The Hemodynamic Basis of Exercise Intolerance in Tricuspid Regurgitation

Mads J. Andersen, MD, PhD; Rick A. Nishimura, MD; Barry A. Borlaug, MD

Background—Patients with severe tricuspid regurgitation (TR) frequently present with exertional fatigue and dyspnea, but the hemodynamic basis for exercise limitation in people with TR remains unclear.

Methods and Results—Twelve subjects with normal left ventricular (LV) ejection fraction and grade ≥3 TR underwent high-fidelity invasive hemodynamic exercise testing with simultaneous expired gas analysis and were compared with 13 age- and sex-matched controls. At rest, TR subjects had lower pulmonary blood flow (3.6±0.4 vs 5.1±1.9 L/min; \( P = 0.01 \)), increased right atrial pressure (12±5 vs 4±1 mmHg; \( P = 0.0002 \)), and higher pulmonary capillary wedge pressure (17±5 vs 9±3 mmHg; \( P = 0.0001 \)). However, LV transmural pressure (pulmonary capillary wedge pressure−right atrial pressure), which reflects LV preload independent of right heart congestion and pericardial restraint, was similar in TR and controls (6±3 vs 4±2 mmHg; \( P = 0.3 \)). With exercise, TR subjects displayed lower peak \( V_O_2 \) (10.3±2.8 vs 13.8±4.2 mL/min per kg; \( P = 0.02 \)), lower pulmonary blood flow (6.4±1.3 vs 10.3±3.3 L/min; \( P = 0.001 \)), and less increase in pulmonary blood flow relative to \( V_O_2 \) (+4.6±1.1 vs +6.2±0.7; \( P = 0.001 \)). TR subjects displayed higher pulmonary capillary wedge pressure with exercise, but this was solely because of RA hypertension (27±9 vs 8±3 mmHg; \( P < 0.0001 \)), because LV transmural pressure dropped with exercise in subjects with TR (−5±6 vs +3±3 mmHg; \( P = 0.0007 \)), suggesting inadequate LV diastolic filling, despite high pulmonary capillary wedge pressure.

Conclusions—Impaired exercise capacity in people with severe TR is related to low cardiac output reserve relative to metabolic needs, coupled with elevated systemic and pulmonary venous pressures. Left heart pressures are elevated with exercise in subjects with TR, despite low LV preload, secondary to enhanced ventricular interaction.

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Key Words: exercise | heart failure | hemodynamics
Methods

Consecutive patients with symptomatic grade 3 or 4 TR (exertional dyspnea and fatigue) and no significant left heart disease undergoing exercise hemodynamic catheterization at Mayo Clinic, Rochester, MN, from 2002 to 2014 were included. Patients with left ventricular (LV) dysfunction (ejection fraction [EF] <45%), significant left-sided valvular disease (>mild), significant pulmonary hypertension (>mild), pulmonary parenchymal disease, prior chest radiation, infiltrative cardiomyopathies, pericardial disease, and congenital heart disease were excluded. TR severity was graded by echocardiography in accordance with current guidelines. Control subjects frequency-matched by age, sex, and body size were referred for invasive exercise assessment for dyspnea but had no demonstrable cardiac pathology after thorough clinical evaluation and invasive hemodynamic assessment, including normal rest and exercise pulmonary artery (PA) pressures (rest <25 mm Hg) and normal pulmonary capillary wedge pressure (PCWP; rest <15 mm Hg; exercise <25 mm Hg).

Clinical data were abstracted from the medical charts. Two-dimensional and Doppler echocardiography was performed according to American Society of Echocardiography guidelines by experienced sonographers and cardiologists with grading of TR severity according to established criteria. Right ventricular (RV) length and diastolic diameters were measured at the base and mid-ventricle perpendicular to septum, and tricuspid annular dimension was measured in the apical 4-chamber view. RV function was assessed by systolic annular tissue velocity of the lateral tricuspid annulus (s′) and tricuspid annular plane systolic excursion. The study was approved by the Mayo Clinic institutional review board, and all subjects provided written informed consent for review of their medical records. There were no eligible participants who refused to provide consent.

Hemodynamic Assessment

Subjects were studied on chronic medication in the fasted state, after minimal sedation in the supine position as previously described. Right heart catheterization was performed using a 7F catheter through a 9F sheath via the internal jugular vein. Transducers were leveled and zeroed at the phlebostatic axis, measured by laser calipers. Pressures in the right atrium (RAP), PA, and PCWP positions were measured at end expiration, taking the average of 3 beats in sinus rhythm and ≥2 in atrial fibrillation (AF). RAP and PCWP were measured mid A wave for subjects in sinus rhythm and at mid C wave for subjects with AF. PCWP position was confirmed by fluoroscopy, characteristic pressure waveforms, and oximetry (saturation >94%). A 4F to 6F cannula was placed in the radial artery for continuous systemic arterial blood pressure recordings and sampling of arterial blood gases. Ventricular interdependence was defined by an increase in RV (or PA) systolic pressure during inspiration coupled with a decrease in systemic arterial pressure. Pressure tracings were recorded continuously throughout each study, digitized (240 Hz), and stored for offline analysis.

Oxygen consumption (VO2) was measured using breath-by-breath expired gas analysis (MedGraphics, St Paul, MN). Arterial–venous O2 difference (A-V O2 diff) was measured directly as the difference between systemic and PA O2 content (ABL80; Radiometer Medical, Brønshøj, Denmark). Pulmonary blood flow (Qp) was calculated using the direct Fick method (Qp=VO2/A-V O2 diff). Stroke volume was determined by Qp/heart rate. Pulmonary vascular resistance (IPAP–PCWP)/Qp), systemic vascular resistance (mean blood pressure–RAP)x80/Qp), and transpulmonary gradient (PA mean–PCWP) were determined using standard formulas. LV transmural pressure (LVTMP), which more accurately reflects LV preload independent of right heart filling and pericardial restraint, was calculated as PCWP–RAP. After baseline data were acquired, hemodynamic assessment and expired gas analysis were performed during supine cycle ergometry, starting at 20 W workload, increasing by 10 W increments in 3-minute stages to subject-reported exhaustion.

Statistical Analysis

Data are reported as means±SD for normally distributed variables. Unless specifically indicated, there was no missing data for any variables. Between-group differences were tested using a 2-sample independent t test, χ2, Fisher exact test, or Wilcoxon rank-sum test. Within-group differences were compared using a paired t test. Multivariable linear regression analysis was used to adjust for relevant baseline group differences in β-blocker use and the prevalence of AF. For non-normally distributed variables entered into regression models, the assumption of normally distributed residuals was verified by Quantile plots, and no violations were observed. All tests were 2-sided, and a P value <0.05 was considered significant. Statistical analyses were performed using JMP 10.0.0 (SAS Institute, Cary, NC).

Results

Patients with TR and age-, sex-, body size–matched controls were predominantly older women with history of systemic hypertension (Table 1). Subjects with TR were more likely to have AF and be treated with rate control medications such as β-blockers and diuretics. There was no statistically significant difference in the prevalence of other comorbidities. Patients with TR had higher N-terminal pro-brain natriuretic peptide and direct bilirubin levels compared with controls, whereas other laboratory variables did not differ significantly.

The majority of TR subjects had severe (grade 4) TR (83%), which was predominantly because of functional TR (92%). Patients with TR displayed larger RV and tricuspid annular dimensions and impaired RV function compared with controls (Table 1). LV size and function was similar in TR patients and controls.

Baseline Hemodynamics

Compared with controls, TR subjects had higher right and left heart filling pressures, with higher PA pressures and pulmonary vascular resistance (Table 2). RA tracings in TR patients showed prominent C–V waves, with ventricularized waveforms (absent×descent) in 60%, and a positive Kussmaul sign (increase or absent decrease in RAP with deep inspiration) in 73% (Table 2; Figure 1A). The majority (83%) of TR patients displayed enhanced ventricular interdependence at rest, whereas this finding was absent in controls. Although PCWP was higher in TR patients than controls, LVTMP was similar in the 2 groups. LV end-diastolic pressure (LVEDP) was measured in 6 TR subjects and was identical to PCWP at rest (15±5 versus 15±5 mm Hg; P=0.9). There were no significant group differences in resting heart rate, blood pressure, or resting VO2. Cardiac output, stroke volume, and mixed venous O2 content were significantly lower, whereas A-V O2 diff was higher in TR subjects compared with controls at rest (Table 2).

Exercise Hemodynamics

Compared with controls, exercise capacity was impaired in TR patients manifest as lower peak VO2 (Table 3; Figure 2). This was related to impaired cardiac output reserve in TR compared with controls, because of both lower stroke volume and heart rate. In contrast, patients with TR developed a higher peak A-V O2 diff with exercise. The increase in Qp relative to metabolic work performed was lower in TR compared with controls (4.6±1.1 versus 6.2±0.7 mL/min; P=0.001; Figure 3A), whereas the increase in A-V O2 diff relative to work
**Table 1. Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=13)</th>
<th>TR (n=12)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>72±7</td>
<td>76±5</td>
<td>0.12</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>9 (69)</td>
<td>8 (67)</td>
<td>0.99</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27±5</td>
<td>28±5</td>
<td>0.3</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.87±0.27</td>
<td>1.97±0.18</td>
<td>0.3</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>9 (69)</td>
<td>6 (50)</td>
<td>0.4</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>2 (15)</td>
<td>2 (17)</td>
<td>0.99</td>
</tr>
<tr>
<td>Coronary disease, n (%)</td>
<td>5 (38)</td>
<td>1 (8)</td>
<td>0.16</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>1 (8)</td>
<td>9 (75)</td>
<td>0.001</td>
</tr>
<tr>
<td>Previous valve surgery, n (%)</td>
<td>0 (0)</td>
<td>3 (25)</td>
<td>0.1</td>
</tr>
<tr>
<td>β-Blockers, n (%)</td>
<td>3 (23)</td>
<td>11 (92)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diuretics, n (%)</td>
<td>5 (38)</td>
<td>12 (100)</td>
<td>0.005</td>
</tr>
<tr>
<td>Laboratories</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>12.7±1.0</td>
<td>12.7±0.9</td>
<td>0.5</td>
</tr>
<tr>
<td>eGFR, ml/min per 1.73 m²</td>
<td>69±26</td>
<td>51±16</td>
<td>0.07</td>
</tr>
<tr>
<td>NT-proBNP, pg/mL</td>
<td>268 (51, 794)</td>
<td>1659 (975, 2118)</td>
<td>0.02</td>
</tr>
<tr>
<td>Bilirubin, direct, mg/dL</td>
<td>0.1 (0.1, 0.1)</td>
<td>0.3 (0.2, 0.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>Bilirubin, total, mg/dL</td>
<td>0.5 (0.4, 0.6)</td>
<td>0.8 (0.4, 0.9)</td>
<td>0.3</td>
</tr>
<tr>
<td>AST, U/L</td>
<td>24 (18, 33)</td>
<td>28 (25, 31)</td>
<td>0.3</td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>21 (18, 34)</td>
<td>27 (18, 32)</td>
<td>0.9</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>4.1 (3.6, 4.5)</td>
<td>3.8 (3.6, 4.4)</td>
<td>0.5</td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF, %, n=12/12</td>
<td>62±8</td>
<td>55±8</td>
<td>0.06</td>
</tr>
<tr>
<td>RVEDD, mm, n=12/12</td>
<td>28.0±6.3</td>
<td>37.4±8.1</td>
<td>0.0005</td>
</tr>
<tr>
<td>RVESD, mm, n=12/12</td>
<td>18.3±4.0</td>
<td>28.0±6.8</td>
<td>0.0005</td>
</tr>
<tr>
<td>LVEDD, mm, n=12/12</td>
<td>47.7±5.5</td>
<td>45.7±4.4</td>
<td>0.3</td>
</tr>
<tr>
<td>LVESD, mm, n=12/12</td>
<td>31.3±5.0</td>
<td>33±5.4</td>
<td>0.5</td>
</tr>
<tr>
<td>D-shaped LV, n, n=12/12</td>
<td>0 (0)</td>
<td>5 (42)</td>
<td>0.02</td>
</tr>
<tr>
<td>TAPSE, mm, n=9/6</td>
<td>24±6</td>
<td>18±3</td>
<td>0.04</td>
</tr>
<tr>
<td>TV annulus diameter, cm²</td>
<td>2.0±0.4</td>
<td>2.6±0.4</td>
<td>0.0009</td>
</tr>
<tr>
<td>n=12/12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TV s, cm/s, n=9/11</td>
<td>13±2</td>
<td>10±2</td>
<td>0.01</td>
</tr>
</tbody>
</table>

ALT indicates alanine transaminase; AST, aspartate transaminase; EDD, end-diastolic dimension; EF, ejection fraction; eGFR, estimated glomerular filtration rate; ESD, end-systolic dimension; LV, left ventricular; NT-proBNP, N-terminal pro-brain natriuretic peptide; RV, right ventricular; TAPSE, tricuspid annular peak systolic excursion; TR, tricuspid regurgitation; and TV, tricuspid valve.

**Table 2. Baseline Hemodynamics**

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=13)</th>
<th>TR (n=12)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats per min</td>
<td>66±13</td>
<td>70±9</td>
<td>0.2</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>145±25</td>
<td>123±29</td>
<td>0.05</td>
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<tr>
<td>Mean blood pressure, mm Hg</td>
<td>93±12</td>
<td>83±15</td>
<td>0.1</td>
</tr>
<tr>
<td>Central pressures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean RA pressure, mm Hg</td>
<td>4±1</td>
<td>12±5</td>
<td>0.0002</td>
</tr>
<tr>
<td>RA V wave, mm Hg</td>
<td>6±2</td>
<td>17±9</td>
<td>0.001</td>
</tr>
<tr>
<td>Kussmaul sign, n (%)</td>
<td>0 (0)</td>
<td>9 (75)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ventricularized RA tracing, n (%)</td>
<td>0</td>
<td>7 (58)</td>
<td>0.0007</td>
</tr>
<tr>
<td>Mean PCWP, mm Hg</td>
<td>9±3</td>
<td>17±5</td>
<td>0.0001</td>
</tr>
<tr>
<td>LVTMP, mm Hg</td>
<td>4±2</td>
<td>6±3</td>
<td>0.3</td>
</tr>
<tr>
<td>RA/PCWP ratio</td>
<td>0.5±0.2</td>
<td>0.7±0.2</td>
<td>0.02</td>
</tr>
<tr>
<td>PA systolic pressure, mm Hg</td>
<td>29±6</td>
<td>39±7</td>
<td>0.001</td>
</tr>
<tr>
<td>PA mean pressure, mm Hg</td>
<td>17±3</td>
<td>25±5</td>
<td>0.0001</td>
</tr>
<tr>
<td>Vascular function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transpulmonary gradient, mm Hg</td>
<td>8±4</td>
<td>8±3</td>
<td>0.9</td>
</tr>
<tr>
<td>PVR, Wood units</td>
<td>1.7±0.8</td>
<td>2.4±0.8</td>
<td>0.05</td>
</tr>
<tr>
<td>SVR, dynes/s×cm²</td>
<td>1551±516</td>
<td>1647±472</td>
<td>0.7</td>
</tr>
<tr>
<td>Integrated function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VO₂, ml/min</td>
<td>206±47</td>
<td>188±28</td>
<td>0.3</td>
</tr>
<tr>
<td>VO₂, ml/min per kg</td>
<td>2.7±0.5</td>
<td>2.4±0.6</td>
<td>0.09</td>
</tr>
<tr>
<td>Systemic O₂ content, ml/dl</td>
<td>16.5±1.5</td>
<td>16.1±1.2</td>
<td>0.8</td>
</tr>
<tr>
<td>Mixed venous O₂ content, ml/dl</td>
<td>12.4±1.3</td>
<td>10.9±1.0</td>
<td>0.005</td>
</tr>
<tr>
<td>A-V O₂ diff, ml/dl</td>
<td>4.2±1.0</td>
<td>5.2±0.8</td>
<td>0.007</td>
</tr>
<tr>
<td>Qp, L/min</td>
<td>5.1±1.9</td>
<td>3.6±0.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Stroke volume, ml</td>
<td>78±25</td>
<td>53±6</td>
<td>0.003</td>
</tr>
</tbody>
</table>

A-V O₂ indicates arterial–venous oxygen; LVTMP, left ventricular transmural pressure; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; Qp, pulmonary blood flow; RA, right atrial; SVR, systemic vascular resistance; and TR, tricuspid regurgitation.

Despite the elevation in PCWP, LVTMP decreased with exercise in TR patients to values lower than those observed in controls, suggesting reduced LV preload in TR subjects despite pulmonary venous hypertension (Figure 4). These differences persisted after adjusting for AF and β-blocker use. The ratio of RAP to PCWP was nearly 2-fold greater in TR compared with controls and approached unity (1.0±0.2 versus 0.6±0.2; P<0.0001), further suggesting increased diastolic ventricular interaction in TR. Pulmonary and systemic vascular resistances decreased with exercise to similar extent in both cases and controls (Table 3). All results were unchanged after repeating analyses using mean pressures averaged throughout the respiratory cycle in place of end-expiratory values (Table I in the Data Supplement).

**Discussion**

This is the first study to evaluate the hemodynamic mechanisms underlying exercise intolerance in patients with significant TR. Impaired exercise capacity in patients with TR was related to an inability to adequately increase cardiac output with stress in proportion to metabolic needs. Abnormal cardiac output reserve was coupled with marked increases in both right- and left-sided filling pressures during exercise. However, the increase in left heart pressures in TR patients appeared to be predominantly...
related to diastolic ventricular interaction, because LVTMP dropped with exercise, consistent with inadequate LV preload, despite pulmonary venous hypertension. Further study is required to determine whether interventions to correct isolated TR might improve cardiac output reserve and abrogate exercise-induced congestion in patients with symptomatic HF.

TR is a common lesion that often coexists with other cardiovascular diseases.1 This confounds determination of which hemodynamic derangements are specific to TR, as opposed to any comorbid left heart or pulmonary vascular disease. Indeed, in various circumstances, TR may act as a mediator, contributor, or even barometer of HF severity. To allow for more focussed insight into the specific hemodynamic effects of TR, we excluded subjects with significant left heart disease and pulmonary hypertension in the current study. Left heart filling pressures were elevated on average in TR patients. However, left heart filling pressures may be elevated even in the absence of left heart disease or increases in LV preload when there is increased right heart congestion and pericardial restraint, because of the phenomenon of diastolic ventricular interaction.16 Indeed, intracavitary LV pressure is equal to the sum of internal forces related to the effective LV distending pressure and external forces mediated across the interventricular septum and via the pericardium.17

The LV distending pressure is defined by LVTMP, the difference between internal cavitary pressure and external pericardial pressure. When RV and pericardial pressures are low, LVEDP (and PCWP) accurately reflects true LV preload (LV end-diastolic volume).17-19 However, when there is right heart overload and pericardial restraint, LVEDP and LV end-diastolic volume become uncoupled. This phenomenon is commonly observed in HF patients, wherein reduction in right-sided venous return may increase LV stroke work.18 This apparent violation of the Frank-Starling principal is explainable by LVTMP, which increases with right heart unloading because RAP decreases more than PCWP.17 In the current study, the opposite phenomenon was observed during exercise-related increases in venous return in TR. These findings are similar to prior observations in a canine model of pulmonary embolism, where acute saline loading decreased LV stroke work even as LVEDP increased—because LV end-diastolic volume was compromised by right heart distention.20 By accounting for the impact of external restraint, LVTMP more effectively measures the effective distending pressure that drives LV end-diastolic volume, as demonstrated in human studies evaluating patients with HF and healthy volunteers.18,21

Pericardial pressure is difficult to measure clinically but can be accurately estimated by RAP.14 In patients with isolated LV HF, LVTMP is elevated, in striking contrast to TR patients in the current study, who displayed similar LVTMP to controls. With exercise, PCWP increased further in TR patients, to levels observed in patients with HF and preserved EF (HFpEF),11,22 but in striking contrast to HFpEF patients, LVTMP significantly decreased in TR patients, suggesting low LV preload despite elevation in PCWP.16-18 This was likely caused by the combination of poor RV output (lower Qp) and acute right heart dilatation, although the latter possibility cannot be addressed in this study as echocardiography was not performed simultaneous with catheterization. Even as LVTMP was reduced, pulmonary venous pressure was elevated with exercise in TR patients, which likely contributes to symptoms of exertional dyspnea in this population.

Hansing and Rowe5 first demonstrated that right heart congestion in TR was associated with reduced cardiac output at rest, becoming lower as the regurgitation severity progressed from mild to severe. In the latter study, the

Figure 1. Typical right atrial (RA; red) and pulmonary capillary wedge pressure (PCWP; black) tracings in a patient with severe tricuspid regurgitation at rest (A) and with exercise (B) and in a control patient at respective states (C and D). Note the prominent C–V waves (ventricularized waveforms) and near-equalization of right and left heart pressures in the tricuspid regurgitation (TR) patient. During inspiration, there is no drop in RA pressure (RAP; Kussmaul sign) despite reduction in PCWP associated with the drop in intrathoracic pressure, such that the transmural pressure gradient becomes transiently negative. In the control patient, PCWP and RAP are normal at rest and with exercise, and PCWP consistently exceeds RAP.
presence and severity of TR was most strongly correlated
with the severity of pulmonary vascular disease. We confirm
and extend on the latter findings at rest in a TR population
where significant pulmonary hypertension and left heart dis-
ease was excluded.

The Qp impairment at rest identified by Hansing and Rowe\(^5\) has
been speculated to explain symptoms of fatigue with exercise
in people with TR,\(^{1,2}\) although this has never been directly shown.
Groves et al\(^7\) observed lower peak VO\(_2\) in patients with TR, which
they interpreted to represent a cardiac output limitation. However,
according to the Fick principle, VO\(_2\) is equal to the product of
cardiac output (Qp) and A-V O\(_2\) diff,\(^23\) and these individual com-
ponents were not measured in their study.\(^3\) Importantly, VO\(_2\) is
strongly associated with the intensity of work performed, thus the
observed impairment in VO\(_2\) in TR patients could be attributed to
either diminished Qp reserve or premature cessation of exercise
because of increased filling pressures or other factors.

To discern the role of Qp reserve limitation in determin-
ing aerobic limitation, both Qp and VO\(_2\) must be directly measured.\(^21,24\) In normal humans, each 1 mL/min increase in
VO\(_2\) is met with a 6 mL/min increase in Qp—defining the
adequacy of cardiac perfusion relative to metabolic require-
ments.\(^24\) Although this normal exercise factor was observed in
the control population of the current study (6.2±0.7 mL/
min), patients with TR displayed 35% lower increases in Qp
relative to VO\(_2\) (4.6±1.1; \(P=0.001\) versus control), indicat-
ing inadequate cardiac output reserve. To compensate for
inadequate perfusion, patients with TR relied more heavily
on O\(_2\) extraction (increased A-V O\(_2\) diff). This cardiac out-
put reserve limitation with exercise is similar to what was
observed in people with left-sided HF,\(^23,24\) but in contrast to
the latter myocardial disorders, the mechanical nature of the
lesion in TR suggests that it may be more amenable to inter-
vention. The presence of moderate or greater TR is associ-
ated with increased risk of death, independent of left heart
disease and pulmonary hypertension,\(^4\) and further studies are
warranted to determine whether surgical correction of TR
may correct the hemodynamic perturbations associated with
TR and allow for improved symptoms and survival.

The prevalence of moderate to severe TR increases strik-
ingly with age, to 5.6% among women aged >70 years in
population-based studies.\(^1\) Although the directional cau-
sality remains unclear, significant TR is clearly associated
with AF.\(^2,25\) TR causes RA enlargement because of pressure
and volume overload, increasing the risk of developing AF;
whereas AF may cause RA enlargement with tricuspid anul-
lar dilatation and secondary functional TR. Thus, a vicious

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### Table 3. Exercise Hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=13)</th>
<th>TR (n=12)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats per min</td>
<td>115±19(^*)</td>
<td>99±22(^*)</td>
<td>0.06</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>184±25(^*)</td>
<td>149±23(^*)</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean blood pressure, mm Hg</td>
<td>111±19(^*)</td>
<td>99±15(^*)</td>
<td>0.1</td>
</tr>
<tr>
<td>Central pressures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean RA pressure, mm Hg</td>
<td>8±3(^*)</td>
<td>27±9(^*)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RA V wave, mm Hg</td>
<td>11±4(^*)</td>
<td>38±12(^*)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Kussmaul sign, n (%)</td>
<td>0 (0)</td>
<td>10 (83)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ventricularized RA tracing, n (%)</td>
<td>0 (0)</td>
<td>10 (83)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean PCWP, mm Hg</td>
<td>16±4(^*)</td>
<td>27±8(^*)</td>
<td>0.0003</td>
</tr>
<tr>
<td>LVTPM, mm Hg</td>
<td>7±3(^*)</td>
<td>1±6(^*)</td>
<td>0.003</td>
</tr>
<tr>
<td>RA/PCWP ratio</td>
<td>0.6±0.2</td>
<td>1±0.02</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PA systolic pressure, mm Hg</td>
<td>45±8(^*)</td>
<td>61±13(^*)</td>
<td>0.002</td>
</tr>
<tr>
<td>PA mean, mm Hg</td>
<td>30±5(^*)</td>
<td>38±11(^*)</td>
<td>0.03</td>
</tr>
<tr>
<td>Vascular function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transpulmonary gradient, mm Hg</td>
<td>15±5(^*)</td>
<td>11±7</td>
<td>0.2</td>
</tr>
<tr>
<td>PVR, Wood units</td>
<td>1.5±0.6</td>
<td>1.8±1.1</td>
<td>0.4</td>
</tr>
<tr>
<td>SVR, dynes/s×cm(^5)</td>
<td>898±307(^*)</td>
<td>905±198(^*)</td>
<td>0.9</td>
</tr>
<tr>
<td>Integrated function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VO(_2), mL/min</td>
<td>1048±413(^*)</td>
<td>817±154(^*)</td>
<td>0.08</td>
</tr>
<tr>
<td>VO(_2), mL/min per kg</td>
<td>13.8±4.2(^*)</td>
<td>10.3±2.8(^*)</td>
<td>0.02</td>
</tr>
<tr>
<td>Systemic O(_2) content, mL/dL</td>
<td>17.4±1.4(^*)</td>
<td>17.2±1.6(^*)</td>
<td>0.7</td>
</tr>
<tr>
<td>Mixed venous O(_2) content, mL/dL</td>
<td>7.5±2.1(^*)</td>
<td>4.6±1.4(^*)</td>
<td>0.0006</td>
</tr>
<tr>
<td>A-V O(_2) diff, mL/dL</td>
<td>10.0±1.8(^*)</td>
<td>12.6±1.7(^*)</td>
<td>0.001</td>
</tr>
<tr>
<td>Qp, L/min</td>
<td>10.3±3.3(^*)</td>
<td>6.4±1.3(^*)</td>
<td>0.001</td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>90±29(^*)</td>
<td>66±12(^*)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

A-V O\(_2\) indicates arterial–venous oxygen; LVTPM, left ventricular transmural
pressure; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure;
PVR, pulmonary vascular resistance; Qp, pulmonary blood flow; RA, right atrial;
SVR, systemic vascular resistance; and TR, tricuspid regurgitation.

\(^{*}\)\(P<0.05\) vs baseline for within-group comparison; paired \(t\) test.
circle ensues wherein regurgitation begets fibrillation and vice versa. In the present study, the majority of TR subjects were older women with AF, and it is unclear if the current results can be generalized to people with TR in the absence of AF.

Ventricular interdependence is bidirectional, making it difficult to prove that pressure-volume changes in one side of the heart are altering properties of the other side, or vice versa. This raises the possibility that LV diastolic dysfunction (as in people with HFpEF) may also increase right heart pressures via interdependence. In the current study of TR patients, the fact that RA pressures increased much more with exercise compared with PCWP provides strong support for our interpretation that right heart overload is the driving problem. Indeed, this observation is in striking contrast to what is observed in HFpEF, where RA pressures increase by 0.4 mmHg for each 1 mmHg increase in PCWP.11 TR risk factors, including older age, female sex, and AF, are also prominent risk factors for HFpEF, which may present with identical symptoms. In these patients, careful assessment for hemodynamically significant TR is warranted, because the treatments may differ.

Limitations
Cases and controls were matched for age, sex, and body size, but TR subjects were more likely to be in AF and more likely to be treated with β-blockers, which may have influenced exercise capacity and hemodynamics. However, this would be unlikely to account for the dramatic differences in cardiac output reserve or the differences in right and left heart filling pressures and LVTMP with exercise. Additionally, the primary findings remained significant after adjusting for AF and β-blocker use. The sample was drawn from a catheter laboratory referral population, which may limit generalizability of these findings. The control population was not truly normal in that they had some prevalent medical comorbidities and by virtue of the fact that they were referred for invasive hemodynamic stress testing, although any abnormalities in the control subjects likely would bias our results toward the null. Participants were encouraged to exercise to maximal volition, but peak VO₂ obtained in the supine position with catheters in place is much lower than would be seen in the absence of instrumentation in the upright position, and it is likely that many of the patients did not achieve true objective maximal workload. Importantly, true maximal workload is not necessary to this analysis, because cardiac output responses were normalized to the amount of metabolic work performed, which is a major strength of this study. Echocardiography was not performed during exercise, precluding any analysis of acute changes in RV size and function as well as TR severity during exercise. Tricuspid annular measurements may underestimate the severity of RV dysfunction in patients with severe TR, thus the true differences in RV function between TR subjects and controls might have been underestimated.

Figure 3. A. Compared with controls (black solid line), tricuspid regurgitation (TR) patients (red dashed line) displayed less increase in cardiac output (Qp) despite greater increases in pulmonary capillary wedge pressure (PCWP; A) and right atrial pressure (RAP; B). However, effective left ventricular distending pressure (transmural pressure; LVTMP; C) decreased in TR compared with controls, indicating relative LV underfilling with stress despite high PCWP. Error bars reflect SEM. P values reflect differences between slopes of the 2 groups tested using 2-sample independent t test.
Conclusions
Impaired exercise capacity in patients with significant TR is caused by impaired cardiac output reserve relative to metabolic needs. This impairment in cardiac output reserve is coupled with a drop in effective LV distending pressures, despite the development of pulmonary venous hypertension, which may contribute to symptoms of dyspnea in addition to fatigue related to poor cardiac output reserve.

Disclosures
None.

References
9. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ; Chamber Quantification Writing Group; American Society of Echocardiography’s Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005;18:1440–1463.

CLINICAL PERSPECTIVE
Tricuspid regurgitation (TR) is a relatively common valvular lesion that is associated with increased morbidity and mortality. Patients with TR typically present with exertional dyspnea and fatigue, but the hemodynamic mechanisms underlying these symptoms remain unclear. In this study we performed invasive hemodynamic assessment at rest and during maximal effort exercise with simultaneous expired gas analysis. We demonstrate that TR patients have significant impairment in cardiac output during exercise relative to metabolic demand. This impairment in perfusion is coupled with abnormal increases in pulmonary capillary wedge pressure that is related to right heart congestion and diastolic ventricular interaction rather than a primary left heart lesion. These data provide greater insight into the hemodynamic basis for exercise intolerance in TR and emphasize the need to consider TR as a potential cause of exertional dyspnea in patients with normal left ventricular ejection fraction and high pulmonary capillary wedge pressure on activity. Further research is required to determine the optimal indications and timing of tricuspid valve surgery in patients with significant TR.
SUPPLEMENTAL MATERIAL

Supplemental Table 1: Pressure Data averaged over the entire respiratory cycle

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=13)</th>
<th>TR (n=12)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Resting Pressures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean RA pressure (mmHg)</td>
<td>4±1</td>
<td>12±6</td>
<td>0.0006</td>
</tr>
<tr>
<td>RA V wave (mmHg)</td>
<td>5±2</td>
<td>16±9</td>
<td>0.002</td>
</tr>
<tr>
<td>Mean PCWP (mmHg)</td>
<td>9±3</td>
<td>17±6</td>
<td>0.0005</td>
</tr>
<tr>
<td>LVTMP (mmHg)</td>
<td>4±2</td>
<td>5±4</td>
<td>0.6</td>
</tr>
<tr>
<td>PA mean pressure (mmHg)</td>
<td>18±3</td>
<td>25±6</td>
<td>0.001</td>
</tr>
<tr>
<td>PA systolic pressure (mmHg)</td>
<td>32±7</td>
<td>39±8</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Exercise Pressures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean RA pressure (mmHg)</td>
<td>8±5</td>
<td>24±9</td>
<td>0.0001</td>
</tr>
<tr>
<td>RA V wave (mmHg)</td>
<td>12±5</td>
<td>31±11</td>
<td>0.0001</td>
</tr>
<tr>
<td>Mean PCWP (mmHg)</td>
<td>15±4</td>
<td>25±8</td>
<td>0.001</td>
</tr>
<tr>
<td>LVTMP (mmHg)</td>
<td>6±6</td>
<td>1±7</td>
<td>0.09</td>
</tr>
<tr>
<td>ΔLVTMP (mmHg)</td>
<td>2±6</td>
<td>-4±6</td>
<td>0.04</td>
</tr>
<tr>
<td>PA mean pressure (mmHg)</td>
<td>29±5</td>
<td>40±8</td>
<td>0.0007</td>
</tr>
<tr>
<td>PA systolic pressure (mmHg)</td>
<td>45±7</td>
<td>55±13</td>
<td>0.03</td>
</tr>
</tbody>
</table>

RA, right atrial; PCWP, pulmonary capillary wedge pressure; LVTMP, left ventricular transmural filling pressure; PA, pulmonary arterial