Assessment of the Relationship Between Functional Capacity and Right Ventricular Ultrasound Tissue Characterization by Integrated Backscatter in Patients With Isolated Mitral Stenosis

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SUMMARY

Aim: The aim of the present study was to investigate right ventricular (RV) myocardial textural properties in asymptomatic and symptomatic mitral stenosis (MS) patients with normal RV systolic function using integrated backscatter (IBS).

Methods: The study included 40 patients with MS of moderate or severe degree. Patients were classified into 2 groups according to NYHA class (asymptomatic group, NYHA class I, symptomatic group, NYHA class II-III). RV pulsed-wave tissue Doppler imaging (TDI) and IBS analyses were performed in all patients. Isovolumic contraction time (IVCT), systolic wave velocity (S), isovolumic relaxation time (IVRT), early diastolic wave velocity (E), and late diastolic wave velocity (A) were measured by TDI. IBS amplitude (IB) and cyclic variation (CV) of the RV lateral wall in the parasternal long-axis view were measured by IBS. CV was calculated by subtracting systolic IB from diastolic IB.

Results: IVRT (54.2 ± 11.9 ms versus 86.2 ± 16.2 ms, P < 0.001) and A wave amplitude (10.2 ± 2.1 cm/s versus 13.6 ± 1.8 cm/s, P < 0.05) were higher whereas E wave amplitude (11.7 ± 1.6 cm/s and 10.3 ± 1.5 cm/s, P < 0.05) and E/A ratio (1.3 ± 0.3 versus 0.7 ± 0.1, P < 0.001) were lower in group 2. Symptomatic patients had a lower CV value of RV (9.5 ± 3.4 dB versus 6.7 ± 1.9 dB, P = 0.004). There was a positive correlation between CV and E/A (∙ = 0.964, P < 0.001)

Conclusion: Symptomatic isolated MS patients had RV echo texture changes and diastolic dysfunction in comparison to asymptomatic ones with similar mitral valve areas in the presence of normal RV systolic function. In isolated MS, both pulsed-wave TDI and IBS may aid in the detection of RV diastolic pathology. (Int Heart J 2007; 48: 87-96)

Key words: Integrated backscatter, Mitral stenosis, Right ventricle, Diastolic function

DETERMINATION of functional capacity in cardiovascular diseases is quite essential for the evaluation of response to treatment, prognosis and timing of...
invasive procedures. Right ventricle (RV) systolic function is an important determinant of clinical symptoms, functional capacity, preoperative survival, and postoperative outcome in patients with mitral stenosis (MS). However, in the presence of normal RV systolic function, some patients with MS of moderate or severe degree suffer symptoms, whereas some patients with similar mitral valve areas (MVA) do not.

Ultrasonic tissue characterization based on the measurements of integrated backscatter (IBS) has provided quantitative information about the structural and functional state of the myocardium. The baseline assumption underlying ultrasonic tissue characterization is that pathologic changes affecting the myocardium such as an aging heart, myocardial ischemia, hypertrophic and dilated cardiomyopathy, hypertensive heart disease, and acute cardiac rejection result in alterations of its fundamental physical properties that can be detected by IBS imaging. The extracellular matrix has been shown to represent an important source of myocardial IBS and several experimental studies have demonstrated that IBS in diastole correlates with the collagen content within the myocardium. Measurements of IBS demonstrate a cyclic variation (CV) during the cardiac cycle with the maximum value at end-diastole and the minimum value at end-systole, which is supposed to reflect the contractile performance of myocardium although the phenomenon is more complex. Recently Maceira, et al showed a direct correlation between diminished CV of backscatter and deterioration of left ventricular diastolic function in hypertensive patients.

The aim of our study was to evaluate RV myocardial textural properties in asymptomatic and symptomatic MS patients with similar mitral valve areas (MVA) in the presence of normal RV systolic function using IBS analysis.

**METHODS**

**Study population:** The study included 40 patients with isolated rheumatic MS in sinus rhythm (17 males, mean age, 32 ± 4 years). Clinical symptoms were assessed according to the New York Heart Association (NYHA) functional class. Patients were classified into 2 groups according to their functional capacity. Group 1 (asymptomatic group) consisted of 19 MS patients with NYHA class I and group 2 (symptomatic group) included 21 patients with class II-III. Exclusion criteria were the presence of diabetes mellitus, coronary artery disease (angina, and/or ECG sign of ischaemia), atrial fibrillation, more than mild aortic or mitral and moderate tricuspid regurgitation, pulmonary arterial hypertension (≥ 50 mmHg), RV systolic dysfunction (RV ejection fraction < 40%), lung disease according to history, physical examination and pulmonary functional tests, and inadequate echocardiograms.
Conventional Doppler echocardiography: Standard Doppler echocardiography was performed with the subjects in a left lateral decubit position using a Vivid Five ultrasound system (General Electric). A variable frequency phased-array transducer (2.5-3.5 MHz) was used for 2-dimensional, M-mode and Doppler imagings. M-mode and 2-dimensional quantitation of the left ventricle was performed according to the standards of the American Society of Echocardiography.\textsuperscript{15} MVA was determined by the pressure-half-time method.\textsuperscript{16} Transmitral velocities and pressure gradients were recorded by the continuous-wave Doppler interrogation of the transmitral and trans-tricuspid flow in the apical 4-chamber view. Doppler-derived pulmonary artery systolic pressure (SPAP) was obtained by adding 10 to the pressure gradient of tricuspid regurgitation jet at follow-up. Doppler colour flow imaging was used for detection and semiquantitation of the tricuspid, mitral and aortic regurgitation. RV global systolic function was assessed according to the ‘ellipsoidal shell method’.\textsuperscript{17} RV volumes were calculated using a formula derived from an ellipsoidal shell model (difference-of-ellipsoids model): $V=2/3Pd$. Area $P$ was measured in a modified 4-chamber projection. The criterion of the correct view was the largest size of the cross-sectional area of RV and good imaging of the apex in the same view. Diameter $d$ is then measured as the longest transverse distance between the RV lateral wall near the tricuspid annulus and RV outflow tract beneath the pulmonic valve in the parasternal short-axis or subcostal sagittal view. All measurements were performed in both systole and diastole. The difference between end-diastolic and end-systolic volume yielded stroke volume. Stroke volume expressed as a percentage of end-diastolic volume represents ejection fraction (EF).

Pulsed-wave tissue Doppler imaging: Pulsed-wave tissue Doppler imaging (TDI) was performed using a transducer frequency of 2.5 MHz after the TDI preset was activated. In the apical 4-chamber view, the pulsed Doppler sample volume was placed in the RV lateral tricuspid annulus. The TDI pattern was characterized by a positive myocardial systolic wave (S) and 2 negative diastolic waves; early (E) and atrial (A). TDI systolic indexes included myocardial peak velocity of S (m/s) and isovolumic contraction time (IVCT), which was measured from the onset of the ECG QRS to the beginning of S (ms). Diastolic indexes included myocardial early (E) and atrial peak velocities (A) (m/s), E/A ratio, and isovolumic relaxation time (IVRT) (ms), which was defined as the time interval occurring between the end of S and the onset of E.

Integrated backscatter analysis: IBS was performed using the same echocardiographic system operating in the acoustic densitometry acquisition mode. Acquisition of IBS images was performed according to 2 different protocols: one for assessing myocardial IBS amplitude (IB) and the other for measuring cyclic variation (CV). In the protocol designed to assess myocardial IB, time and lateral
gain compensations were set to the off position, and the imaging depth and transmit power were set to optimize image quality in the first patient of the study and then left unchanged. In this way we could ensure that the IB values were obtained under comparable conditions.\(^{18}\) In the protocol designed to measure cardiac cycle-dependent CV, transmit power and time compensation values were set to optimize quality in each subject so that the maximum CV could be obtained.\(^{19}\) Data were obtained from the parasternal long axis view. A digitized ECG waveform was used to synchronize the data acquisition with the QRS complex. The region of interest (ROI) was placed in the mid portion of the RV lateral wall. A depth setting of 155 mm was always used. Digital sequences of IBS images were acquired at a rate of 30 frames per second, stored on optimal disk, and then analyzed with the acoustic densitometry analysis package. In IBS images aimed to assess myocardial IB, 4 consecutive frames with the highest values of IB (diastolic frames) were selected from each cardiac cycle, and the mean value was calculated and averaged. In IBS images aimed to assess the CV of IBS, 4 consecutive frames with the highest and 4 with the lowest values of IB (systolic frames) were selected. CV was determined as the difference between the diastolic and systolic IB. CV and IB are expressed in decibels (dB).

**Statistical analysis:** Statistical analyses were performed using SPSS for Windows (version 11.0). Continuous variables are expressed as the mean ± SD and categorical variables are expressed as percentage. Comparison of categorical and continuous variables between groups was performed using the chi-square test and unpaired \( t \) test, respectively. A \( P \) of < 0.05 was considered statistically significant. The relationship between the tricuspid annular E/A ratio and CV of RV was determined using the Pearson correlation test.

**Table 1.** Demographic and Transthoracic Echocardiographic Variables of the Patients With Isolated Mitral Stenosis

<table>
<thead>
<tr>
<th>Isolated mitral stenosis patients ((n = 40))</th>
<th>Group 1 ((n = 19))</th>
<th>Group 2 ((n = 21))</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>31 ± 4</td>
<td>32 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>Female/male ratio</td>
<td>19/17</td>
<td>21/19</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index ((\text{kg/m}^2))</td>
<td>24.7 ± 1.8</td>
<td>25.3 ± 1.5</td>
<td>NS</td>
</tr>
<tr>
<td>Mitral valve area ((\text{cm}^2))</td>
<td>1.2 ± 0.2</td>
<td>1.2 ± 0.2</td>
<td>NS</td>
</tr>
<tr>
<td>Mean transmitral gradient ((\text{mmHg}))</td>
<td>9.8 ± 1.9</td>
<td>9.9 ± 1.8</td>
<td>NS</td>
</tr>
<tr>
<td>Left atrial diameter ((\text{cm}))</td>
<td>4.2 ± 0.2</td>
<td>4.3 ± 0.1</td>
<td>NS</td>
</tr>
<tr>
<td>SPAP ((\text{mmHg}))</td>
<td>37.1 ± 10.3</td>
<td>36.7 ± 10.8</td>
<td>NS</td>
</tr>
<tr>
<td>Left ventricle end-diastolic diameter ((\text{cm}))</td>
<td>4.4 ± 0.18</td>
<td>4.4 ± 0.22</td>
<td>NS</td>
</tr>
<tr>
<td>Left ventricle ejection fraction (%)</td>
<td>64.1 ± 2.7</td>
<td>63.8 ± 3.9</td>
<td>NS</td>
</tr>
<tr>
<td>Right ventricle ejection fraction (%)</td>
<td>44.3 ± 2.1</td>
<td>43.9 ± 2.4</td>
<td>NS</td>
</tr>
<tr>
<td>Right ventricle end-diastolic diameter</td>
<td>3.0 ± 0.3</td>
<td>3.0 ± 0.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

\(^{\text{NS}}\) indicates systolic pulmonary artery pressure and NS, nonsignificant.
RESULTS

There was no significant difference among the groups in terms of mean age, gender distribution, body mass index, left and right ventricle end-diastolic diameters and ejection fractions, mean MVA, transmitral mean gradient, mean left

| Table II. Right Ventricular Functional Parameters Measured by Pulsed-Wave Tissue Doppler |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Isolated mitral stenosis patients (n = 40) | Group I (n = 19) | Group II (n = 21) | P               |
| IVCT (ms) | 110.5 ± 8.4 | 113.5 ± 25.4 | NS |
| S wave velocity (cm/s) | 12.1 ± 1.3 | 11.4 ± 1.2 | NS |
| E wave velocity (cm/s) | 11.7 ± 1.6 | 10.3 ± 1.5 | < 0.05 |
| A wave velocity (cm/s) | 10.2 ± 2.1 | 13.6 ± 1.8 | < 0.05 |
| E/A ratio | 1.3 ± 0.3 | 0.7 ± 0.1 | < 0.001 |
| IVRT (ms) | 54.2 ± 11.9 | 86.2 ± 16.2 | < 0.001 |

IVCT indicates isovolumic contraction time; IVRT, isovolumic relaxation time; S, systolic wave; E, early diastolic wave; A, atrial wave; and NS, nonsignificant.

Figure 1. Tricuspid annular E/A ratio is compared between asymptomatic and symptomatic patients with isolated mitral stenosis by tissue Doppler imaging.

Figure 2. Cyclic variation (CV) of right ventricle was compared between asymptomatic (group 1) and symptomatic patients (group 2) with isolated mitral stenosis by integrated backscatter analysis.
atrial dimension, and maximal SPAP ($P > 0.05$). All patients had moderate to severe MS with an MVA of $\leq 1.5 \text{ cm}^2$. Demographic and transthoracic echocardiographic variables of the patients are shown in Table I.

Tricuspid annular TDI parameters are presented in Table II. There were no statistically significant differences in systolic parameters (S, IVCT) between the 2 groups. However, IVRT ($54.2 \pm 11.9 \text{ ms}$ versus $86.2 \pm 16.2 \text{ ms}, P < 0.001$) and A wave amplitude ($10.2 \pm 2.1 \text{ cm/s}$ versus $13.6 \pm 1.8 \text{ cm/s}, P < 0.05$) were higher whereas E wave amplitude was lower ($11.7 \pm 1.6 \text{ cm/s}$ and $10.3 \pm 1.5 \text{ cm/s}, P < 0.05$) in group 2. In addition, the RV E/A ratio was determined to be significantly different between the groups ($P < 0.001$) (Figure 1).

### Table III. Integrated Backscatter Amplitudes and Cyclic Variation of the Right Ventricle in Patients With Isolated Mitral Stenosis

<table>
<thead>
<tr>
<th></th>
<th>Group 1 ($n = 19$)</th>
<th>Group 2 ($n = 21$)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diastolic IB of right ventricle</td>
<td>$78.6 \pm 5.9$</td>
<td>$79.4 \pm 4.3$</td>
<td>NS</td>
</tr>
<tr>
<td>CV of right ventricle</td>
<td>$9.5 \pm 3.4$</td>
<td>$6.7 \pm 1.9$</td>
<td>0.004</td>
</tr>
</tbody>
</table>

IB indicates integrated backscatter amplitude; CV, cyclic variation; and NS, nonsignificant.

![Figure 3. Correlation between cyclic variation of the right ventricle and tricuspid annular E/A ratio in symptomatic patients with isolated mitral stenosis (group 2). CV indicates cyclic variation and EA, tricuspid annular E/A ratio.](image-url)
Compared to the asymptomatic patients in group 1, symptomatic patients in group 2 had a lower CV of RV (6.7 ± 1.9 dB versus 9.5 ± 3.4 dB, P = 0.004) (Figure 2). However, no significant difference was determined in maximal IB of RV among the groups (Table III). There was a positive correlation between the CV of the RV lateral wall and tricuspid annular E/A ratio (r = 0.964, P < 0.001) (Figure 3).

DISCUSSION

It has recently been reported that in valvular diseases and heart failure, RV EF might be an independent determining factor in the estimation of exercise capacity and prognosis. In MS, RV systolic function is believed to be an important determinant of clinical symptoms, exercise capacity, preoperative survival, and postoperative outcome. However, in the presence of normal RV ejection fraction, some patients with MS of moderate or severe degree suffer symptoms, whereas some patients with similar MVAs do not.

Pulsed-wave TDI analysis is a technique that is not adversely influenced by preload and shows tissue contraction and relaxation rates with high resolution, and thus, enables the measurement of RV systolic and diastolic function. Imaging of the tricuspid annulus by tissue Doppler in healthy individuals and in patients with MS makes the measurement of RV diastolic and systolic functions possible. Tricuspid TDI E velocity represents relaxation activity of the RV, while A reflects atrial activity, the E/A ratio passive lengthening of myocardial fibres, and IVRT of the RV the energy-dependent phase of isometric relaxation. An E/A ratio < 1 indicates ventricular compliance impairment. In the present study we found that IVCT of the RV and tricuspid S-wave velocity which represent the systolic performance of the RV were statistically not different between the 2 groups (P > 0.05). However, in the symptomatic group, tricuspid E-wave velocity declined, supporting the theory of RV relaxation impairment, while A-wave velocity was much more prominent showing much more atrial contribution to diastolic ventricular filling that is essential due to relaxative impairment of the RV. In the symptomatic group, the E/A ratio was found to be < 1 which is indicative of impairment of RV diastolic compliance. Likewise, IVRT of the RV was found to be more prolonged in this group, which were all representative of RV diastolic dysfunction.

IBS analysis represents a recent advance in ultrasonic instrumentation technology that can be used to characterize changes in the myocardium at the cellular level. It is based on analyzing the reflection of an ultrasound wave (scattering), which is derived from the interaction of myocardial tissue elements that are smaller than the ultrasound wavelength. Time-domain analysis of this radiofre-
quency signal provides its IBS intensity and the systolic-to-diastolic CV of the intensity. CV diminishes in a substantial way in the presence of contractile dysfunction, variation of the elastic properties, or alterations of the geometry of the scatter.\textsuperscript{14} Although IBS analysis has been used more often on the left ventricle, its ability to differentiate normal versus abnormal RV myocardium was demonstrated in a recent study.\textsuperscript{27)}

Whereas no significant changes were found in this study in RV myocardial IB, CV was seen to decrease in symptomatic MS patients with RV diastolic dysfunction detected by TDI. Furthermore, we detected a significant correlation between CV of the RV and tricuspid annular E/A. The mechanism for the reduction of CV of backscatter in MS patients with diastolic dysfunction is not clear. Several structural components of the myocardium affect its acoustic properties, among them collagen with its complex structure, quantity, geometry, and orientation of the fibers. Giorgi, \textit{et al} reported a direct correlation between CV and the maximal mitral annular E/A ratio in a small group of essential hypertensive patients which was related to increased collagen content.\textsuperscript{28)} Similarly Maceira, \textit{et al} showed an association between diminished CV of backscatter and deterioration of diastolic function in hypertensive patients, while no difference in IB intensity was found between these subjects who had diastolic abnormality of different severities.\textsuperscript{14)} Finally Pacileo, \textit{et al} reported an increased RV averaged intensity, suggestive of myocardial fibrosis, and a reduced CV suggestive of myocardial impairment in patients who underwent surgery for tetralogy of Fallot.\textsuperscript{27)}

In isolated MS, RV diastolic functions may be impaired due to myocardial and hemodynamic factors including pulmonary arterial hypertension and right and left ventricular interaction.\textsuperscript{29)} Since the size of the left atrium, MVA, mean transmitial gradient, and SPAP were not different among the groups, the effect of hemodynamic factors was considered to be trivial. Myocardial factors including myocardial involvement by the rheumatic process were reported to contribute to the deterioration of left ventricular functions regardless of the severity of MS reflected in the echocardiographic and hemodynamic data.\textsuperscript{30,31)} It was suggested that there were varying degrees of ultrastructural pathological alterations in the left ventricle myocardium of all patients with MS regardless of left ventricular contractile function. Nevertheless, extensive myocardial involvement was implicated to contribute to left ventricular dysfunction.\textsuperscript{30,31)} The rheumatic process has also been suggested to involve RV myocardium and contribute to RV functional abnormalities.\textsuperscript{32)} Hence our finding that symptomatic isolated MS patients had RV diastolic dysfunction in comparison to asymptomatic ones with similar MVA in the presence of normal RV systolic function may be related to the difference in the extent of rheumatic involvement. However, larger studies with histopathological examinations are needed to firmly establish this hypothesis.
In summary, this study has demonstrated that in the presence of normal RV systolic function, RV textural properties measured by IBS were significantly different among symptomatic and asymptomatic isolated MS cases with similar MVA which may be associated with RV diastolic dysfunction. Due to the complex structure and asymmetrical shape of the RV, assessment of RV function is often problematic. RV IBS and TDI analyses may be considered as relatively simple methods for the evaluation of RV diastolic dysfunction.

**Conclusion:** RV textural properties measured by IBS are significantly different among symptomatic and asymptomatic MS cases with similar MVA and normal RV systolic function which may be associated with RV diastolic dysfunction.

**REFERENCES**


