Excessive respiratory variation in tricuspid regurgitation systolic velocities in patients with severe tricuspid regurgitation

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Aims
Respiratory changes in tricuspid regurgitation (TR) systolic velocities are occasionally demonstrated by Doppler echocardiography in patients with TR. We tested the hypothesis that excessive respiratory changes in TR velocities are diagnostic of severe TR.

Methods and results
The difference between the maximal (expiratory) and minimal (inspiratory) TR systolic velocities during spontaneous respiration was measured by Doppler echocardiography in 68 patients with severe TR and 68 patients with moderate TR. The diagnostic value of the respiratory changes in TR velocity for detecting severe TR was assessed. The respiratory differences in TR velocities were greater in patients with severe TR (0.72 ± 0.30 m/s), compared with patients with moderate TR (0.28 ± 0.18; P < 0.001). Using receiver-operating characteristics analysis, the area under the curve for the respiratory difference in TR velocities for diagnosing severe TR was 0.92 (95% confidence interval: 0.87–0.96; P < 0.001). A difference in TR velocity ≥ 0.6 m/s had a sensitivity of 66%, specificity of 94%, positive predictive value of 92%, and a negative predictive value of 74% for diagnosing severe TR. Among patients with severe TR, excessive values of TR velocity difference were associated with signs of more severe TR (greater right ventricular size and malcoaptation of the tricuspid valve leaflets).

Conclusion
Excessive respiratory changes in Doppler measurements of TR systolic velocities are a specific sign of severe TR.

Keywords
Echocardiography • Doppler • Tricuspid regurgitation • Respiration

Introduction
Severe tricuspid regurgitation (TR) is a common valve abnormality and its major clinical and prognostic implications are increasingly recognized. Echocardiography is the most common modality used in detecting TR and, although there are multiple echocardiographic signs indicative of TR severity, the diagnosis of severe TR is not infrequently overlooked.

In our clinical experience, excessive respiratory variation in TR systolic velocities, representing the large changes in systolic pressure gradient between the right ventricle (RV) and right atrium (RA) are commonly demonstrated during spontaneous respiration in patients with severe TR. On the other hand, this phenomenon is rarely observed in patients with lesser degrees of TR, in whom TR velocities are relatively constant or exhibit only minor changes during respiration.

On the basis of these preliminary observations, the objectives of our study were as follows:

(i) To determine the magnitude of respiratory changes in TR systolic velocities in patients with severe TR, in comparison to patients with non-severe (moderate) TR.
(ii) To assess the diagnostic value of the respiratory changes in TR systolic velocities in differentiating severe from moderate TR.
(iii) Among patients with severe TR, to examine whether excessive respiratory changes in TR velocities are indicative of more severe degrees of TR.

**Methods**

**Patients and data collection**

The computerized database of the echocardiographic laboratory at our institution, a tertiary medical centre, was searched to identify all patients who had an echocardiographic diagnosis of severe TR during a 22 month study period. The diagnosis of severe TR was based on the combination of colour flow imaging (absolute size of TR jet and size of TR jet relative to RA size) and the presence of mid-to-late systolic flow reversal in the hepatic veins (sampled by pulsed-wave Doppler), as proposed by the American Society of Echocardiography (ASE) guidelines on evaluation of valve regurgitation. The control group consisted of an equal number of patients with moderate TR (consecutive patients from the last 9 months of the study period), in whom the diagnosis of moderate TR was based on a smaller TR colour flow jet size and the absence of hepatic venous systolic flow reversal. All the echocardiographic studies were reviewed by a single observer (D.M.), who validated the diagnoses of severe or moderate TR according to the above criteria. The high interobserver agreement in our laboratory in the qualitative estimation of TR severity has been previously published.

Patients were included in the current analysis if they fulfilled the following inclusion criteria: (i) the presence of a regular heart rhythm during the echocardiographic study (sinus rhythm or regular ventricular pacing) and (ii) the presence of at least one continuous-wave Doppler strip of the TR jet with at least four consecutive good-quality TR Doppler signals. There was no routine clinical use of respiratory monitoring during the echocardiographic studies. The difference between the highest (presumably inspiratory) and lowest (presumably expiratory) TR systolic velocities [delta velocities (ΔV)] within a Doppler strip recorded during spontaneous respiration was determined (Figure 1). In patients with more than one appropriate Doppler strip fulfilling the above inclusion criteria, the maximal ΔV was taken for the current analysis. None of the patients in our study had significant pericardial disease (pericardial tamponade or constrictive pericarditis).

Additional relevant echocardiographic data [the size and the function of right and left heart chambers, aetiology of TR, presence and degree of malcoaptation of the tricuspid valve (TV) leaflets, additional valve dysfunction, presence of a pacemaker electrode, estimated RA, and pulmonary artery pressures] were collected by a detailed review of all the echocardiographic examinations. RA size, RV size, and RV systolic function were assessed qualitatively by ‘eyeballing’. Notably, the high interobserver agreement in our laboratory in the qualitative estimation of the size of the right heart chambers and RV systolic function has been previously published. In addition, RA end-systolic area and RV end-diastolic area were measured from the apical four-chamber view. TV leaflets malcoaptation was defined as the presence of a visible gap between the TV leaflets during systole (gap of any size, visible at least during inspiration). Among patients with TV malcoaptation, ‘severe’ TV malcoaptation was defined as a gap between the TV leaflets that is continuously visible throughout the respiratory cycle and exceeds 2 mm in its largest diameter (during inspiration). RA pressure was estimated using a modification of the diagnostic scheme proposed by the ASE guidelines, based on the size of the inferior vena cava (IVC) and the degree of its inspiratory collapse during normal respiration: (a) a normal IVC size (IVC diameter < 2 cm) with normal inspiratory collapse (>50% decrease in IVC diameter) indicate normal RA pressure (≈5 mmHg); (b) a dilated IVC (diameter > 2 cm) or <50% collapse indicate mildly elevated RA pressure (≈10 mmHg); (c) both a dilated IVC and <50% collapse indicate moderately elevated RA pressure (≈15 mmHg); (d) a dilated IVC without visible collapse indicate severely elevated RA pressure (≈20 mmHg); (e) a severely dilated IVC (diameter > 3 cm) without any respiratory collapse indicate an RA pressure of ≈25 mmHg.

**Statistical analysis**

Continuous data were compared by the Student’s t-test or Wilcoxon rank-sum test and categorical data were compared by the χ² statistic or Fisher’s exact test, as appropriate. Initially, patients with severe TR were compared with those without severe (moderate) TR. The diagnostic value of ΔV in discriminating between severe and moderate TR was examined using a receiver-operating characteristics (ROC) analysis and the sensitivity, specificity, as well as positive and negative predictive values of a specific ΔV cut-off in diagnosing severe TR were calculated. Subsequently, among the subgroup of patients with severe TR, patients with ΔV above the diagnostic cut-off were compared with patients with ΔV below the cut-off.

The echocardiographic studies of a random stratified sample of 20 patients (10 patients with severe TR and 10 patients with moderate TR) were reviewed by a second blinded reviewer and the interobserver variability in ΔV measurements was assessed.

**Results**

**Study population**

During the 22 months study period, 68 patients with severe TR fulfilled the inclusion criteria. An equal number of patients with moderate TR (n = 68) were identified during the last 9 months of the study period (consecutive patients with moderate TR who fulfilled the inclusion criteria).

The baseline characteristics of the two groups (severe TR vs. moderate TR) are presented in Table 1. There were no differences in age, gender, and heart rate between the two groups. A pacemaker electrode was much more frequent in patients with severe TR. Left ventricular ejection fraction was lower and mitral regurgitation (moderate or severe) was slightly more frequent in patients with severe TR (the latter difference not achieving statistical significance). The size of the right-sided chambers was larger in patients with severe TR and the frequency of significant RV dysfunction was slightly higher in patients with severe TR (the latter difference not achieving statistical significance). The frequency of significant organic TV disease was very low in both groups. Pulmonary artery pressure, calculated using the maximal (expiratory) trans-tricuspid systolic pressure gradients, and estimated RA pressure were higher in patients with severe TR.

The differences in TR velocities between patients with severe and moderate TR are presented in Table 2 and Figure 2. There were no differences in maximal (expiratory) TR velocities between the two groups, whereas minimal (inspiratory) TR velocities were lower in patients with severe TR. This resulted in a higher ΔV and a higher relative ΔV (ΔV divided by maximal TR velocities) in patients with severe TR.
As shown in Figure 3, there was no significant correlation between maximal TR velocities and ΔV in the whole study population (P = 0.20). There was, however, a significant positive relationship between estimated RA pressure and ΔV, with elevated RA pressures being associated with higher values of ΔV (Figure 3; P for trend <0.001 in the total study population). Notably, this trend was mainly driven by the higher RA pressures observed in patients with severe TR (Table 1; Figure 3), in whom ΔV was also higher, whereas the trend between RA pressure and ΔV within each TR subgroup separately was very weak and insignificant (P for trend = 0.09 and P = 0.14 in patients with moderate and severe TR, respectively). Pulmonary artery systolic pressure showed a very poor correlation with ΔV in the total study population (R² = 0.06; P = 0.004) and in the subgroup with severe TR.

Table 1. Characteristics of patients with severe or moderate TR

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Severe TR (n = 68)</th>
<th>Moderate TR (n = 68)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>70 ± 12</td>
<td>69 ± 14</td>
<td>0.45</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>30 (44.1%)</td>
<td>24 (35.3%)</td>
<td>0.29</td>
</tr>
<tr>
<td>Heart rate, beats per minutes</td>
<td>73 ± 16</td>
<td>75 ± 16</td>
<td>0.39</td>
</tr>
<tr>
<td>Pacemaker electrode, a n (%)</td>
<td>29 (42.6%)</td>
<td>3 (4.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>47 ± 20</td>
<td>54 ± 18</td>
<td>0.04</td>
</tr>
<tr>
<td>MR, b %</td>
<td>25 (36.8%)</td>
<td>16 (23.5%)</td>
<td>0.09</td>
</tr>
<tr>
<td>RV enlargement, b %</td>
<td>24 (35.3%)</td>
<td>6 (8.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RV end-diastolic area, cm²</td>
<td>29.4 ± 7.5</td>
<td>22.7 ± 7.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RV systolic dysfunction, b %</td>
<td>16 (23.5%)</td>
<td>9 (13.2%)</td>
<td>0.12</td>
</tr>
<tr>
<td>RA enlargement, b %</td>
<td>42 (61.8%)</td>
<td>6 (8.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RA end-diastolic area, cm²</td>
<td>29.2 ± 8.8</td>
<td>20.4 ± 5.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Organic TV disease, %</td>
<td>3 (4.4%)</td>
<td>1 (1.5%)</td>
<td>0.31</td>
</tr>
<tr>
<td>PA systolic pressure, c mmHg</td>
<td>60 ± 16</td>
<td>54 ± 17</td>
<td>0.04</td>
</tr>
<tr>
<td>RA pressure, mmHg</td>
<td>16 ± 5</td>
<td>10 ± 5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data presented as mean ± standard deviation for continuous variables and as numbers (percentages in parentheses) for categorical variables.

LVEF, left ventricular ejection fraction; MR, mitral regurgitation; PA, pulmonary artery; RA, right atrium; RV, right ventricle; TR, tricuspid regurgitation; TV, tricuspid valve.
aWith or without active pacing.
bModerate or severe (qualitative assessment).
cPA pressure was calculated using the maximal (expiratory) TR pressure gradient during the respiratory cycle.

Table 2. Tricuspid regurgitation velocities in patients with severe or moderate TR

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Severe TR (n = 68)</th>
<th>Moderate TR (n = 68)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximal (expiratory) velocities, m/s</td>
<td>3.2 ± 0.6</td>
<td>3.2 ± 0.5</td>
<td>0.99</td>
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<tr>
<td>Minimal (inspiratory) velocities, m/s</td>
<td>2.5 ± 0.6</td>
<td>3.0 ± 0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Difference in velocities, b m/s</td>
<td>0.72 ± 0.30</td>
<td>0.28 ± 0.18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Relative difference in velocities b</td>
<td>0.23 ± 0.10</td>
<td>0.09 ± 0.06</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

TR, tricuspid regurgitation.
aMaximal (expiratory) minus minimal (inspiratory) velocities.
bDifference in velocities divided by maximal (expiratory) velocity.
(R² = 0.07; P = 0.03), but not in the subgroup with moderate TR (P = 0.83).

The diagnostic value of ∆V in diagnosing severe TR was examined by a ROC analysis (Figure 4). The area under the curve for ∆V in diagnosing severe TR was 0.92 (95% confidence interval 0.87–0.96; P < 0.001). There was no diagnostic advantage for using the relative ∆V (∆V divided by maximal TR velocities), rather than the absolute value of ∆V, for diagnosing severe TR (area under the curve for relative ∆V = 0.92; 95% confidence interval 0.88–0.97; P < 0.001). Among patients with severe TR, excessive values of ∆V (≥0.6 m/s) were observed in 45 of 68 patients (66%) vs. only five patients (7%) with moderate TR (P < 0.001). A cut-off of ∆V ≥ 0.6 m/s had a sensitivity of 66%, specificity of 94%, positive predictive value of 92%, and a negative
predictive value of 74% for diagnosing severe TR. Among the subgroup of patients with severe TR, those with ΔV ≥ 0.6 m/s were characterized by a greater RV size as well as more frequent and severe malcoaptation of the TV leaflets (Table 3), indicating more severe TR and RV volume overload in patients with excessive values of ΔV.

In the interobserver variability substudy (20 patients), ΔV measured by the first (original) and second reviewer averaged 0.50 ± 0.30 and 0.55 ± 0.32 m/s, respectively (P = 0.43). There was a statistically significant correlation between the measurements of ΔV by the two reviewers (R² = 0.59; P < 0.001). The average of the differences in ΔV between the two reviewers was 0.06 ± 0.21 m/s (median = 0) and the average of the absolute values of the differences in ΔV between the two reviewers was 0.17 ± 0.13 m/s (median = 0). Using a cut-off of ΔV ≥ 0.6 m/s for defining excessive respiratory changes in TR velocities, there was a 90% agreement between the two reviewers in classifying the patients above or below this specific cut-off.

### Discussion

Our study demonstrated that marked respiratory changes in TR systolic velocities are frequently demonstrated in patients with severe TR, whereas TR velocities change to a minor degree in patients with less severe (moderate) TR. Respiratory changes in TR velocities beyond a threshold of ≥0.6 m/s were highly specific for severe TR, with a high (>90%) positive predictive value for diagnosing this haemodynamic abnormality. Among patients with severe TR, those with excessive respiratory variation in TR velocities had features consistent with more severe TR (RV volume overload and more malcoaptation of the TV leaflets). These findings suggest that the respiratory changes in TR systolic velocities can be used as an echocardiographic sign of severe TR.

In the European Association of Echocardiography recommendations for the assessment of valvular regurgitation, marked respiratory changes in TR velocities (lower TR velocities with inspiration) were proposed as a sign of severe TR, but there were no references in that document to support this recommendation. This document suggests that this Doppler phenomenon is related to elevated RA pressure and is an echocardiographic manifestation of the Kussmaul sign, but this hypothesis is not backed up by scientific evidence. Moreover, in the ASE recommendations for evaluation of the severity of native valvular regurgitation there were no recommendations regarding the use of respiratory-dependent TR haemodynamics for the assessment of TR severity.

Recently, Topilsky et al. described the respiratory changes in TR haemodynamics in 41 patients with variable degrees of TR (mild to...
severe), using quantitative assessment of TR severity (via the proximal isovelocity surface area method) and measurements of the dimensions of the TV and right heart chambers. During inspiration, effective tricuspid regurgitant orifice increased dramatically by a median of 69%, compared with its lower values during expiration. In contrast, TR driving force (peak TR velocity) decreased by a median of 0.4 m/s (25–75th percentile: 0.3–0.6 m/s). These contrasting effects of respiration on TR regurgitant orifice and driving force resulted in a smaller inspiratory change in TR regurgitant volume (20% increase, compared with expiratory values).

The striking changes in TR regurgitant orifice during respiration were related to an inspiratory increase in RV size and morphology (increase in RV width), resulting in tricuspid annular dilatation, increased tricuspid leaflet tethering, and eventually impaired tricuspid leaflet coaptation. In this study, the respiratory changes of peak TR velocity were similar in the patients with mild TR (TR regurgitant orifice <0.20 cm²; n = 17 patients) and in patients with moderate or greater TR (regurgitant orifice ≥0.20 cm²; n = 24). However, the small number of patients with severe TR were not analysed separately and the diagnostic value of the respiratory changes in TR velocity for differentiating severe from non-severe TR was not examined in this study.

The inspiratory decline in peak TR velocity is a manifestation of a lower RV–RA pressure gradient during inspiration. Normally, in the absence of pericardial constriction, an inspiratory drop in intra-thoracic pressure will be transmitted to the pulmonary vasculature as well as the cardiac chambers, thereby lowering pulmonary artery, RV, and RA pressures. Since RV and RA pressure are expected to decline to a similar extent, the RV–RA pressure gradient should not vary significantly during respiration. Indeed, this is the case in most patients without severe TR in whom TR velocity is relatively constant, with only minor respiratory variation. In patients with greater degrees of TR, the inspiratory increase in TR severity will prevent the normal decline in RA pressure or may even elevate RA pressure during inspiration (‘ventricularization’ of RA pressure resulting in a positive Kussmaul sign), thereby decreasing the RV–RA pressure gradient during inspiration. Another possible mechanism for the respiratory changes in TR velocities may be related to the large respiratory changes in the TR regurgitant orifice in patients with severe TR, at times resulting in very large regurgitant orifices. Inspiration may induce severe malcoaptation of the TV leaflets in patients with severe TR, thereby resulting in near-equalization of pressures between the RV and RA and eventually lowering of the RV–RA pressure gradient. Notably, in this setting of severe malcoaptation of the valve leaflets, the clinical validity of the Bernoulli equation in assessing pulmonary artery pressure is questionable.

The following study limitations should be acknowledged. First, our study was conducted retrospectively, using a prospectively collected computerized database. Based on our inclusion criteria (adequate Doppler strips for analysis), only a subgroup of patients with TR could be included in this analysis. Thus, the results of our study need to be confirmed prospectively in consecutive unselected patients with TR. Secondly, TR severity and the right heart chambers were assessed qualitatively, without the use of quantitative methods. Nevertheless, this scenario simulates the routine clinical practice in our echocardiography laboratory, as well as in many other laboratories, and suggests that the respiratory variation in TR velocities can be used clinically as a sign of severe TR. Thirdly, we did not routinely use respiratory monitoring to validate the timing of the TR Doppler signals in the respiratory cycle. However, unless constrictive pericarditis is present, TR velocities are not expected to rise during inspiration and it can be safely assumed that the higher and lower TR velocities occur during expiration and inspiration, respectively. The representative example in Figure 1 confirms our assumption. Finally, our study population was limited to patients with a regular heart rhythm, since an irregular heart rhythm may affect TR velocities. Nevertheless, based on our limited experience, it is occasionally possible to appreciate the respiratory variation in TR velocities even in patients with atrial fibrillation, using long Doppler strips with restriction of the analysis to Doppler recordings with a relatively regular heart rhythm.

In summary, excessive respiratory changes in TR velocities are common in patients with severe TR, usually very severe TR. This Doppler sign can be used to support the diagnosis of severe TR. Furthermore, this sign may occasionally be the first hint for the presence of severe TR, when the classic signs of TR are not obvious (e.g. eccentric TR jets, technically difficult imaging). Additional studies are warranted to examine our observation prospectively in less selected patient populations.

Conflict of interest: None declared.

References