grading, and ESVI prediction (all $P < .01$).

For the combined end point of death–CHF (the endpoint of CHF or death) under conservative management (68 events), traditional surgical indicators (symptoms or EF <50%; HR, 2.9; 95% CI, 1.3–5.8; $P = .01$), ESVI of 45 mL/m² or greater (HR, 1.9; 95% CI, 1.1–3.4; $P = .02$), and QASE severe AR (HR, 3.1; 95% CI, 1.4–7.3; $P = .004$) were independent predictors. Addition of quantitative echocardiographic variables provided incremental power (model χ^2 increment = 21, $P < .001$).

Predictive Value of Quantitative Versus Traditional CHF Markers

Yearly CHF rates and numbers of events are displayed for traditional indicators (symptoms and EF <50%) in Figure 3 and for newer quantitative parameters (QASE grade and ESVI ≥ 45 mL/m²) in Figure 4. Patients with baseline symptoms (Figure 3) had high CHF yearly rates (43.2 vs 2.5 per 100 patient-years, $P < .001$), contrasting with small number of CHF events predicted ($n = 5$, 12.5% of CHF events). In contrast, QASE grading (Figure 4) shows less impressive difference in CHF rates (6.7 vs 2.0 vs 1.0 per 100 patient-

years for QASE severe versus moderate versus mild AR, $P < .001$), but most CHF events are detected by QASE severe AR grading ($n = 22$, 55% of CHF events). Thus symptoms showed higher specificity ($P < .001$), and QASE grading showed higher sensitivity ($P < .001$). Similarly, an EF of less than 50% was associated with high CHF rates (20.7 vs 2.7 per 100 patient-years, $P < .001$) but detected only 15% of CHF episodes (Figure 3), whereas an ESVI of 45 mL/m² or greater was associated with a less striking difference in CHF rates (8.5 vs 1.6 per 100 patient-years, $P < .001$) but detected most CHF episodes (52.5%, Figure 4). Thus an EF of less than 50% had higher specificity ($P < .001$), and an ESVI of 45 mL/m² or greater had a higher sensitivity ($P < .001$). Patients with both QASE severe AR and an ESVI of 45 mL/m² or greater incurred frequent CHF (48% $\pm$ 10% at 5 years and 69% $\pm$ 13% at 10 years or 14.4% per 100 patient-years) close to that of patients with symptoms or low EF.

Traditional AR measures (jet-width ratio by means of color flow imaging⁶ and LV end-systolic diameter normalized or not to body surface area^{2,21}) univariately predicted CHF under conservative management (all $P < .001$) but lost significance when adjusting for quantitative AR grading, the significance of which remained unaffected (all

TABLE 3. CHF risk under conservative management associated with traditional surgical markers, ESVI of 45 mL/m² or greater, and QASE severe AR

Models	Traditional surgical markers (symptoms or EF <50%)		ESVI ≥ 45 mL/m ²		QASE severe AR*	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Unadjusted	1.18 (1.1–1.3)	<.001	4.6 (2.5–8.7)	<.001	5.7 (2.2–19.8)	<.001
Adjusted for age, sex, comorbidity	8.3 (3.7–17.6)	<.001	3.9 (2.0–7.8)	<.001	5.4 (1.9–19.5)	<.001
Fully adjusted model†	4.9 (2.1–11.0)	<.001	2.1 (1.03–4.4)	.04	3.6 (1.3–13.0)	.015
χ^2 Increment‡	21	<.001	6	.02	11	.005

CHF, Congestive heart failure; ESVI, end-systolic volume index; QASE, quantitative American Society of Echocardiography; AR, aortic regurgitation; EF, ejection fraction. *Using QASE-Mild AR grading as comparison. QASE severe AR is defined as a regurgitant volume of 30 mL/beat or greater or an effective regurgitant orifice area of 20 mm² or greater, QASE mild AR is defined as a regurgitant volume of less than 30 mL/beat and an effective regurgitant orifice area of less than 10 mm². †Model with age, sex, comorbidity, traditional surgical markers, ESVI of 45 mL/m² or greater, and QASE moderate and QASE severe AR. ‡Sequentially modeled χ^2 increment for traditional surgical markers (symptoms or EF <50%) over age, sex, and comorbidity; then for ESVI of 45 mL/m² or greater added (middle panel); and then for QASE severe AR added (right panel). Note that QASE severe AR is incremental over ESVI, which is incremental over traditional surgical markers (symptoms or EF <50%), which are incremental over age, sex, and comorbidity.

FIGURE 1. Congestive heart failure (CHF) event rates after the diagnosis of aortic regurgitation (AR) under medical management according to quantitative American Society of Echocardiography (QASE) AR grading. QASE severe AR is defined as a regurgitant volume of 60 mL/beat or greater or an effective regurgitant orifice area of 30 mm² or greater, QASE mild AR is defined as a regurgitant volume of less than 30 mL/beat and an effective regurgitant orifice area of less than 10 mm², and QASE moderate AR is defined as greater than QASE mild criteria (regurgitant volume ≥30 mL/beat or effective regurgitant orifice area ≥10 mm²) but not reaching QASE severe criteria. The numbers associated with each curve indicate the 5-year and 10-year CHF rate ± standard error.

models $P < .03$). Traditional variables were less sensitive than QASE grading (all $P < .001$) and ESVI (all $P < .001$). For death or CHF under conservative management, quantitative echocardiography had incremental sensitivity over traditional surgical indicators (symptoms or EF <50%, 11/68 events [16%]) of an ESVI of 45 mL/m² or greater (28/68 events [41%], $P < .001$) and QASE severe AR (30/68 events [44%], $P < .001$).

Cardiac Surgery and Clinical Outcome

A total of 106 patients underwent cardiac surgery for AR during follow-up for symptoms in 56 patients, LV dysfunction in 16 patients, aortic dilatation in 14 patients, endocarditis in 4 patients, and physician/patient preference in 16 patients. After surgical intervention for AR, 24 deaths were noted, with a 5-year survival of 83% ± 4%. Adjusting for age, sex, and comorbidity, symptoms or an EF of less than 50% at diagnosis was associated with excess postoperative mortality (HR, 3.0; 95% CI, 1.3–7.1; $P = .01$). Five-year postoperative survival was 63% ± 10% with traditional surgical markers at diagnosis versus 89% ± 4% without ($P < .001$). Conversely, a preoperative ESVI of 45 mL/m² or greater ($P = .09$) or QASE severe AR ($P = .10$) was not independently associated with excess postoperative mortality.

During 710 patient-years after surgical intervention, 6 episodes of CHF occurred so that surgical intervention

FIGURE 2. Congestive heart failure (CHF) event rates after the diagnosis of aortic regurgitation under medical management according to the left ventricular end-systolic volume index (ESVI; <45 or ≥45 mL/m²). The numbers associated with each curve indicate the 5-year and 10-year CHF rate ± standard error.

as a time-dependant variable (accounting for time to operation) decreased CHF risk for patients with QASE severe AR (linearized yearly rate of CHF = 6.7%, decreasing to 0.9%; HR, 0.23; 95% CI, 0.08–0.68; $P = .008$). Conversely, in patients with QASE moderate AR, there was no detectable CHF difference ($P = .84$). Adjusting for age, sex, symptoms, comorbidity, LV function, and QASE AR grading, surgical intervention for AR markedly reduced CHF (adjusted HR, 0.14; 95% CI, 0.05–0.41; $P = .0003$).

DISCUSSION

The present prospective cohort of patients with AR shows that CHF is frequent after AR diagnosis and is associated with excess subsequent mortality. In routine clinical practice, despite the presence of traditional surgical markers (symptoms or EF <50%) in patients with age and comorbidity similar to those of our entire cohort, surgical intervention is often delayed, resulting in high rates of CHF and death—CHF under medical management. Also worrisome is the association of traditional surgical markers with excess mortality after surgical intervention. In contrast, novel quantitative markers (QASE AR grading and ESVI ≥45 mL/m²) have distinctive clinical value as independent CHF predictors under medical management. Patients with QASE severe AR (RVol ≥60 mL/beat or ERO ≥30 mm²) incur CHF 3 to 6 times more frequently than with QASE mild AR, and QASE grading superseded traditional markers of severe AR (color jet assessment and LV diameters). Patients with ESVIs of 45 mL/m² or greater incur doubling of CHF risk. Importantly, symptoms and EF of less than 50% are specific, with very high rates of subsequent CHF (>20

FIGURE 3. Linearized yearly rate of congestive heart failure (CHF; *left histograms*) and number of CHF events (*right histograms*) observed according to stratification by the presence or absence of symptoms at baseline (*left panel*) or by baseline ejection fraction of 50% or greater or less than 50% (*right panel*). Note the high yearly rate of CHF in the subsets with symptoms or an ejection fraction of less than 50% at baseline but also the low actual number of CHF events in these subsets, demonstrating the low sensitivity of these predictors.

per 100 patient-years), but lack sensitivity. Conversely, QASE grading and an ESVI of 45 mL/m² or greater are associated with less striking CHF rates (6-9 per 100 patient-years) but are more sensitive. In these high-risk quantitatively defined subsets, cardiac surgery markedly reduces CHF risk without excess postoperative mortality. Thus rescue operations in patients with traditional surgical markers (symptoms and EF <50%) should be emphasized but are not sufficient in view of the mediocre postoperative outcome of these patients. In contrast, quantitative echocardiographic indices allow restorative indications of surgical intervention for AR, which reduces CHF risk without excess mortality.

Rationale of the Study

In patients with isolated AR, CHF development has been insufficiently studied. Rates of CHF complicating AR are rarely mentioned,² and most often composite end points were the main measures of outcome.^{3,4,22} Thus rates and predictors and effect on outcome of CHF are unclear.²⁻⁵ These

FIGURE 4. Linearized yearly rate of congestive heart failure (CHF; *left histograms*) and number of CHF events (*right histograms*) observed according to stratification by end-systolic volume index (ESVI) greater than and less than 45 mL/m² (*left panel*) or by quantitative American Society of Echocardiography (QASE) AR grading (*right panel*). QASE severe AR is defined as a regurgitant volume of 60 mL/beat or greater or an effective regurgitant orifice area of 30 mm² or greater, QASE mild AR is defined as a regurgitant volume of less than 30 mL/beat and an effective regurgitant orifice area of less than 10 mm², and QASE moderate AR as greater than QASE mild criteria (regurgitant volume ≥30 mL/beat or effective regurgitant orifice area ≥10 mm²) but not reaching QASE severe criteria. Note the high CHF rates in the subsets with ESVIs of 45 mL/m² or greater or QASE severe AR but also the high actual number of CHF events in these subsets, demonstrating the high sensitivity of these predictors.

differences might result from patient selection but also from differences in AR severity that might not have been uncovered by using the crude noninvasive AR assessment available at the time.²⁻⁵

Most importantly, AR management is essentially guided by traditional surgical markers (symptoms or low EF),¹ and a strategy of symptom-guided management was emphasized as safe and most appropriate for patients with isolated AR.²³ However, other studies raised concerns regarding outcome with this strategy, even after surgical correction.^{8,10} Thus doubts remain on the respective value of traditional surgical markers (symptoms or low EF) and emerging quantitative measures. Quantitative echocardiography^{6,19} measures absolute AR degree (RVol or ERO) and LV volumes and in our experience is useful in asymptomatic patients¹² in contrast to the rudimentary methods previously available,^{1,9} but its predictive and management values, relative to symptoms and EF, are undefined.

CHF and AR

In this prospective study we observed that CHF occurs relatively frequently overall (5.2 per 100 patient-years)² but with considerable differences between subsets of patients. Patients with QASE mild AR rarely incur CHF, whereas other subsets incur much higher rates. We found that baseline symptoms, LV characteristics, and quantified severity of AR independently predict CHF. Symptoms and an EF of less than 50% are known to influence outcome and are listed in current guidelines.^{1,9} However, the link to outcome is not sufficient, and it is essential to analyze sensitivity and specificity of CHF prediction in clinical practice. CHF in AR has been linked to reduced EF,²⁴ and indeed, we also observe that an EF of less than 50% predicts high CHF rates. Reduced EF also predicts lower survival with medical management² and is considered a strong indication of surgical intervention.^{1,9} Similarly, baseline symptoms, which are known to affect survival,² are associated in our study with high CHF rates, despite improvement with medical treatment. However, outcome with these traditional surgical markers raises several concerns. First, despite existing guidelines,^{1,9} in routine clinical practice surgical intervention for patients with these traditional surgical markers is often delayed, leading to frequent CHF and excess mortality. Second, in agreement with previous surgical series,^{10,11,25} excess mortality follows operations performed for symptoms or reduced EF, which represent late indicators of rescue operations rather than restorative operations conducive to favorable postoperative outcomes.¹³ Third, symptoms and low EF are insufficient²³ because they are insensitive and detect only a small minority of the CHF events to come. Therefore in view of the excess mortality after CHF and of the reduction of CHF risk by AR surgery, our data unquestionably show that additional predictors of outcome are needed to more sensitively predict CHF events and poor outcome.

Our results verify the hypotheses that quantitative echocardiography provides objective indices (quantitative AR grading and ESVI) that can alleviate the CHF burden in patients with AR. These measures independently predict CHF incrementally to symptoms and EF and with higher sensitivity. In high-risk patients examined by using quantitative measures, surgical intervention for AR is not associated with excess mortality (as it is for symptoms and low EF) and reduces the risk of CHF.

Although qualitative AR degree predicts CHF, it is superseded by quantitative grading, emphasizing the importance of the quantitative approach.⁶ Our prospective data show that QASE severe AR is the most sensitive CHF predictor, filling a demand unmet by other outcome predictors.¹³ Low CHF rates with QASE mild AR probably represent the background population CHF rate, which is inconsistently associated with low EF.²⁶ In contrast to this background rate, QASE severe AR multiplies CHF risk between 3 and 6 times. LV volume measurements provide another important independent CHF predictor. End-systolic LV characteristics predict outcome under medical management^{2,4} and after surgical intervention.²⁷ Importantly, ESVI supersedes LV diameters (even adjusted for body surface area) and is more sensitive than EF; that is, the measures currently in clinical guidelines^{1,2,27} and an ESVI of 45 mL/m² or greater apply equally to men and women by normalizing to body size.²¹

Thus this prospective study contrasts value and complementarity of traditional surgical markers (symptoms and EF), specific and associated high CHF rates, and novel quantitative echocardiographic measures (QASE grading and ESVI), both sensitive and incremental. Because these markers carry different implications for postoperative outcome, they emphasize different clinical implications.

Clinical Implications

Patients with traditional surgical markers (symptoms or EF <50%) are at high and immediate risk of CHF or death, irrespective of apparent improvements with medical treatment, but disappointingly, surgical intervention is often delayed. Thus our study emphasizes the need for speedy rescue operations for patients with these ominous characteristics. In view of excess postoperative mortality in these patients, rescue operations should not be the preferred timing of surgical correction of AR.

Quantitative echocardiographic variables allow restorative surgical intervention without excess postoperative mortality and with CHF risk reduction. Quantitative AR grading predicts CHF independently of all other clinical characteristics incrementally to traditional surgical markers and supersedes qualitative AR grading. Hence quantitative AR assessment should be encouraged and generalized.⁶

Patients with both QASE severe AR and an ESVI of 45 mL/m² or greater incur a progressive but high risk,¹² particularly of CHF. These characteristics represent the optimal

target for consideration of surgical correction of AR with low postoperative mortality and marked CHF reduction and thus with the potential to provide true restorative surgical intervention.

Subsets with isolated QASE severe AR or an ESVI of 45 mL/m² or greater (but not both) or those with QASE moderate AR are at moderate CHF risk but might progress and should be monitored closely. Vasodilators for preventing AR progression are disputed,^{28,29} and there is no defined process to stabilize AR or LV function in such patients.

Limitation of the Study

The occurrence of CHF is complex and implies multiple pathways, and a causal link between AR and CHF is difficult to prove. Coronary artery disease and atrial fibrillation can contribute to CHF,^{30,31} but in the current study they were not independently predictive. Our scope was not to address all possible CHF contributors but to focus on AR-specific CHF prediction.²⁶ The link between AR and CHF is supported by strong association of CHF rates with AR degree and by considerable CHF risk reduction after surgical intervention for AR.

Inclusion of baseline symptoms or an EF of less than 50% might be disputed in that guidelines recommend surgical intervention in such patients. However, our study shows that in clinical practice physicians inconsistently refer such patients to surgical intervention, with delays causing CHF events and death. Thus it is essential to emphasize the need for speedy rescue operations in such patients. The new observation that symptoms and EF are specific but insensitive in predicting CHF in comparison with objective measurements, such as QASE grading and ESVI, could only be revealed by means of inclusion, irrespective of symptoms or EF, of all patients prospectively examined.

CONCLUSION

This prospective cohort of patients with AR shows that CHF is frequent after diagnosis and is followed by excess mortality. Traditional surgical markers (symptoms and EF <50%) predict CHF but are insensitive, and rescue operations are often delayed and associated with excess mortality. QASE severe AR and an ESVI of 45 mL/m² or greater independently predict CHF and provide incremental and sensitive prediction of risk for CHF or for CHF or death. Surgical intervention for AR markedly reduces CHF risk without excess postoperative mortality in these high-risk patients with AR and should be carefully considered in clinical practice.

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