Valvular Heart Disease

Pathophysiology of Tricuspid Regurgitation
Quantitative Doppler Echocardiographic Assessment of Respiratory Dependence

Yan Topilsky, MD; Christophe Tribouilloy, MD; Hector I. Michlelena, MD; Sorin Pislaru, MD; Douglas W. Mahoney, MS; Maurice Enriquez-Sarano, MD

Background—Respiratory dependence of tricuspid regurgitation (TR), a long-held concept suggested by murmur variation, remains unproven and of unclear mechanisms.

Methods and Results—In 41 patients with mild or greater TR (median age, 67 years), we performed triple Doppler echocardiographic quantification (TR severity, right ventricular, and right atrial quantification) with simultaneous respirometer recording of respiratory phases. Expiration to inspiration changes (median) affected TR peak velocity (−40 cm/s; 25th to 75th percentile, −60 to −30 cm/s), duration (−12 milliseconds; 25th to 75th percentile, −45 to 2 milliseconds), and time-velocity integral (−17 cm; 25th to 75th percentile, −23.4 to −10 cm; all P<0.001), consistent with decreased TR driving force. Nevertheless, inspiratory TR augmentation was demonstrated by increased effective regurgitant orifice (0.21 cm²; 25th to 75th percentile, 0.09 to 0.34 cm²) and volume (18 mL per beat; 25th to 75th percentile, 10 to 25 mL per beat; all P<0.001) infrequently detected clinically (2 of 41, 5%). As a result of reduced TR driving force, regurgitant volume increased less than effective regurgitant orifice (120% [25th to 75th percentile, 78.6% to 169%] versus 169% [25th to 75th percentile, 12.9% to 226.1%]; P<0.001). During inspiration, right ventricular area increased (diastolic, 27.8 [25th to 75th percentile, 22.6 to 36.3] versus 26.5 [21.1 to 31.9]; P<0.0001) with widening of right ventricular shape (length-to-width ratio, 1.6 [25th to 75th percentile, 1.37 to 1.95] versus 1.7 [1.46 to 2.1]; P<0.0001), increased systolic annular diameter (P=0.003), valve tenting height (P<0.0001) and area (P<0.0001), and reduced valvular-to-annular ratio (P=0.006). Effective regurgitant orifice during inspiration was independently determined by inspiratory valvular-to-annular ratio (P=0.026) and inspiratory change in right ventricular length-to-width ratio (P=0.008) and valve tenting area (P=0.015).

Conclusions—TR is dynamic with almost universal respiratory changes of large magnitude and complex pathophysiology. During inspiration, a large increase in effective regurgitant orifice causes, despite a decline in regurgitant gradient, a notable increase in regurgitant volume. Effective regurgitant orifice changes are independently linked to inspiratory annular enlargement (decreased valvular coverage) and to inspiratory right ventricular shape widening with increased valvular tenting. These novel physiological insights into TR respiratory dependence underscore right-side heart plasticity and are important for clinical TR severity evaluation. (Circulation. 2010;122:1505-1513.)

Key Words: echocardiography ▪ regurgitation ▪ surgery ▪ valves function

Tricuspid regurgitation (TR) is a common condition, but it is poorly understood with regard to physiology and outcome.1 The sketchy pathophysiological knowledge of TR2 emphasized in American Heart Association clinical guidelines3 and in comprehensive reviews4 probably contributes to current uncertainties about TR management and outcome.5

Clinical Perspective on p 1513

Among TR pathophysiological characteristics, a widely accepted fact is the old description of clinical observation of respiratory variation of the TR systolic murmur.6 However, mechanistically, such variations have received little explanation, and potential clinical implications are unknown. These uncertainties stem in great part from the challenging assessment of TR severity, well known for invasive methods,7 but also remaining often imprecise for Doppler echocardiography, as underscored by the current guidelines.8 Quantitative methods of TR assessment have been validated9–12 and offer the opportunity to obtain physiological insights,12 but these methods remain inconsistently used.

Another source of confusion is the variety of potential theories on respiratory TR variations that are based on scant facts. TR systolic murmur respiratory variation has been variably assumed to arise from preload-determined right
ventricular (RV) contractility changes causing changes in TR turbulence\textsuperscript{13,14} or from possible changes in TR velocity or ventriculoatrial pressure gradient, counterintuitive to observed gradient respiratory changes.\textsuperscript{15–17} An alternative hypothesis of TR murmur changes based on respiratory TR severity changes is doubted because patients with tricuspid valvulectomy, who obviously have very severe TR, are not reported to have respiratory TR murmur variation.\textsuperscript{18} Hence, TR physiological characteristics and the presence and magnitude of respiratory TR changes remain uncertain. These gaps in knowledge affect not only TR physiological comprehension but also clinical evaluation and assessment of its impact on outcome and management.\textsuperscript{3}

Thus, we performed a prospective and comprehensive study of TR physiology with the hypothesis that TR displays physiological variations during respiration that are due to a change in TR effective regurgitant orifice (ERO). Consequently, we conducted a triple quantitative study involving TR quantification, quantification of RV and right atrial (RA) characteristics, and quantification of tricuspid valvular deformation with combined respirometer to assess changes during the respiratory cycle to assess pathophysiological changes in TR with respiration.

**Methods**

**Patient Population**

We prospectively and consecutively enrolled 41 patients with variable degrees (mild to severe) of TR in this study of TR pathophysiology. The inclusion criteria for the present study were (1) the presence of TR by color-flow Doppler imaging of at least mild degree and holosystolic; (2) comprehensive quantitative Doppler echocardiography (as detailed in the section on echocardiographic methods), (3) simultaneous recording of all Doppler echocardiographic imaging with respirometer tracing to determine the respiratory phase of each measurement, and (4) regular cardiac rhythm. Exclusion criteria were absent or trivial TR, poor-quality flow convergence or flow convergence that was impossible to image proximal to the TR, and irregular rhythm caused by atrial fibrillation or flutter. The study was powered to detect at least a 30\% change with respiration in one of the variables measuring TR with at least 80\% power (\(P<0.05\)). Clinically, patients had measurement of heart rate and blood pressure and standard clinical assessment by senior cardiologists with at least 10 years of postfellowship experience. Specifically for TR, we noted by careful detailed cardiac examination if there was a murmur consistent with TR (holosystolic and maximally projected at the xiphoid or lower left sternum), if the murmur increased with inspiration in the recumbent and sitting positions, and if there were signs of right-side heart failure (jugular venous distension and liver enlargement with hepatopulmonary reflux).

**Doppler Echocardiography**

All patients had a complete 2-dimensional and Doppler echocardiographic study using multiple windows during the same examination. All echocardiographic examinations were performed with a respirometer for precise timing of respiratory cycles. Patients were instructed to breathe normally. All measurements of TR were determined in midsystole during inspiration and expiration.

The mean of systolic pulmonary pressure was estimated using the mean of peak systolic TR velocity in inspiration and expiration.\textsuperscript{19} RA pressure was estimated by the inferior vena cava diameter and its response to inspiration as previously described.\textsuperscript{20}

From 2-dimensional echocardiographic 4-chamber views allowing complete imaging of the cavities examined, the following morphological measurements were performed with inspiration and expiration: (1) RV end-systolic and end-diastolic areas, RV length, and midventricular RV width with calculation of RV area shortening fraction and RV length-to-width ratio; (2) tricuspid annulus systolic and diastolic diameters with shortening fraction calculation; (3) RA end-systolic area and length measured by calculation of RA volume with the area-length method; and (4) tricuspid valve tenting area (between the annular line and leaflet contour) and tenting height. The length of tricuspid leaflets (sum of the septal and anterior leaflet) was measured, and the ratio to systolic annulus diameter was calculated.

Assessment of TR degree and its changes between inspiration and expiration used color-flow imaging and quantitative measures.\textsuperscript{8} TR jet area was measured by color Doppler with a sector allowing visualization of the entire RA. The images were reviewed frame by frame, and planimetry of the maximal area of the regurgitant jet was performed. The ratio of the maximal jet area to the RA area measured on the same image was also calculated. The width of the vena contracta was measured with inspiration and expiration.\textsuperscript{9,21} TR quantification relied on the proximal flow convergence (proximal isovelocity surface area) method as validated previously\textsuperscript{22–24} and was performed with all measurements done during inspiration and expiration and using multiple (at least 3) measurements of each variable during each respiratory phase. Practically, color Doppler images of the proximal flow convergence of TR were obtained from apical or para-apical views after maximal depth reduction and zoom of the region of interest. The transducer was positioned to minimize the angle between the centerline of regurgitant flow and the ultrasonic beam. The color-flow velocity scale was maximized, and the baseline was shifted downward until the flow convergence region was clearly visualized. The aliasing velocities selected ranged from 21 to 43 cm/s. Radial distance between the first aliasing velocity (red/blue interface) and the center of the tricuspid orifice was measured along the centerline of the flow convergence region in midsystole during inspiration and expiration. Corrections for the angle of leaflets and for the ratio of aliasing velocity to peak TR velocity were applied as previously validated,\textsuperscript{10,12–14} allowing calculation of regurgitant flow. The ERO area was then calculated as the ratio of regurgitant flow to the peak velocity of the TR jet (by continuous-wave-Doppler), and the regurgitant volume (RVol) was calculated as the product of ERO by the regurgitant time-velocity integral of the TR.\textsuperscript{10} An example of the proximal isovelocity surface area measurement during inspiration and expiration is presented in Figure 1.

**Statistical Analysis**

Descriptive results were expressed as median and 25th to 75th percentile for continuous variables and as percentages for categorical variables. The distribution of continuous variables is depicted in figures through box-and-whisker plots. Comparison between groups used standard Wilcoxon rank-sums test for continuous variables and the \(\chi^2\) test for categorical variables. The changes for each variable between inspiration and expiration were analyzed by use of the signed Wilcoxon rank-sums test. The differences between inspiratory and expiratory measurements were presented as absolute values and as percent change from expiration to inspiration. Comparison of the magnitude of inspiratory changes between subgroups relied on the Wilcoxon rank-sums test. The subgroups examined were those with versus those without pulmonary hypertension (based on mean systolic pulmonary pressure \(\geq 50\) mm Hg), and those with organic versus functional tricuspid valve disease (based on the presence or absence of intrinsic tricuspid valve lesions). Multiple linear regression was used to define correlates of inspiratory ERO (adjusting for expiratory ERO). Statistical significance was set at \(P<0.05\).

**Results**

The study included 41 patients (age, 67 years [25th to 75th percentile, 57 to 74 years]; 13 men and 28 women) with TR fulfilling the eligibility criteria. Thirty-five patients were in normal sinus rhythm, and 6 had regular paced rhythm. TR was of organic cause in 8 patients (2 rheumatic, 2 prolapse, 1
endocarditis, 2 carcinoid, and 1 congenital) and functional in 33. Calculated systolic pulmonary artery pressure was 55 mm Hg (25th to 75th percentile, 40.5 to 75.5 mm Hg), and pulmonary hypertension with systolic pulmonary artery pressure ≥50 mm Hg was noted in 26 patients. Moderate or severe TR, with ERO ≥0.20 cm², was observed in 24 patients. The baseline characteristics of the overall population and of patients with and without moderate to severe TR are reported in Table 1. Of note, few patients had a murmur suggestive of TR, and even fewer had inspiratory increase or appearance of the systolic murmur by clinical examination.

Table 1. Baseline Characteristics of Patients With TR Overall and Stratified by Severity of Regurgitation

<table>
<thead>
<tr>
<th>Variables</th>
<th>Entire Sample (n=41)</th>
<th>ERO &lt;0.2 cm² (n=17)</th>
<th>ERO ≥0.2 cm² (n=24)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (y)</td>
<td>67 (57–74)</td>
<td>65.5 (51–70)</td>
<td>68 (57–78)</td>
<td>0.17</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>32</td>
<td>29</td>
<td>39</td>
<td>0.53</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>129 (119,150)</td>
<td>128 (120,142)</td>
<td>130 (114–151)</td>
<td>0.82</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>78 (70–88)</td>
<td>80 (72–86)</td>
<td>77 (70–89)</td>
<td>0.68</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>76 (61–85)</td>
<td>71 (60–81)</td>
<td>79 (62–88)</td>
<td>0.1</td>
</tr>
<tr>
<td>Systolic murmur of TR, %</td>
<td>20</td>
<td>12</td>
<td>25</td>
<td>0.43</td>
</tr>
<tr>
<td>Inspiratory increase of murmur, %</td>
<td>5</td>
<td>0</td>
<td>8</td>
<td>0.50</td>
</tr>
<tr>
<td>Right heart failure, %</td>
<td>20</td>
<td>12</td>
<td>25</td>
<td>0.43</td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>65 (45–78)</td>
<td>74 (49–84)</td>
<td>54 (44–69)</td>
<td>0.056</td>
</tr>
<tr>
<td>Cardiac index, L/m²</td>
<td>2.5 (1.9–3.1)</td>
<td>2.6 (2.2–3.5)</td>
<td>2.35 (1.7–3.0)</td>
<td>0.15</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>60 (47.5–65)</td>
<td>60 (57–62.7)</td>
<td>55 (27–65)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; and LV, left ventricular. Data are presented as median (25th to 75th percentile) for continuous variables or as percentages for categorical variables.
Overall Respiratory Changes
Changes in TR driving forces and severity with respiration are reported in Table 2. An example of the measurement of TR regurgitant flow, peak velocity, and ERO in inspiration and expiration is shown in Figure 1. With inspiration, there is a notable decline in the driving force to TR whether it is expressed as peak TR velocity (from expiration), peak TR gradient (from expiration), or regurgitant time-velocity integral (from expiration). ERO also increased but less in percentage than the ERO (120% [25th to 75th percentile, 78.6% to 169%] versus 169% [25th to 75th percentile, 129% to 226%]; P<0.001) as a result of the decline in the regurgitant time-velocity integral (the entire systolic integrated driving force) for TR. Contrasting with these considerable changes in ERO and RVol, the maximum TR jet in the RA and its ratio to RA area showed no significant increase. Color-flow imaging jet extent lack of sensitivity for TR severity changes could be palliated by measuring the vena contracta width of TR, which demonstrated a significant increase with inspiration. All changes were observed coherently in the vast majority of patients, as shown by Figure 2, which presents TR variations in individual patients. Percent changes of major measures of TR are presented graphically in Figure 3.

Morphological measurements of RV, RA, tricuspid valve, and tricuspid annulus are presented in Table 3. RV systolic and diastolic areas increased during inspiration (both P<0.01), but the RV area shortening showed no change with

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### Table 2. Variations of TR With Respiration

<table>
<thead>
<tr>
<th>Variable</th>
<th>Expiration</th>
<th>Inspiration</th>
<th>Change With Inspiration</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TR peak velocity, cm/s</td>
<td>336 (286–406)</td>
<td>290 (222–371)</td>
<td>−40 (−30–−60)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TR TVI, cm</td>
<td>107 (88–140)</td>
<td>88 (66–125)</td>
<td>−17 (−10–−23)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TR peak gradient, mm Hg</td>
<td>45 (33–66)</td>
<td>34 (20–55)</td>
<td>−11 (−6–−15)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TR duration, ms</td>
<td>407 (373–446)</td>
<td>396 (338–442)</td>
<td>−12 (−45–2)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>TR flow convergence radius, cm</td>
<td>0.55 (0.4–0.74)</td>
<td>0.80 (0.6–1.04)</td>
<td>0.25 (0.2–0.37)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Regurgitant flow, mL/s</td>
<td>47 (23.5–79.5)</td>
<td>104 (56.5–179.5)</td>
<td>64 (30–112)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>ERO, cm²</td>
<td>0.13 (0.05–0.24)</td>
<td>0.36 (0.16–0.63)</td>
<td>0.22 (0.09–0.37)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>RVol, mL per beat</td>
<td>15 (5.5–24)</td>
<td>33 (19.5–47.5)</td>
<td>18 (11–25)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Jet area, cm²</td>
<td>4.9 (3–8.6)</td>
<td>4.9 (3.2–9.8)</td>
<td>0 (−0.5–0.8)</td>
<td>0.58</td>
</tr>
<tr>
<td>Jet/atrial ratio, %</td>
<td>20.1 (12.3–36.6)</td>
<td>21.6 (12.6–36)</td>
<td>0 (−1.6–3.2)</td>
<td>0.49</td>
</tr>
<tr>
<td>TR vena contracta width, mm</td>
<td>5 (3–8.4)</td>
<td>5.1 (3.2–8.6)</td>
<td>0.15 (0–0.63)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

TVI indicates time-velocity integral. Data are presented as median (25th to 75th percentile).

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Figure 2. Individual patient changes in TR hemodynamic characteristics with respiration. Each patient is represented by an individual line symbolizing the change from expiration (E) to inspiration (I). Top left, ERO (cm²); bottom left, peak TR velocity (Vmax; cm/s); top right, TR duration (seconds); and bottom right, regurgitant (Reg) volume (mL per beat). All changes are significant and affect most individual patients.
Inspiration. However, there were important RV changes with inspiration. Indeed, with inspiration, the RV “stroke area” (ie, the difference between the diastolic and systolic areas) increased, consistent with increased stroke volume. The RV shape also changed, with RV length showing very little increase (P < 0.055) and the RV width increasing markedly so that the length-to-width ratio decreased significantly, denoting a marked widening of RV with inspiration. Conversely, RA volume did not change notably. Important changes were seen at the valvular level. The tricuspid annulus diameter increased with inspiration in both systole and diastole (both P < 0.01). Thus, with inspiration, there was a significant decrease in the coverage ratio of the annulus by the combined anterior and septal leaflet length (P = 0.006). Furthermore, the tenting height and tenting area of the tricuspid valve in systole increased notably (Figure 3), further reducing the ability of leaflet to coapt in systole.

In multivariable analysis (multiple linear regression), inspiratory ERO adjusted for expiratory ERO was independently associated with valvular-to-annular length ratio with inspiration (P = 0.026) and by the inspiratory changes in RV length-to-width ratio (P = 0.008) and tricuspid valve tenting area (P = 0.015).

### Subgroup Analysis of TR Respiratory Changes

When patients were stratified according to TR severity (ERO ≥ 0.20 or < 0.20 cm²), there was no difference relative to

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**Table 3. Change in Right-Side Cardiac Cavities and Tricuspid Valvular Morphology With Respiration**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Expiration</th>
<th>Inspiration</th>
<th>Change With Inspiration</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV diastolic area, cm²</td>
<td>26.5 (21.1–31.9)</td>
<td>27.8 (22.6–36.3)</td>
<td>2.1 (0.1–3.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RV systolic area, cm²</td>
<td>16 (12.9–26.4)</td>
<td>16.9 (13.1–27.4)</td>
<td>0.8 (0.1–1.8)</td>
<td>0.003</td>
</tr>
<tr>
<td>RV area shortening fraction, %</td>
<td>33.4 (17.8–47.5)</td>
<td>33.4 (20.8–49.7)</td>
<td>0.9 (–4–5)</td>
<td>0.37</td>
</tr>
<tr>
<td>RV diastolic length, cm</td>
<td>6.9 (6.5–7.7)</td>
<td>6.9 (6.5–7.9)</td>
<td>0 (–0.02–0.31)</td>
<td>0.55</td>
</tr>
<tr>
<td>RV diastolic midventricular width, cm</td>
<td>4.1 (3.4–4.7)</td>
<td>4.5 (3.8–5.1)</td>
<td>0.41 (0.26–0.65)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RV diastolic length/width ratio</td>
<td>1.7 (1.46–2.1)</td>
<td>1.6 (1.37–1.95)</td>
<td>–0.15 (–0.04–0.24)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RA volume, mL</td>
<td>85.8 (52.7–132.3)</td>
<td>89 (51.7–128.5)</td>
<td>1.5 (–3–5)</td>
<td>0.36</td>
</tr>
<tr>
<td>Systolic annulus diameter, mm</td>
<td>2.9 (2.7–3.6)</td>
<td>3.1 (2.7–3.8)</td>
<td>0.1 (0–0.2)</td>
<td>0.003</td>
</tr>
<tr>
<td>Diastolic annulus diameter, mm</td>
<td>3.7 (3.4–4.3)</td>
<td>3.9 (3.5–4.4)</td>
<td>0.1 (0–0.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>Systolic valvular/annular coverage, %</td>
<td>104 (94–110)</td>
<td>100 (93–109)</td>
<td>–2 (1–7)</td>
<td>0.006</td>
</tr>
<tr>
<td>Tenting height, cm</td>
<td>0.7 (0.53–0.92)</td>
<td>0.92 (0.74–1.2)</td>
<td>0.2 (0.11–0.42)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Tenting area, cm²</td>
<td>1.1 (0.66–1.5)</td>
<td>1.4 (1.15–1.7)</td>
<td>0.29 (0.04–0.54)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Systolic valvular/annular coverage is the ratio of the sum of the length of septal and anterior leaflets to the systolic annulus diameter. Data are presented as median (25th to 75th percentile).
inspiratory change in TR peak velocity ($P=0.24$) or time-velocity integral ($P=0.33$) between groups. There was a trend for a larger decline in TR duration ($P=0.07$) and a definitely larger increase in ERO (0.24 to 0.66 cm$^2$ [25th to 75th percentile, 0.06 to 0.13 cm$^2$]; $P<0.0001$) in patients with mean ERO ≥0.20 cm$^2$. However, expressed in relative terms, the percent change in ERO was similar (156% [25th to 75th percentile, 129% to 185%]; $P=0.30$) in both groups (ERO ≥0.20 or <0.20 cm$^2$). Thus, with inspiration, a relatively fixed proportional increase in ERO is observed regardless of TR severity. Relative changes in TR peak velocity, duration, ERO, and RVol are stratified by TR pathogenesis (organic versus functional TR; top row) and by pulmonary hypertension (systolic pulmonary artery pressure ≥50 vs ≤50 mm Hg; bottom row) in Figure 4. There was no difference in any inspiratory change according to pathogenesis of TR. With pulmonary hypertension, there was a smaller change in TR peak velocity, but the ERO change with inspiration was identical to that without pulmonary hypertension. Thus, the relative change in ERO with inspiration was similar regardless of the severity, pathogenesis, or association of pulmonary hypertension with TR.

Discussion

The present study, the first to analyze quantitatively the pathophysiology of TR changes with respiration, reveals new insights into TR physiological characteristics based on instantaneous proximal isovelocity surface area quantification of TR severity during respiration phases timed by simultaneous respirometer recording. Indeed, inspiratory TR accentuation is not just an auscultatory phenomenon but also involves an increase in volumetric TR severity. However, although TR ERO accentuation is almost universal, it is infrequently audible clinically and is undetected by color jet extent. Inspiratory TR variations are complex, with TR driving force (RV-RA gradient) and TR duration declining with inspiration, which is more than compensated for by a large ERO increase. These changes in opposite directions compound the inspiratory RVol increase, less impressive than the ERO increase, but more than doubling the TR volume on average. ERO magnitude of change is higher in those with large expiratory ERO, but expressed as percent change, the inspiratory ERO increase is similar across categories of TR severity, pathogenesis, or pulmonary hypertension. Mechanistically, we observed marked RV (not RA) plasticity with inspiratory changes in size and shape, particularly RV widening. RV widening is associated with valvular changes and inspiratory annular enlargement, leading to less systolic annular coverage by tricuspid leaflets and increased valvular tenting, both of which contribute to coaptation loss. These new observations have important clinical implications. The association with loading changes of marked RV plasticity and TR variations suggests that clinically optimization of loading conditions may have beneficial effects on TR severity. Other implications regard TR evaluation, which can be difficult because jet size changes do not clearly reveal even marked changes in TR severity, and measurement of vena contracta width is more sensitive. Additionally, because large TR variations can be observed over the respiratory cycle, it is essential that we do not rely on a single TR measurement but on multiple measurements averaged over the respiratory cycle. These concepts applied in clinical practice should enhance comprehension of this “forgotten valve” pathophysiology and clinical management.4

Respiratory Dependence of TR

A classic feature of TR is respiratory variation of systolic murmur,6 described decades ago but still poorly understood.13 TR pathophysiology remains elusive,4 in part because of the
lack of adequate methods to measure all specific components of the condition. However, Doppler echocardiographic progress now allows us to instantaneously measure TR regurgitant gradient, duration, and regurgitant flow. Although it is well established that venous return to the heart increases with inspiration, hypotheses about TR murmur variation range from increased turbulence to increased gradient to increased regurgitant flow. In TR, as in all regurgitations, RVol depends on regurgitant flow and duration. In turn, regurgitant flow is determined directly by the ERO area through which it is forced by the systolic RV-RA pressure gradient. The present study shows that TR is undeniably dynamic with respiration, demonstrating increased RVol during inspiration. Clinically, auscultatory changes are infrequent whereas TR almost universally increases in volume during inspiration. Inspiratory increase in RVol is not due to increased TR pressure gradient or duration but to inspiratory ERO increase. In fact, the RV-RA gradient decreases with inspiration, probably owing to decreased pulmonary vascular resistance with decreased intrathoracic pressure. An alternative explanation for decreased TR velocity with inspiration would be a "ventricularization" of atrial pressure during inspiration secondary to increased TR. Previous reports mentioning increased TR velocity during inspiration pondered that it may affect patients with pulmonary hypertension, but we observed inspiratory decline in TR velocity with and without pulmonary hypertension. Regardless, because of the decline in TR gradient and duration, inspiratory RVol augmentation is of lesser magnitude than ERO. This complex counterbalancing of TR components may explain the lack of TR inspiratory color-flow jet increase. Indeed, color-flow jet extent is determined by its momentum and complex interaction with the receiving chamber. Jet momentum is proportional to regurgitant flow and velocity, and with inspiration, the TR flow increase is compensated for by a TR velocity decrease, so the jet extent and jet RA-to-area ratio do not significantly change. Conversely, vena contracta width, directly related to TR severity, shows a definite increase during inspiration coherently to ERO and RVol. Thus, TR dynamic nature may be missed by casual examination of color-flow imaging and requires comprehensive quantitative assessment. Importantly, TR dynamic changes are similar in percentage across ranges of TR severity, pathogenesis, and pulmonary hypertension.

Morphological Alterations Associated With TR Changes

Detailed information on the annular-valvular complex and RV by comprehensive high-resolution prospectively recorded multiview 2-dimensional imaging with simultaneous respirometry sheds unique light on RV and TR pathophysiology. With inspiration, the RV enlarges with increased stroke volume, in contrast to the unchanged RA. End-systolic RV size increases and the RV becomes wider without elongation. Such changes affect the tricuspid valve through 2 mechanistic pathways. First, an enlarged systolic annulus accompanies the larger RV, leading to decreased valve coverage of the annulus. Second, RV enlargement and widening centrifugally displace RV walls and tricuspid papillary muscles attached to each wall away from the tricuspid valve, causing increased tethering and tenting height and area, which, similar to functional mitral regurgitation, yield decreased leaflet coaptation. These annular and valvular mechanisms of decreased coaptation independently determine larger ERO with inspiration. Thus, respiratory changes provide unique insights into the plasticity of the right-side ventriculo-valvular complex, particularly the RV, that may have important clinical implications.

Clinical Implications

For TR assessment, clinical appraisal is infrequently typical, even to experienced cardiologists, and suspicion of significant TR should be verified by Doppler echocardiography. Comprehensive TR grading is recommended by guidelines, but in clinical practice, color flow is often the main method of assessing TR. Because jet assessment is insensitive to changes in TR severity, we believe that focusing on measuring the vena contracta and/or quantifying the TR should be preferred. The dynamic nature of regurgitation should not contraindicate quantitative methods, but measurement should be cognizant of large respiratory TR variations, avoiding measurement of largest values and instead obtaining measurements covering the entire respiratory cycle. In addition, a large RV pressure inspiratory decrease suggests that measuring only the highest velocities (in expiration) may overestimate pulmonary hypertension. Thus, for all measurements relative to TR, it is essential to account for both phases of the respiratory cycle.

Marked plasticity of the right-side ventriculo-valvular complex leads to marked inspiratory TR accentuation. Such plasticity may explain the load sensitivity of TR, which may rapidly regress with medical treatment. Although aggressive surgical TR management has been advocated, optimizing RV unloading before proceeding with TR surgery may be desirable.

Limitations

The study was powered to detect notable respiratory TR changes and did not aim to define all issues relative to TR, especially outcome, which will require further longitudinal studies. We observed no trend of difference between TR pathogeneses, but specific pathophysiology of each TR cause should be established by future studies now that these important pathophysiological insights have been clarified.

To instantaneously quantify TR completely, one should measure color-flow convergence and continuous-wave Doppler simultaneously. Such technology does not exist, so we performed optimally each measurement timed to the cardiac and respiratory cycle with the patient in a steady state and stable position. Future developments of 3-dimensional ultrasound technology may provide comprehensive imaging tools and quantitative software that are currently unavailable. It is important that physiological concepts revealed by current technology be incorporated into practice.

Conclusions

The present quantitative physiological study shows that inspiratory accentuation of TR severity is almost universal
but clinically infrequently audible. Respiratory variations of TR characteristics are complex, with decreased TR driving force and duration with inspiration that are more than compensated for by a large ERO increase, compounds the marked inspiratory RVol increase. Mechanistically, we observed marked RV plasticity with striking inspiratory widening. Inspiratory valvular changes and annular enlargement leading to less systolic annular coverage by tricuspid leaflets and increased valvular tenting contribute to coaptation loss. These new observations have important clinical implications for TR severity assessment in clinical practice that should be comprehensive throughout the respiratory cycle but also for RV plasticity associated with large TR severity variations. These concepts should enhance TR pathophysiological comprehension and clinical management.4

Disclosures

Dr Enriquez-Sarano is a consultant for Valtec Inc, Tel Aviv, Israel. The other authors report no conflicts.

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Tricuspid regurgitation (TR) is present in most humans in variable degrees, but its pathophysiology is poorly understood. Previous clinical observations suggested that the murmur of TR may vary with respiration, but the reality, magnitude, pathophysiology, and clinical implications of this potential variation with respiration have not been investigated. However, progress in Doppler echocardiographic assessment of TR with instantaneous quantification of its degree and quantification of cardiac cavity changes, coupled with the ability to record the respiratory phases with a respirometer, allowed us to obtain unique insights into the pathophysiology of TR. Applying these methods, we first observed that TR is indeed markedly dynamic but with complex changes of opposite directions. Indeed, during inspiration, TR driving force and duration decrease, but because this decline is more than compensated for by a considerable increase in effective regurgitant orifice, TR volumetric severity increases with inspiration by >100%. The marked effective regurgitant orifice inspiratory increase is in turn due to reduced valve coverage of an enlarging annulus and increased valve tenting, resulting in reduced valve coaptation. These valve changes causing TR inspiratory augmentation are in turn linked to right ventricular shape changes with inspiratory right ventricular widening. These profound pathophysiological respiratory changes, poorly detected clinically, underscore the TR respiratory dependence linked to valve deformation and right ventricular plasticity. In practice, the major respiratory variation of TR requires multiplying measurements throughout the cardiac cycle to appropriately assess TR and right ventricular pressure.
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