

Prevalence and Clinical Determinants of Valvular Regurgitation

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INTRODUCTION

In the wake of controversy surrounding anorectic drugs and valvular regurgitation (1,2) there has been a sudden surge of interest in the prevalence and predictors of valvular regurgitation. Little information however, is available on the prevalence and determinants of regurgitant valvular lesions in the general population. Color Doppler echocardiography, a sensitive technique for detecting valvular regurgitation, provides a semiquantitative method for estimating the severity of regurgitation (3). Previous color Doppler echocardiography studies reporting prevalence of valvular regurgitation have been limited to small subsets of individuals (4-6), athletes (7), children (8) and to subjects with structurally normal hearts (4,6,9). There is limited information available regarding the prevalence rates of mitral, tricuspid or aortic regurgitation in a large unselected sample of middle-aged men and women. The purpose of this study was 2 fold; 1) to use color Doppler echocardiography to establish the prevalence and distribution of mitral (MR), tricuspid (TR) and aortic regurgitation (AR) in a population-based cohort and 2) to study the clinical determinants of these regurgitant valvular lesions.

METHODS

Study Sample

The Framingham Heart Study is a prospective epidemiological study established in 1948 to evaluate potential risk factors for coronary heart disease. The original study cohort included 5209 men and women, aged 28 to 62 years. In 1971, 5124 additional subjects were entered into the Framingham Offspring Study. Study design and selection criteria have been published (10-12)

Subjects for the present investigation were Framingham Offspring Study subjects who had color Doppler echocardiographic examinations performed between 1991 and 1995 during their routine fifth examination cycle at the Framingham Heart Study clinic. Subjects were excluded if they met any of the following criteria: 1) technically poor echocardiogram (i.e. color Doppler of insufficient quality to accurately assess the severity of regurgitation), 2) mitral stenosis, 3) more than mild aortic stenosis or 4) prosthetic or bioprosthetic heart valve.

The clinical variables included in this investigation were age, sex, hypertension, body mass index, smoking, total cholesterol level, diabetes mellitus and history of myocardial infarction or congestive heart failure. The association between tricuspid regurgitation and percent predicted FEV₁ (a measure of airflow obstruction) was also examined. The diagnoses of myocardial infarction and congestive heart failure were confirmed by a committee of three physicians who evaluated records from the Framingham Heart Study clinic examinations, interim hospitalizations, and visits to personal physicians in accordance with published criteria (13). Diabetes was defined as a fasting blood glucose level ≥ 140 mg/dL (> 7.7 mmol/liter) or the use of insulin or an oral hypoglycemic agent. Body height and weight measurements, medical history, physical examination, blood pressure measurements and pulmonary function tests were performed

routinely at the same examination.

Color Doppler Echocardiography

Color Doppler examinations were performed with a commercially available system (Hewlett Packard, Sonos 1000) using a 2.5 Mhz transducer. All images were recorded on videotape using a Panasonic VCR system (AG 7350). Conventional pulsed Doppler echocardiography was performed routinely in apical 4- and 5-chamber views by selective placement of the sample volume on the color Doppler echocardiographic regurgitation signals when present.

Color Doppler variations were represented by different groups of brightness and color intensity. Flow directed toward the transducer was conventionally coded in red and flow away from the transducer in blue. Valvular regurgitation was diagnosed using color-coded Doppler imaging proximal to the valve plane during its closure and extended into the chamber proximal to the valve. For color Doppler studies, gain settings were adjusted to eliminate background speckling and to maximize the extent of intracavitary velocity coding. Mitral regurgitation was sought from the parasternal long axis, apical 4- and 2-chamber, apical long axis and subcostal views. Tricuspid regurgitation was sought from the parasternal right ventricular inflow, parasternal short axis, apical 4 chamber and subcostal views. Aortic regurgitation was sought using the parasternal long axis, parasternal short axis, apical 5-chamber and apical long axis view.

Mitral regurgitation was considered to be present if blue, green or mosaic signals were seen originating from the mitral valve and spreading into the left atrium during systole. Tricuspid regurgitation was considered to be present if blue, green or mosaic signals were seen originating from the tricuspid valve and spreading into the right atrium during systole. Aortic regurgitation was considered to be present if red, yellow or mosaic signals (blue in parasternal long axis) were seen originating from the aortic valve and spreading into the left ventricle during diastole. Valvular regurgitation was assessed qualitatively using semi-quantitative guidelines and graded none, trace, mild, moderate or severe (Table 1).

Table 1 Definitions of Grades of Regurgitation

Grades	Mitral Regurgitation	Tricuspid Regurgitation	Aortic Regurgitation
Absent	-	-	-
Trace	w/in 1cm of valve	w/in 1cm of valve	JH/LVOH < 10%
Mild	RJA/LAA < 19%	RJA/RAA < 19%	10-24%
Moderate	20-40%	20-40%	25-49%
Severe	> 41%	> 41%	> 50%

RJA = regurgitant jet area; LAA = left atrial area; RAA = right atrial area; JH = jet height; LVOH = left ventricular outflow height; w/in = within. Valvular regurgitation was assessed qualitatively using these semi-quantitative categories as guidelines

Statistical Analysis

All statistical analyses were valve specific. Prevalence rates of MR, TR and AR were examined by grade of regurgitation in different age groups. Age- and sex-adjusted Spearman rank correlations were used to examine associations between clinical variables and each regurgitant lesion. The clinical variables included body mass index, hypertension, cholesterol, diabetes, smoking, history of myocardial infarction or congestive heart failure.

Multivariable regression analyses (14) were performed to assess the strength and independence of the clinical variables with MR and TR (\geq mild severity) and AR (\geq trace severity). This analysis was performed after excluding subjects with a history of myocardial infarction or congestive heart failure, since these disease states are known to be associated with valve regurgitation. Results are expressed as odds ratios

(OR) and 95% confidence intervals (CI). Odds ratios are expressed for 1 standard deviation of the continuous variables. Statistically significant values were defined as a two-tailed $p < 0.05$. All analyses were done on a Sparcstation 2 (SUN Microsystems) using the Statistical Analysis System (SAS) (15).

RESULTS

Subjects

Of 3589 subjects (1696 men and 1893 women) who attended the baseline examination and underwent color Doppler echocardiographic examination, 21 subjects were excluded for mitral stenosis or more than mild aortic stenosis and 9 for prosthetic heart valves. Subjects with technically poor color Doppler echocardiograms were also excluded (344 men and 334 women for MR, 354 men and 340 women for AR, and 668 men and 639 women for TR). A total of 2881 subjects (1336 men and 1545 women) were eligible for assessing MR, 2252 (1012 men and 1240 women) were eligible for assessing TR and 2865 (1326 men and 1539 women) were eligible for assessing AR. Subjects selected for analyses (mean age, 54 ± 10 years) had a lower body mass index (men, 27.6 ± 3.6 and women, 26.0 ± 4.7 kg/m²) compared to subjects excluded from analysis for technically poor echocardiograms (men, 30.1 ± 4.7 and women, 29.8 ± 6.9 kg/m², $p < 0.0001$).

Prevalence of valvular regurgitation

Mitral regurgitation was detectable in 87.7% men and 91.5% of women, whereas TR was detectable in 82.0% men and 85.7% women. Aortic regurgitation was less prevalent and was observed in 13.0% men and 8.5% women. The prevalence of \geq mild severity MR was 19.0% in men and 19.1% in women and of TR was 14.8% in men and 18.4% in women. The prevalence of regurgitation of \geq moderate severity was much lower for all 3 valves in both sexes (range 0.4 -2.0%). When examined across different age groups the prevalence of MR and TR \geq mild severity, and AR \geq trace severity, increased with advancing age in both sexes ([Table 2a](#) and [2b](#)).

Table IIa. Prevalence of Valvular Regurgitation Stratified by Age and Severity in Men

Age (years)	26 - 39	40 - 49	50 - 59	60 - 69	70 - 83
Mitral Regurgitation	(n=91)	(n=351)	(n= 432)	(n=372)	(n=90)
None (%)	14.4	13.3	11.3	12.7	9.0
Trace (%)	76.7	72.9	74.6	60.3	51.7
Mild (%)	8.9	13.5	12.5	24.6	28.1
\geq Moderate (%)	0.0	0.3	1.6	2.4	11.2
Tricuspid Regurgitation	(n=77)	(n=289)	(n=320)	(n=260)	(n=66)
None (%)	14.3	17.8	19.0	18.3	16.7
Trace (%)	72.7	72.5	71.5	59.8	47.0
Mild (%)	13.0	9.4	9.2	21.9	25.8
\geq Moderate (%)	0.0	0.3	0.3	0.0	1.5
Aortic Regurgitation	(n=91)	(n=352)	(n=433)	(n=359)	(n=91)
None (%)	96.7	95.4	91.1	74.3	75.6
Trace (%)	3.3	2.9	4.7	13.0	10.0
Mild (%)	0.0	1.4	3.7	12.1	12.2
\geq Moderate (%)	0.0	0.3	0.5	0.6	2.2

Table IIb Prevalence of Valvular Regurgitation Stratified by Age and Severity in Women

Age (years)	26 - 39	40 - 49	50 - 59	60 - 69	70 - 83
Mitral Regurgitation	(n=93)	(n=452)	(n=515)	(n=395)	(n=90)
None (%)	14.0	8.6	9.0	7.2	5.6
Trace (%)	76.3	75.0	74.0	66.5	70.8
Mild (%)	9.7	15.5	16.0	24.0	23.6
≥ Moderate (%)	0.0	0.9	1.0	2.3	0.0
Tricuspid Regurgitation	(n=84)	(n=371)	(n=414)	(n=300)	(n=71)
None (%)	20.5	16.0	14.5	10.4	14.1
Trace (%)	65.1	70.0	70.7	62.2	56.4
Mild (%)	13.2	13.5	14.1	25.7	23.9
≥ Moderate (%)	1.2	0.5	0.7	1.7	5.6
Aortic Regurgitation	(n=93)	(n=451)	(n=515)	(n=390)	(n=90)
None (%)	98.9	96.6	92.4	86.9	73.0
Trace (%)	1.1	2.7	5.5	6.3	10.1
Mild (%)	0.0	0.7	1.9	6.0	14.6
≥ Moderate (%)	0.0	0.0	0.2	0.8	2.3

Data are presented as percent of subjects.

A total of 944 men and 1225 women had color Doppler echocardiograms technically adequate for all three valves. Regurgitation (MR or TR ≥ mild severity or AR ≥ trace severity) involving a single valve was more common than regurgitation of two or more valves ([Figure 1](#)).

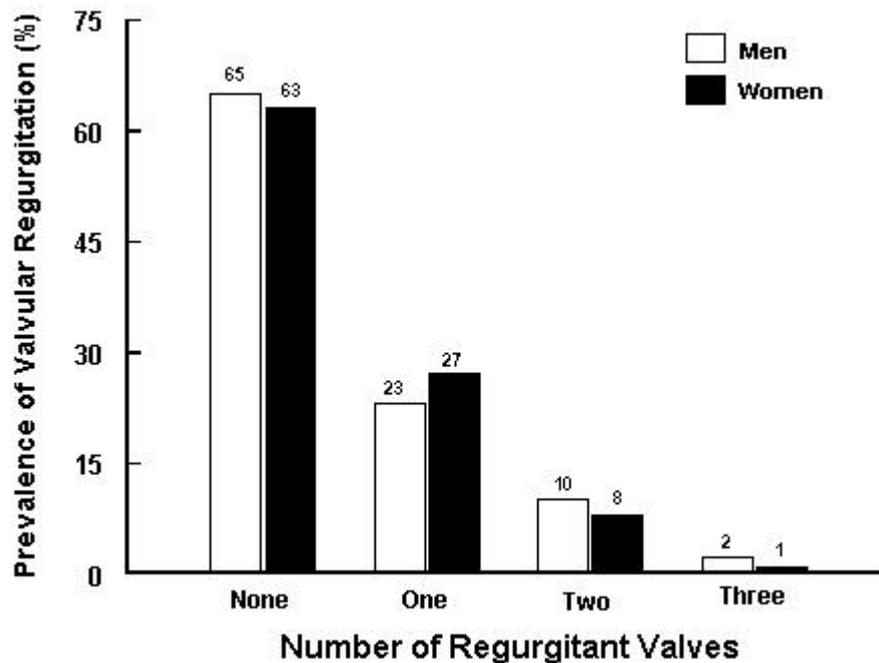


Figure 1: Histogram showing prevalence of valvular regurgitation by number of regurgitant valves. One indicates any single regurgitant valve; Two, any two regurgitant valves; Three, combined aortic, mitral and tricuspid regurgitation. Regurgitation was defined as ≥ mild severity for mitral and tricuspid regurgitation and ≥ trace severity for aortic regurgitation.

Determinants of valvular regurgitation

Age was related positively to the severity of MR, TR and AR ($p < 0.0001$, [Tables 3a, b & c](#)). The prevalence of AR was greater in men, whereas tricuspid regurgitation was more common in women. In models that

adjusted for age and sex, the severity of MR and TR correlated with lower body mass index, and history of congestive heart failure and myocardial infarction. Mitral regurgitation was also related to presence of systemic hypertension.

Table IIIa
Clinical Characteristics and Severity of Mitral Regurgitation

Clinical Characteristics	Degree of Regurgitation				r	p value
	None	Trace	Mild	≥ Moderate		
Male / Female (%)	55/45	45/55	45/55	60/40	0.03	0.09
Age (years)	54±10	54±10	57±10	62±9	0.13	0.0001
BMI (kg/m ²)	26.9±0.2	26.8±0.1	26.1±0.2	26.3±0.6	-0.06	0.0006
Systemic HTN (%)	29	30	35	43	0.05	0.004
Total CHOL (mg/dl)	210±2	204±1	204±2	200±5	-0.04	0.052
Diabetes Mellitus (%)	6	5	7	4	0.02	0.30
Smoking (pack years)	17	16	15	22	-0.02	0.23
CHF or MI (%)	2	3	5	10	0.09	0.0001

Table IIIb
Clinical Characteristics and Severity of Tricuspid Regurgitation

Clinical Characteristics	Degree of Regurgitation				r	p value
	None	Trace	Mild	≥ Moderate		
Male / Female (%)	50/50	45/55	39/61	38/62	0.06	0.003
Age (years)	53.0±9.9	53.1±9.7	57.0±10.5	62.2±12.8	0.12	0.0001
BMI (kg/m ²)	27.2±0.2	26.2±0.1	25.3±0.2	23.9±0.8	-0.15	0.0001
Systemic HTN (%)	33	28	28	13	-0.03	0.11
Diabetes Mellitus (%)	6	5	3	2	-0.03	0.20
Smoking (pack years)	15±1	16±1	14±1	19±4	-0.01	0.60
CHF or MI (%)	2	3	4	4	0.04	0.04
Airflow Obstruction (%)	12	9	10	9	-0.14	0.50

Table IIIc
Clinical Characteristics and Severity of Aortic Regurgitation

Clinical Characteristics	Degree of Regurgitation				r	p value
	None	Trace	Mild	≥ Moderate		
Male / Female (%)	45 /55	54/46	60/40	54/46	-0.07	0.0001
Age (years)	53±10	60±10	63±8	63±10	0.24	0.0001
BMI (kg/m ²)	26.7±0.8	26.5±0.3	26.5±0.4	25.6±1.2	-0.009	0.62
Systemic HTN (%)	30	34	32	12	0.029	0.12
Total CHOL (mg/dl)	205±1	201±3	207±3	195±10	-0.01	0.54
Diabetes Mellitus (%)	5	6	10	0	0.03	0.18
Smoking (pack years)	16±1	15±2	16±2	11±6	-0.24	0.19
CHF or MI (%)	3	4	6	0	0.006	0.76

r = Spearman rank correlations; BMI = body mass index; CHF or MI = history of congestive heart failure or myocardial infarction; CHOL = cholesterol; HTN = hypertension

Multiple logistic regression analyses were performed after excluding subjects with a history of myocardial infarction or congestive heart failure (Table 4). The clinical determinants of MR (≥ mild severity) were age,

lower body mass index and systemic hypertension; the determinants of TR (\geq mild severity) were age, lower body mass index and female sex and the determinants of AR (\geq trace severity) were age and male sex.

Table IV. Results of Multivariable Regression Analyses

Clinical Determinants	Unit	Mitral Regurgitation	Tricuspid Regurgitation	Aortic Regurgitation
		OR (95% CI)	OR (95% CI)	OR (95% CI)
Age (years)	9.9	1.3 (1.2, 1.5)	1.5 (1.3, 1.7)	2.3 (2.0, 2.7)
Sex	M/F	1.1 (0.9, 1.3)	1.2 (1.0, 1.6)	0.6 (0.5, 0.8)
BMI (kg/m ²)	4.3	0.8 (0.7, 0.9)	0.7 (0.6, 0.8)	1.0 (0.8, 1.1)
HTN	Y/N	1.6 (1.2, 2.0)	1.1 (0.8, 1.4)	1.2 (0.9, 1.5)

Data expressed as odds ratio (95 % confidence intervals). BMI= body mass index; HTN= hypertension; OR= odds ratio; CI= confidence interval; M/F= male/female; Y/N= yes/no. Odds ratios for continuous variables expressed for 1 standard deviation of age and BMI.

DISCUSSION

The results of our study show that valvular regurgitation detectable by color Doppler echocardiography was highly prevalent in the general population. Mitral and tricuspid regurgitation were most common, followed by AR. Obesity was associated with a lower prevalence of TR and MR. These data provide population-based estimates for comparison with patients taking anorectic drugs.

Prevalence of valvular regurgitation

Previous studies using conventional pulsed Doppler methodology have varied widely in their estimates of the prevalence of valvular regurgitation. In normal subjects, prevalence rates of TR have ranged from 24 to 96%, MR from 10 to 80% and AR from 0 to 33% (16-20). Color Doppler flow imaging, which superimposes color-coded flow patterns on the real-time 2-dimensional image, is a more comprehensive and sensitive, yet less tedious method compared to conventional pulsed wave Doppler echocardiography (4,21). Consequently, color Doppler echocardiography has become the procedure of choice to detect and measure valvular regurgitation. The reported prevalence has varied widely ranging from 15 to 100% for TR, 38 to 58% for MR and 0 to 18% for AR (4-6,9). The discrepancies in prevalence rates can be explained by the fact that the earlier studies have been limited to small numbers of subjects (4-6) and have varied in their definitions of regurgitation (4-6,9). Also, in contrast to previous reports, our study is not limited by selection bias (by virtue of echocardiography laboratory referral patterns) (4-6,9) or by interpretation of echocardiograms unblinded to the clinical status of patients (4-9).

Prevalence rates in the Framingham Heart Study sample differed markedly according to threshold definitions (i.e. trace versus mild severity). The high prevalence of trace regurgitation suggests that this, may be an artifact of valve closure (17) or may be, a feature related to closure of anatomically normal valves (16).

Clinical determinants

Age was observed to exert a profound influence on the prevalence of valve regurgitation in the population. Our findings that the prevalence of mitral, tricuspid and aortic regurgitation increased with age are consistent with earlier Doppler studies (6,9,16). Long-standing mechanical stress may play a role in the wear and tear of the valve resulting in valvular regurgitation (22). Although left-sided valves (aortic and mitral) are exposed to high pressures and are likely to undergo degenerative changes earlier than right sided valves, the prevalence rates of MR and TR were comparable at all ages.

Systemic hypertension was associated with MR but not with AR. Increased afterload may play an

important role in the genesis of minor degrees of MR. Earlier reports have suggested that hypertension predisposes to aortic root enlargement and, consequently, to AR (23). Our observation of a lack of association between hypertension and aortic regurgitation is supported by a recent study demonstrating the lack of an association between blood pressure and dilatation of the aortic root at the site of commissural attachment and AR (24). The present investigation and previous studies (24, 25) have shown a strong association between aortic regurgitation and age, which in turn may explain the lack of association between hypertension and AR after adjusting for age in the multivariable model.

Obesity and Regurgitation

The severity and prevalence of MR and TR decreased as a function of increasing body mass index. This may be because ultrasonic penetration becomes poorer in individuals with obesity and that the ultrasound may be too attenuated to permit adequate detection of Doppler signals from distally located areas. To minimize this bias we purposefully excluded subjects with technically poor Doppler echocardiograms. The inverse relation between body mass index and MR and TR persisted despite exclusion of technically limited studies. Since obesity is associated with changes in cardiac structure, hemodynamics and altered ventricular inflow patterns (26,27) it might be speculated that mechanisms other than technical factors may be involved in the inverse association between body mass index and valvular regurgitation. Further studies are needed to examine this association.

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