Early detection of right ventricular systolic dysfunction by using myocardial acceleration during isovolumic contraction in patients with mitral stenosis

Yelda Tayyareci*, Yilmaz Nisanci, Berrin Umman, Aytac Oncul, Selen Yurdakul, Ibrahim Altun, Sabahattin Umman, and Zehra Bugra

Istanbul University, Istanbul Faculty of Medicine, Department of Cardiology, Capa, Istanbul, Turkey

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Aim The aim of the study was to determine if the tissue Doppler imaging (TDI)-derived myocardial acceleration during isovolumic contraction (IVA) of tricuspid lateral annulus could be used in early detection of RV systolic dysfunction in patients with mitral stenosis (MS), before the clinical signs of systemic venous congestion occur.

Methods One hundred and twelve patients with rheumatic MS without relevant regurgitation and 60 control subjects were enrolled in the study. Conventional echocardiographic parameters (mitral valve area, transmitral diastolic gradients, pulmonary artery pressure, RV fractional shortening, pulmonary flow acceleration time, tricuspid annular plane systolic excursion) and TDI-derived systolic velocities of tricuspid annulus (isovolumic myocardial acceleration: IVA, peak myocardial velocity during isovolumic contraction: IVV, peak systolic velocity during ejection period: Sa and RV Tei index) were recorded from all patients.

Results TDI-derived IVA, IVV, Sa and Tei index were found to be significantly decreased in patients with MS. IVA was the only parameter which had a significant negative correlation with the traditional echocardiographic parameters and RV Tei index in patients with MS. Additionally, in subgroup analyses, IVA was significantly lower in patients with severe degree of MS.

Conclusion TDI-derived right ventricular IVA may be used as an adjunctive, reliable, noninvasive parameter for the early detection of right ventricular systolic dysfunction in patients with MS but without signs of systemic venous congestion.

Keywords
Right ventricular systolic function; Isovolumic myocardial acceleration; Tissue Doppler imaging; Echocardiography

Right ventricular (RV) systolic function significantly affects symptoms, exercise capacity and mortality rates in patients with mitral stenosis (MS). Clinical assessment of RV dysfunction is difficult in patients without clinical signs of systemic venous congestion. However, in the pathogenesis of the MS, RV dysfunction occurs early before the systemic venous congestion develops. RV functions cannot reliably be evaluated by conventional echocardiographic techniques because of its asymmetrical shape, narrow acoustic window and geometrical assumptions for volume calculations. Radioisotope ventriculography, cardiac catheterization, cardiac magnetic resonance imaging (MRI) and 3-dimensional echocardiography could be used for the assessment of RV function. However, these methods are time consuming and not widely available.

In previous studies, ejection phase myocardial velocities measured by tissue Doppler imaging (TDI) have been shown to be well correlated with right ventricular ejection fraction. However, they were found to be preload and afterload dependent. Recently a new TDI-derived index of myocardial acceleration during isovolumic contraction (IVA) has been validated to be a reliable and relatively load independent measure of RV systolic functions.

The aim of the study was to determine if the IVA measured by TDI of tricuspid lateral annulus could be used in early detection of RV systolic dysfunction in patients with mitral stenosis, before the signs of systemic venous congestion occur.
Material and methods

Study patients

The study included 112 patients (33 with severe MS, MVA < 1.0 cm²; and 79 with mild to moderate MS; MVA > 1.0 cm²) with rheumatic mitral stenosis without clinical evidence of systemic venous congestion. Sixty age and sex matched healthy subjects were involved as control group. The patients had no relevant mitral regurgitation and concomitant hemodynamically significant valvular disease and were all on sinus rhythm. Exclusion criteria were low quality echocardiographic image of tricuspid annular velocities by TDI, any disease that could affect myocardial functions (e.g. coronary artery disease, chronic lung disease, cardiomyopathies), atrioventricular conduction abnormalities, atrial fibrillation and having signs of systemic venous congestion and right heart failure. Study protocol was approved by local Ethics Committee of our institute and a detailed written informed consent was obtained from each patient. The study was carried out according to the Declaration of Helsinki.

Echocardiographic measurements

All the patients were examined on the left lateral decubitus position by M-mode, two-dimensional (2D), Doppler and TDI echocardiography (GE, Vingmed Vivid 7, Norway) using a 2.5-MHz transducer. Left atrial (LA) diameter was calculated from the parasternal long axis view by M-mode echocardiography. Tricuspid annular plane systolic excursion (TAPSE, mm) was measured in M-mode, using cursor in apical four-chamber view, at juncture of tricuspid valve with the right ventricular free wall. Maximum displacement during systole was evaluated. By using apical four-chamber view, end-diastolic and end-systolic areas of RV cavity were calculated using planimetry and RV fractional shortening (RVFS%) was calculated (((end-diastolic area – end-systolic area)/end-diastolic area) × 100). RV anterior wall thickness (RWWT, mm) in end-diastole was also measured. Mitral valve area (MVA) was expressed as the mean of two values obtained by planimetric measurements and pressure half time method. Maximum and mean transmitral diastolic gradients were calculated by Doppler scanning. We estimated the pulmonary artery systolic pressure (PAP, mmHg) by continuous-wave Doppler imaging using the Bernoulli equation. Pulmonary flow acceleration time (Pat, ms) was measured as the period between the onset of pulmonary systole and point of peak velocity by Doppler imaging. By using apical four-chamber view, end-diastolic and end-systolic areas of RV cavity were calculated using planimetry and RV fractional shortening (RVFS%) was calculated (((end-diastolic area – end-systolic area)/end-diastolic area) × 100). RV anterior wall thickness (RWWT, mm) in end-diastole was also measured. Mitral valve area (MVA) was expressed as the mean of two values obtained by planimetric measurements and pressure half time method. Maximum and mean transmitral diastolic gradients were calculated by Doppler scanning. We estimated the pulmonary artery systolic pressure (PAP, mmHg) by continuous-wave Doppler imaging using the Bernoulli equation. Pulmonary flow acceleration time (Pat, ms) was measured as the period between the onset of pulmonary systole and point of peak velocity by Doppler imaging. We measured mitral leaflet separation index (MLSI) which is shown as a reliable predictor of the severity of MS. MLSI was measured both in parasternal long axis and apical four-chamber view and the calculated mean of two values was taken as the MLSI.

Additionally, guided by the 2D, four-chamber view, a 5-mm sample volume was placed on the tricuspid annulus at the place of attachment of the anterior leaflet of the tricuspid valve for measuring TDI-derived systolic velocities. Settings were adjusted for a frame rate between 120 and 180 Hz and a cine loop of 3–5 consecutive heartbeats was recorded. We took rigorous care to obtain an ultrasound beam parallel to the direction of tricuspid annular motion. The pulsed wave TDI-derived systolic indices; peak myocardial velocity during isovolumic contraction (IVV, cm/s); myocardial acceleration during isovolumic contraction (IVA, m/s²), defined as the ratio of IVV divided by the acceleration time, and peak velocity during systolic ejection (Sa, cm/s) were measured. RV Tei index was calculated as the sum of isovolumic contraction time (IVCT) and isovolumic relaxation time (IVRT) divided by ejection time (ET). All the measurements were calculated from three consecutive cycles and average of three measurements was recorded (Figure 1).

Reproducibility

Intraobserver and interobserver variabilities of TDI-derived tricuspid lateral annulus systolic velocities were assessed. For interobserver variability a second observer calculated 20 measurements and for intraobserver variability first observer measured 20 measurements on another day.

Statistical analysis

All statistical data were processed using the Graph-Pad Prisma V statistical package. The results were expressed as mean and standard deviation (SD) together with one-way ANOVA analysis was used for comparisons of the groups. Tukey multiple comparison test was used for comparison in subgroups. Test and control groups were compared using unpaired t-test. Correlation analyses were derived by using Pearson’s analysis. The results were considered significant when the p-value was less than 0.05.

Results

Clinical characteristics and conventional echocardiographic parameters

Age, gender and body mass index were similar both in control and patient groups. The mean MVA was 1.48 ± 0.4 cm in patients with MS and 3.6 ± 1.6 cm in control group (p = 0.0001). In MS group the average value of mean transdiastolic pressure was 6.3 ± 4.3 mmHg and the maximum gradient was 12.6 ± 7.3 mmHg. Mild degree of mitral regurgitation was detected 15% of the MS patients and 12% of the control group (p = 0.86) (Table 1).

LA diameter and estimated pulmonary artery pressure were significantly higher in patients with MS as expected (p = 0.0001). RVFS% was found to be reduced in patients with MS while it was in normal range in control group (p = 0.0001). RV anterior wall hypertrophy was also observed in patients with MS (p = 0.0001). Pat was significantly reduced in mitral stenosis group (p = 0.0001). TAPSE was relatively lower in patient group but did not attain...
statistical significance ($p = 0.14$). Additionally, MLSI which was shown to be related with the degree of MS was found to be significantly lower in patient group ($p = 0.0001$) (Table 1).

### Tissue Doppler imaging findings

There were significant differences between the patient and control groups on tricuspid Sa wave ($0.13 \pm 0.03$ cm/s, MS and $0.19 \pm 0.02$ cm/s, controls; $p < 0.0001$), right ventricular IVV ($0.11 \pm 0.04$ cm/s, MS and $0.15 \pm 0.02$ cm/s, controls; $p < 0.0001$). Additionally, IVA was significantly decreased in patients with MS ($2.09 \pm 0.05$ m/s$^2$, MS and $3.2 \pm 0.3$ m/s$^2$, controls; $p = 0.0001$). RV Tei index was significantly increased in patients with MS ($0.69 \pm 0.2$, MS and $0.28 \pm 0.06$, controls; $p = 0.0001$) supporting impairment of both RV systolic and diastolic function (Table 1).

### Correlation analyses between TDI-derived systolic velocities and conventional echocardiographic parameters

There was a significant positive correlation between IVA and IVV ($r = 0.39$, $p < 0.0001$) (Figure 2A). However, Sa correlated neither with IVA ($r = 0.158$, $p = 0.097$) nor with IVV ($r = 0.095$, $p = 0.32$). IVA was also very well correlated with LA diameter ($r = -0.578$, $p < 0.0001$) and pulmonary artery pressure ($r = -0.474$, $p < 0.0001$) (Figure 2B,C). Additionally, there was a strong relation between the degree of mitral stenosis and the RV IVA ($p < 0.0001$). IVA was significantly correlated with the parameters which demonstrate the degree of MS (MVA, transmitral diastolic gradients and mitral leaflet separation index) ($p < 0.0001$). But neither Sa nor IVV showed correlation with the degree of mitral stenosis. Furthermore IVA negatively correlated with RV Tei index ($r = -0.813$, $p < 0.0001$) (Figure 2D).

Both the correlations between RV IVA and Pat ($r = 0.39$, $p = 0.0001$) and RV IVA and RVAWT ($r = -0.27$, $p = 0.004$) were statistically significant (Figure 3A,B). There was no relation between TAPSE and RV IVA ($r = 0.03$, $p = 0.73$). Additionally, IVA did not correlate with RVFS% ($r = -0.09$, $p = 0.31$). Moreover, RV IVV and Sa did not correlate with any of the conventional RV systolic parameters.

### Subgroup analysis of right ventricular IVA

When patient group was divided into two subgroups as patients with mild to moderate MS (MVA $\geq 1.0$ cm$^2$) and severe MS (MVA $< 1.0$ cm$^2$), we observed that TDI-derived IVA was markedly lower in severe MS group compared to mild to moderate MS group ($p < 0.0001$). However, RV IVV ($p = 0.22$) and Sa ($p = 0.19$) were similar in the two subgroups (Table 2). The analyses of conventional parameters showed that RVAWT was the only parameter that showed difference between subgroups ($2.74 \pm 0.44$ mm in mild to moderate and $3.22 \pm 0.42$ mm in severe MS, $p = 0.0001$). Pat, RVFS% and TAPSE were all found to be similar between two subgroups.

### Reproducibility

Interobserver and intraobserver reliability were very good for IVA ($r = 0.96$ and 0.93, respectively). Interobserver difference for IVA was $0.01 \pm 0.2$ m/s$^2$ while intraobserver difference was $0.05 \pm 0.22$ m/s$^2$.

### Discussion

Results of our study have demonstrated that TDI-derived RV IVA had a good correlation with right ventricular systolic dysfunction in patients with MS. IVA had a significant negative correlation with the conventional parameters of PAP, RVAWT, Pat, LA diameter and RV Tei index.

Mitral stenosis has a physiopathologic process which results in RV failure. During the initial period of MS, pulmonary venous hypertension is followed by pulmonary artery hypertension due to combined effects of back pressure pulmonary arteriolar constriction and obliteratorive changes in pulmonary vascular bed which increases RV afterload. A significant chronic increase in afterload ultimately results in failure with RV dilatation, tricuspid regurgitation and systemic venous congestion. RV failure with signs of systemic venous congestion is easy to detect, however, clinical assessment of RV function is not possible in all patients without signs of systemic venous congestion.

Traditional echocardiographic surrogates of RV systolic function are problematic because of its complex geometry. Various studies have demonstrated the dissociation between the pulmonary artery pressure and RV functions in the
presence of tricuspid regurgitation and atrial fibrillation. Tricuspid regurgitation may falsely normalize RV ejection fraction. Besides, atrial fibrillation and irregular ventricular rate make correct calculations impossible to get. Thus, there is a tendency to search for new modalities which may present data that are more reliable than traditional echocardiographic indices. Radionuclide ventriculography, 3-dimensional echocardiography and MRI are alternative techniques which are being used to evaluate RV functions. Particularly, in recent studies, radionuclide ventriculography is shown to have outstanding reproducibility for the quantification of RV global systolic function. Problems still exist with low spatial resolution and attenuation artifacts. MRI and 3D echocardiography can be accurately used to measure end-systolic and end-diastolic volumes and calculate EF; however, these methods are time consuming and not cost-effective. Besides all these indices are load dependent.

Echocardiography is a noninvasive and reproducible method for evaluating cardiac functions. TDI-derived ejection phase myocardial velocities gained importance due to problems experienced, with the traditional indices in evaluation of RV functions. Despite having the potential to give relatively more reliable data on RV ventricular contractile function, these indices have been shown to be preload and afterload dependent. Recently, a new parameter, IVA, has been validated to be accurate and relatively load independent measure of RV systolic function. IVA is hypothesized to be a robust index of contractility like dP/dtmax because both indices reflect the rate change of contractile force during isovolumic contraction. Dickstein et al. showed, in an experimental study, that IVA reflected an earlier isovolumic event thus may be more robust compared to dP/dtmax and more sensitive to changes in contractile state than maximal elastance. There are also clinical studies that support the data. Harada et al. revealed that after the repair, in patients with tetralogy of Fallot IVA was lower compared to control group. A different study by Toyono et al. also reported decreased RV myocardial velocities and IVA in patients with repaired Fallot tetralogy compared to control group. Additionally, Lytrivi et al. confirmed that color TDI indices of tricuspid annular motion in patients with congenital heart disease show positive correlation with MRI-derived RV ejection fraction.

Supporting these studies, in this study we demonstrated that IVA may be used as an accurate, noninvasive parameter
for assessment of RV systolic functions in patients with mitral stenosis. All the TDI-derived RV systolic myocardial velocities decreased in MS patients compared to control group showing impaired RV systolic function. Additionally, TDI-derived RV Tei index increased significantly in MS patients showing decreased global RV function. Another outcome with the study is that IVA shows good correlation with the conventional parameters of PAP, LA diameter, RVAWT and Pat. In contrast, IVV and Sa did not correlate with those traditional indices. Additionally, IVA had a significant correlation with RV Tei index. Subgroup analyses showed that IVA was the only parameter that demonstrated significant difference between the mild to moderate and severe MS. With the suspicion of RV systolic dysfunction

Table 2  Subgroup analysis of the TDI-derived myocardial systolic velocities obtained from tricuspid lateral annulus

<table>
<thead>
<tr>
<th></th>
<th>Mild to moderate mitral stenosis (n = 79)</th>
<th>Severe mitral stenosis (n = 33)</th>
<th>Control group (n = 60)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV Sa (cm/s)</td>
<td>0.14 ± 0.03</td>
<td>0.13 ± 0.03</td>
<td>0.19 ± 0.02</td>
<td>0.0001</td>
</tr>
<tr>
<td>RV IVV (cm/s)</td>
<td>0.12 ± 0.04</td>
<td>0.11 ± 0.03</td>
<td>0.15 ± 0.02</td>
<td>0.0001</td>
</tr>
<tr>
<td>RV IVA (m/s²)</td>
<td>2.34 ± 0.45</td>
<td>1.68 ± 0.55</td>
<td>3.2 ± 0.29</td>
<td>0.0001</td>
</tr>
</tbody>
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RV, right ventricle; IVV, peak myocardial velocity during isovolumic contraction; Sa, peak velocity during ejection period of systole; IVA, myocardial acceleration during isovolumic contraction.
as well as pulmonary artery pressure getting obvious along with an increased MS severity, this is an expected result. But IVA seems to be more sensitive parameter compared to IVV and Sa in this situation. This finding may be supported by studies showing that Sa was highly afterload dependent. The IVA reflects RV systolic function during isovolumic contraction. In contrast to Sa, IVA has the advantage of being relatively preload and afterload independent.

In conclusion, due to the importance of RV systolic impairment detection in early stages of the MS, in this study we assessed the RV systolic dysfunction in MS patients without signs of systemic venous congestion by using a new TDI-derived parameter, IVA. Because the determination of RV ejection fraction by MRI or radionuclide ventriculography is costly and time consuming and cardiac catheterization is an invasive method and cannot be applied to all patients, our results suggest that TDI-derived right ventricular IVA may be used as an alternative and accurate, noninvasive parameter in early detection of RV systolic dysfunction in MS patients.

Limitations

In this study we used TDI-derived tricuspid annular systolic myocardial velocities and traditional 2-dimensional and Doppler parameters to evaluate RV function in patients with MS. We did not compare our results with gold standard modalities which analyze RV systolic function, like 3D echocardiography and MRI. Further studies are needed to evaluate the diagnostic value of RV IVA in patients with MS by comparing with other new diagnostic modalities.

Conflict of Interest: Part of this study has been presented in EUROECHO 10, Prague, 2006, at a poster session.

References