Doppler Echocardiographic Evaluation of Right Ventricular Diastolic Function in Patients with Mitral Regurgitation

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Background and aim of the study: **The effect of left ventricular (LV) pressure overload on right ventricular (RV) diastolic function has been extensively studied. In contrast, no data are available concerning the influence of LV volume overload on RV diastolic function. Accordingly, RV diastolic function was studied in patients with mitral regurgitation (MR) using Doppler echocardiography.**

Methods: **RV diastolic indices were calculated, using pulsed Doppler echocardiography, in 30 patients (mean age 56.87 ± 8.58 years) with severe MR, and in 30 healthy control subjects (mean age 56.67 ± 8.52 years).**

Results: **Compared with controls, MR patients had a significantly lower RV E/A ratio (0.85 ± 0.12 versus 1.21 ± 0.16, p <0.001), a significantly prolonged RV isovolumic relaxation time (70 ± 20 versus 30 ± 10 ms, p <0.001), a significantly prolonged deceleration time of the transtricuspid E wave (210 ± 20 versus 140 ± 10 ms, p <0.001), and a significantly greater right atrial filling fraction (38.58 ± 4.59 versus 32.58 ± 3.14%, p <0.001). There was no statistically significant correlation between RV diastolic indices and LV mass index and interventricular septum thickness.**

Conclusion: **RV diastolic function in patients with MR is impaired, reflecting prolonged relaxation and redistribution of RV filling into late diastole. Ventricular interdependence constitutes the most likely mechanism of this action.**

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It is well known that the loading conditions of one ventricle affect the function of the other ventricle (1-4). The influence of left ventricular pressure overload on the diastolic performance of the right ventricle has been studied in the past. Prolonged relaxation of the right ventricle and redistribution of right ventricular filling into late diastole have been described in conditions associated with left ventricular pressure overload, such as systemic hypertension (5,6), aortic stenosis (7) and hypertrophic cardiomyopathy (8). By contrast, the influence of left ventricular volume overload on right ventricular diastolic function has not been investigated. In the present study, the right ventricular diastolic function was evaluated in patients with mitral regurgitation, a condition characterized by left ventricular volume overload.

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Clinical material and methods

Patient population

The study population comprised 30 patients with severe isolated non-rheumatic mitral regurgitation who had a left ventricular ejection fraction (LVEF) ≥55%, left ventricular end-diastolic pressure (LVEDP) ≤15 mmHg, right ventricular systolic pressure ≤30 mmHg, and normal coronary arteries.

Initially, patients were selected according to the following criteria. Between January and December 2000, 56 patients with severe isolated mitral regurgitation, diagnosed by transthoracic and/or transesophageal echocardiography were referred to the present authors' unit for coronary arteriography and cardiac catheterization. Ten patients with coexistent coronary artery disease, five with a low LVEF (<55%), and six with LVEDP >15 mmHg were excluded from the study. Likewise, five patients with right ventricular systolic pressure >30 mmHg, as evaluated by Doppler echocardiography and right ventricular catheterization pressures recording, were also excluded in order to avoid the influence of elevated right ventricular pressure on right ventricular diastolic function. The remaining 30 patients (mean age 56.87 ± 8.58 years; range: 36 to 69 years) comprised the final study cohort. None of the patients had coexistent other valvular disease, arterial hypertension, diabetes mellitus, pericardial or lung disease, anemia or other systemic disease. None of the patients enrolled in the study had an epicardial coronary artery lesion occupying ≥50% of the lumen diameter as confirmed by arteriography, and all were in sinus rhythm. None had tricuspid regurgitation $>1^+/4^+$ as assessed by Doppler echocardiography. The right atrial mean pressure (as assessed by catheterization) was <5 mmHg in all participating patients. The patients complained chiefly of exertional dyspnea and were classified as NYHA class II (n = 10) or III (n = 20). All patients enrolled in the study had systolic murmur which was loudest at the apex, with radiation to the left axilla; no parasternal lift was palpable in any of the patients. All medications were withdrawn at least 72 h before Doppler echocardiography was performed. Cardiac catheterization was performed at 2 h after echocardiography. The grade of mitral regurgitation was estimated using color-Doppler according to Helmcke (9) criteria; that is, the fraction of regurgitant jet area towards the apex of left atrium and left atrial area. Regurgitation was considered mild, moderate or severe when this fraction was <20%, 20-40% or >40%, respectively.

The control group comprised 30 healthy subjects (mean age 56.67 ± 8.52 years; range: 35 to 60 years) who had no history of hypertension, coronary artery or other cardiovascular disease, diabetes or other systemic disease. All had an entirely normal physical examination, laboratory evaluation, electrocardiogram, chest radiography, and M-mode, two-dimensional and Doppler echocardiographic findings. None of the control subjects was receiving medication at the time of the study.

The study protocol was approved by the relevant Ethics Committee on April 6, 1999. Informed consent was acquired from each individual included in the study.

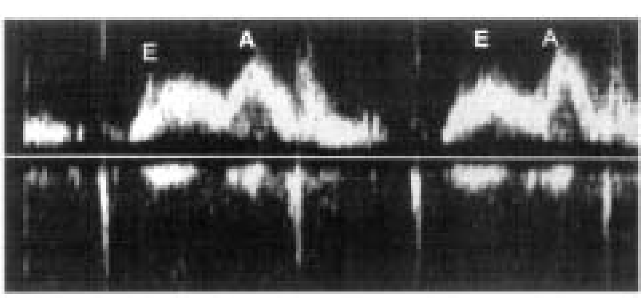

Figure 1: Pulsed-wave Doppler interrogation of the tricuspid valve, demonstrating an impaired transtricuspid flow velocity pattern in a patient with mitral regurgitation. Note the increased peak velocity of atrial contraction wave, the reversal (<1) of the E/A-wave ratio, and the prolonged deceleration time of early filling.

Echocardiography

Transthoracic M-mode, two-dimensional and spectral Doppler (pulsed- and continuous-wave) echocardiographic images were generated in all participating patients and control subjects, using commercially available equipment. Standard M-mode measurements were obtained from the left parasternal long-axis view according to the recommendations of the American Society of Echocardiography (10). The following parameters were calculated: interventricular septum thickness; left ventricular posterior wall thickness; left ventricular end-diastolic diameter, left ventricular end-systolic diameter; left ventricular end-diastolic volume; left ventricular end-systolic volume; left ventricular mass index; stroke volume; right

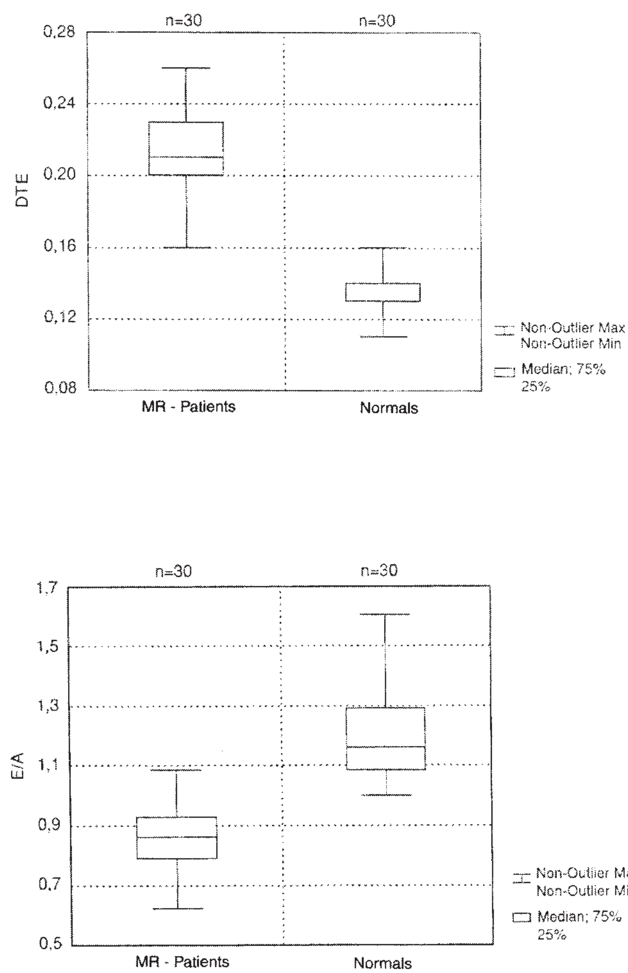

Figure 2: E/A-wave ratios (lower graph) and deceleration time (DTE; upper graph) in mitral regurgitation (MR) patients and normal subjects.

ventricular end-diastolic diameter; right ventricular free wall thickness; left atrium size; left atrium area; right atrium area; left ventricular fractional shortening; and right ventricular fractional area change. The left ventricular mass index was calculated according to the Devereaux-Reicheck formula (11). Right ventricular systolic function was assessed as the percentage change in cavity area from end-diastole to end-systole in a four-chamber view. Right ventricular fractional area change was calculated by using the following formula: (end-diastolic area - end-systolic area)/end-diastolic area (12). Doppler signals with a simultaneous electrocardiographic tracing were recorded on paper at a speed of 50 mm/s using a Video Graphic VP-850 printer (Sony Co., Japan). Right ventricular diastolic indices were assessed from the left parasternal short-axis view at the level of the aortic valve by positioning a sized 2-4 mm sample volume at the tips of the tricuspid leaflets during diastole. The Doppler beam was aligned so as to be parallel to the blood flow vector. The following right ventricular diastolic indices were calculated: peak velocity of E wave, representing early filling; peak velocity of A wave, representing late filling; the ratio of peak early to peak late velocity; the acceleration time of E wave; the deceleration time of E wave; the velocity-time integral of E and A waves; the time duration of E and A waves; the atrial filling fraction of right ventricle; and the isovolumic relaxation time of right ventricle. The last variable was calculated according to previously described methods (7,13). Diastolic indices were measured for six consecutive beats and their values averaged in order to minimize the effect of respiration on diastolic filling. Intra-observer variability was established by having one observer measure right ventricular diastolic indices on at least two occasions in 10 subjects selected at random from the patient population under study (r = 0.94). Inter-observer variability was determined by having a second echocardiographer independently measure the same Doppler indices in these subjects (r = 0.89).

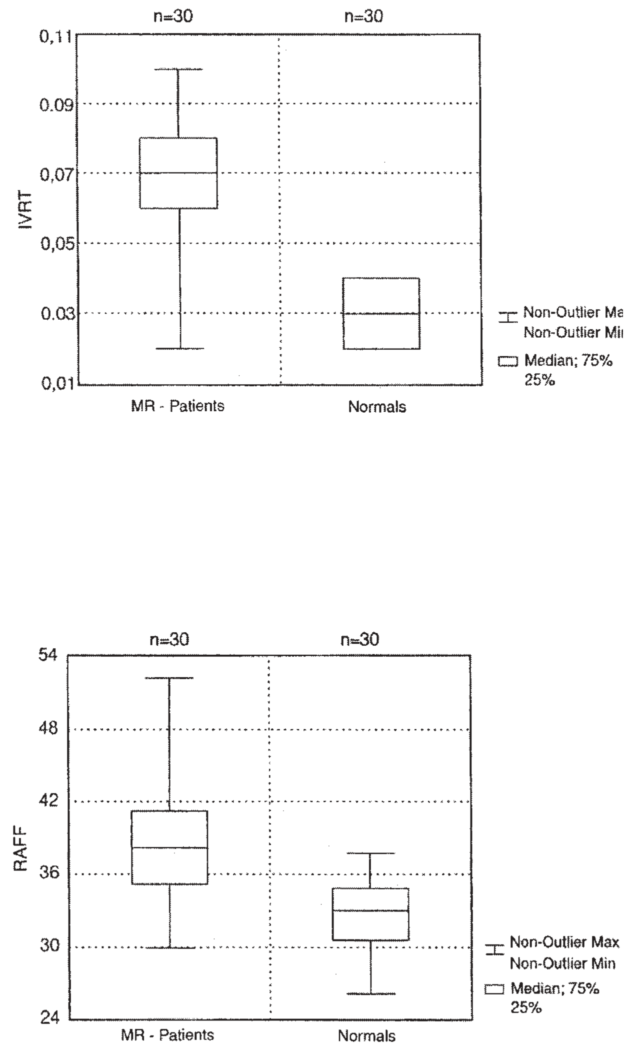

Figure 3: Right atrial filling fraction (RAFF; lower graph) and right ventricular isovolumic relaxation time (RV-IVRT; upper graph) in mitral regurgitation (MR) patients and normal subjects.

Table I: Comparison of clinical data between mitral regurgitation (MR) patients and controls.

Variable	Control group	MR group	p-value
Age (years)	56.67 ± 8.52	56.87 ± 8.58	NS
SBP (mmHg)	130.17 ± 5.94	130.67 ± 7.16	NS
DBP (mmHg)	75.83 ± 4.17	76.33 ± 3.92	NS
HR (beats/min)	70.67 ± 3.58	72.27 ± 7.99	NS
Height (cm)	170 ± 8	170 ± 7	NS
Body weight (kg)	73.17 ± 9.23	72.97 ± 9.08	NS

Values are mean ± SD.
DBP: Diastolic blood pressure; HR: Heart rate; NS: Not significant; SBP: Systolic blood pressure.

Table II: Comparison of echocardiographic data between mitral regurgitation (MR) patients and controls.

Variable	Control group	MR group	p-value
LVMI (g/m^2)	98.57 ± 13.67	180.43 32.12	<0.001*
LVEDD (mm)	50.97 ± 3.15	62.83 ± 4.60	<0.001*
LVEDV (ml)	67.33 ± 11.27	139.91 ± 34.21	<0.001*
LVESD (mm)	31.62 ± 2.34	40.12 ± 3.80	<0.001*
LVESV (ml)	14.82 ± 3.25	37.94 ± 12.14	<0.001*
SV (ml)	52.51 ± 8.19	100.90 ± 25.48	<0.001*
IVST (mm)	8.97 ± 0.83	10.35 ± 0.44	<0.001*
LVPWT (mm)	8.40 ± 0.74	10.03 ± 0.51	<0.001*
LVFS (%)	35.11 ± 4.02	36.17 ± 3.61	0.054
RVEDD (mm)	19.29 ± 1.51	20.25 ± 2.18	0.053
RVFWT (mm)	3.80 ± 0.15	3.74 ± 0.11	0.250
RVFAC (%)	49.4 ± 6.5	47.2 ± 5.2	0.74
LAS (mm)	35.41 ± 0.15	40.25 ± 0.21	<0.001*
LAA (cm^2)	13.08 ± 0.65	18.43 ± 1.31	<0.001*
RAA (cm^2)	14.27 ± 0.38	14.25 ± 0.43	0.909

Values are mean ± SD.
*Statistically significant difference.
IVST: Interventricular septum thickness; LAA: Left atrium area; LAS: Left atrium size; LVEDD: Left ventricular end-diastolic diameter; LVEDV: Left ventricular end-diastolic volume; LVESD: Left ventricular end-systolic diameter; LVESV: Left ventricular end-systolic volume; LVFS: Left ventricular fractional shortening; LVMI: Left ventricular mass index; LVPWT: Left ventricular posterior wall thickness; RAA: Right atrium area; RVEDD: Right ventricular end-diastolic diameter; RVFAC: Right ventricular fractional area change; RVFWT: Right ventricular free wall thickness; SV: Stroke volume.

Cardiac catheterization

LVEDP and LVEF were calculated according to conventional methodology. Right heart catheterization and coronary arteriography were performed in all patients.

Statistical analysis

Data were expressed as mean ± SD. Student's *t*-test was used to assess the significant differences of mean values between patients and controls. Pearson's correlation coefficient was used to assess statistically significant correlations between right ventricular diastolic indices and interventricular septum thickness, as well as between right ventricular diastolic indices and left ventricular mass index. A p-value <0.05 was considered statistically significant.

Table III: Comparison of right ventricular diastolic indices between mitral regurgitation (MR) patients and controls.

Variable	Control group	MR group	p-value
PVE (cm/s)	54 ± 5	48 ± 5	<0.001*
PVA (cm/s)	45 ± 6	57 ± 8	<0.001*
E/A ratio	1.21 ± 0.16	0.85 ± 0.12	<0.001*
ATE (ms)	80 ± 10	80 ± 10	0.625
DTE (ms)	140 ± 10	210 ± 20	<0.001*
ETE (ms)	220 ± 10	300 ± 30	<0.001*
ETA (ms)	130 ± 10	160 ± 10	<0.001*
VTiE (cm)	5.90 ± 0.56	7.05 ± 0.85	<0.001*
VTiA (cm)	2.86 ± 0.45	4.45 ± 0.78	<0.001*
RAFF (%)	32.58 ± 3.14	38.58 ± 4.59	<0.001*
IVRT (ms)	30 ± 10	70 ± 20	<0.001

Values are mean ± SD.
*Statistically significant difference.
ATE: Acceleration time of E wave; DTE: Deceleration time of E wave; E/A ratio: PVE to PVA ratio; ETA: Ejection time of A wave; ETE: Ejection time of E wave; IVRT: Isovolumic relaxation time; PVA: Peak velocity of transtricuspid A wave; PVE: Peak velocity of transtricuspid E wave; RAFF: Right atrial filling fraction; VTiA: Velocity time integral of A wave; VTiE: Velocity time integral of E wave.

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Table IV: Correlation between right ventricular diastolic indices and inter-ventricular septum (IVST) thickness and left ventricular mass index (LVMI).

Index	IVST		LVMI	
	r	p-value	r	p-value
E/A	-0.068	NS	-0.186	NS
DTE	-0.057	NS	-0.005	NS
RAFF	0.015	NS	0.174	NS
IVRT	-0.051	NS	-0.095	NS

NS: Not significant. Other abbreviations as in Tables II and III.

Results

Clinical, ECG and echocardiographic data

There were no statistically significant differences between patients and controls with regard to age, height, body weight, heart rate, systolic and diastolic blood pressure (Table I). The left ventricular end-diastolic diameter, left ventricular end-systolic diameter, left ventricular end-diastolic volume, left ventricular end-systolic volume, stroke volume, interventricular septum thickness, left ventricular posterior wall thickness, left atrium size, left atrium area and left ventricular mass index were all statistically significantly greater in patients compared with controls. There was no statistically significant difference between the two groups with regard to left ventricular fractional shortening, right ventricular end-diastolic diameter, right ventricular free wall thickness right ventricular fractional area change, and right atrium area (Table II). Five patients had a normal ECG, ten had repolarization changes, and 15 had left anterior hemiblock with left axis deviation. The right ventricular systolic pressure, as assessed by Doppler using the tricuspid regurgitation jet, was <30 mmHg in all patients enrolled in the investigation.

Right ventricular diastolic indices

Compared with controls, patients with mitral regurgitation had a lower peak velocity of E wave, a greater peak velocity of A wave, a lower E/A ratio, greater right atrial filling fraction, and greater isovolumic relaxation time of the right ventricle. All these differences were statistically significant. The deceleration time of E wave, ejection time of E wave, ejection time of A wave, velocity-time integral of E wave and velocity-time integral of A wave were also statistically significantly greater in patients compared with controls. There was no statistically significant difference between the two groups with regard to the acceleration time of E wave (Table III). Correlations between right ventricular diastolic indices, left ventricular mass index and interventricular septum thickness proved not to be statistically significant (Table IV). With regard to the four basic right ventricular diastolic indices, 18 patients (60%) had an impaired E/A ratio, 30 (100%) had impaired deceleration time of the E wave, 14 (47%) had impaired right atrial filling fraction, and 27 (90%) had impaired isovolumic relaxation time (diastolic indices were considered abnormal when their values were more than the mean value (± 2SD) of diastolic indices in the control group) (Table V).

Discussion

Doppler echocardiography has been established as a standard method to evaluate right ventricular diastolic function in both healthy controls (14,15) and diseased patients (3,5-8,16).

The present study was the first to investigate right ventricular diastolic function in patients with mitral regurgitation, a condition which is characterized by left ventricular volume overload. The main findings were a prolongation of right ventricular relaxation and a redistribution of diastolic filling into late diastole - conditions which have also been described in conditions characterized by left ventricular pressure overload, such as systemic hypertension (5,6), aortic stenosis (7) and hypertrophic cardiomyopathy (8). A very high proportion of the present patients had an abnormal relaxation time (90%) or impaired right ventricular filling (such as the 100% impaired deceleration

Table V: Total number of patients with impaired right ventricular diastolic indices.

Index	No. of patients	%
E/A	18	60
DTE	30	100
RAFF	14	47
IVRT	27	90

Abbreviations as in Table III.

time of early filling, the 60% reversal of early to late filling ratio, and the ~50% dominated late ventricular filling). Another interesting point was the finding that the right ventricular diastolic indices were independent of either left ventricular mass or interventricular septum thickness. Additionally, the right ventricular pressures, diameter and free wall thickness ranged within normal limits in all patients.

These findings indicate that augmented left ventricular volume and a rightward interventricular septum shift constitute possible mechanisms of right ventricular diastolic impairment, a phenomenon which is well known as ventricular interdependence. Conversely, right-sided pressure or volume overload affects left ventricular systolic or diastolic function, as has been observed in chronic obstructive pulmonary disease (16), primary pulmonary hypertension (1) and atrial septal defect (17). In one study, Louie et al. (2) found that systolic overload of the right ventricle was associated with prolongation of left ventricular isovolumic relaxation and redistribution of left ventricular filling from early to late diastole, whereas diastolic overload of the right ventricle redistributed left ventricular filling from late to early diastole without influencing the left ventricular isovolumic relaxation period. In conclusion, left ventricular volume overload conditions affect right ventricular relaxation and filling, although right ventricular structure is still normal.

Study limitations

Doppler-derived data related to right ventricular diastolic function are limited in number, and consequently further studies in this area are essential. Diastole is a complex phenomenon, and diastolic filling patterns - as currently assessed by Doppler echocardiography - do not necessarily reflect all diastolic right ventricular properties. In additional, a number of uncontrollable factors also influence right ventricular filling, such as the tone of the autonomic nervous system and the constant alterations of preload. Although in the present study, six consecutive beats were measured in order to minimize the effect of preload on transtricuspid flow during respiration, right ventricular diastolic indices are still to some extent influenced by (inescapable) variations in the respiratory cycle. The evaluated stroke volume was the total, rather than the effective stroke volume. Left ventricular diastolic parameters, although measured, were not taken into account because left ventricular volume overload affects the mitral valve Doppler signal. A paradox finding of the present study was the low percentage of grade III mitral regurgitation patients who presented with elevated pulmonary artery pressures. Helmcke criteria, although acceptable, are not the 'gold standard' by which to assess the severity of mitral regurgitation. Moreover, during diastole there is a substantial increase in tricuspid annulus perimeter (18).

Clinical implications

An important finding of the present study was that patients with mitral regurgitation, whilst having no clinical signs of right ventricular dysfunction, had evidence of right ventricular diastolic dysfunction. Although the clinical significance of this finding is unclear at present, it is possible that patients with mitral regurgitation have a subclinical impairment of right ventricular diastolic function at a stage of the condition when clinical right ventricular dysfunction is not evident. Hence, long-term follow up is necessary to estimate changes in diastolic indices as the disease progresses, when signs of right ventricular dysfunction become evident. It is possible that, eventually, right ventricular diastolic indices will prove to be prognostically important. Consequently, further investigations may need to be carried out in this area.

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