Right ventricular (RV) dysfunction has been associated with worse prognosis in patients with heart failure and left ventricular (LV) systolic dysfunction.1–5 Cardiac resynchronization therapy reduces the risk of death and heart failure events in patients with heart failure, low ejection fraction, and a wide QRS,6–11 in conjunction with improvement in both LV size and function, as well as RV size and function.12–16 In patients with severe heart failure and those with severe RV dysfunction may respond poorly to cardiac resynchronization therapy (CRT).17,18 The effect of CRT on RV function (RVF) and the relationship between RVF and outcomes in patients with mild heart failure are less clear.

Background—Right ventricular function (RVF) is an important determinant of outcome in patients with heart failure, and those with severe RV dysfunction have worse outcome after cardiac resynchronization therapy (CRT). We used data from the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) Trial to determine whether therapy with CRT is influenced by or affects RV function and to define the relationship between RV function and outcomes.

Methods and Results—A total of 1820 patients were randomly assigned to CRT plus implantable cardioverter defibrillator or implantable cardioverter defibrillator-only in a 3:2 ratio. We assessed RVF as RV fractional area change by echocardiography at baseline and after 1 year of therapy (n=1511 and 1273, respectively). The median RV fractional area change was 41%, with 10.9% of patients <35% at baseline. Baseline RVF did not modify the treatment effect of CRT on the primary outcome (interaction P=0.19). Randomization to CRT-implantable cardioverter defibrillator was associated with a greater improvement in RVF (ARV fractional area change 8.1% versus 5.4%; P<0.001), and improvement in RVF was related to subsequent outcomes. Every 5-point increase in RV fractional area change was associated with a 22% reduction in event rates (hazard ratio, 0.78; 95% confidence interval, 0.66–0.92; P=0.003), although this was not independent of the concurrent improvement in left ventricular function. Baseline tricuspid regurgitant velocity, a measure of pulmonary systolic pressure, was predictive of events in a multivariate analysis (hazard ratio, 1.86; 95% confidence interval, 1.24–2.8; P=0.003).

Conclusions—In this population with mild heart failure symptoms, CRT was associated with improvement in RVF, which improved in parallel with improvement in left ventricular function. Patients with the best RVF at 1 year demonstrated the lowest subsequent event rates.


Key Words: cardiac resynchronization therapy ▪ heart failure ▪ right ventricle

Right ventricular (RV) dysfunction has been associated with worse prognosis in patients with heart failure and left ventricular (LV) systolic dysfunction.1–5 Cardiac resynchronization therapy reduces the risk of death and heart failure events in patients with heart failure, low ejection fraction, and a wide QRS,6–11 in conjunction with improvement in both LV size and function, as well as RV size and function.12–16 In patients with severe heart failure and those with severe RV dysfunction may respond poorly to cardiac resynchronization therapy (CRT).17,18 The effect of CRT on RV function (RVF) and the relationship between RVF and outcomes in patients with mild heart failure are less clear.

Clinical Perspective on p 442

The Multicenter Automatic Defibrillator Implantation Trial—Cardiac Resynchronization Therapy (MADIT-CRT) Trial was designed to test the hypothesis that CRT would reduce death and heart failure events in patients with New York Heart Association (NYHA) class I and II symptoms of heart failure, low ejection fraction, and a wide QRS complex.
MADIT-CRT showed a 34% reduction in the primary end point of death or heart failure events in patients randomized to the CRT plus implantable cardioverter defibrillator (ICD) group (CRT-D group).\textsuperscript{11} We used echocardiographic data at baseline and after 1-year follow-up from MADIT-CRT to determine the prevalence of RV dysfunction in patients with NYHA class I and II heart failure being considered for CRT, to assess the effect of CRT on RVF, and to determine whether RVF modified the treatment effect of CRT.

**Methods**

**Study Population**

The MADIT-CRT Trial enrolled 1820 patients from 110 centers in the United States, Canada, and Europe from December 2004 to April 2008. Included patients were >21 years of age with mildly symptomatic heart failure (NYHA class I and II if ischemic cardiomyopathy, and NYHA class II if nonischemic cardiomyopathy), low ejection fraction (\(\leq 30\%\)), as determined by the enrolling site, with a QRS duration of \(\geq 130\) ms. The details on inclusion and exclusion criteria and the primary results from the study have been published previously.\textsuperscript{11,19} Individual institutional review boards approved the protocol, and each patient provided written informed consent that included consent for echocardiographic analyses.

Patients were randomly assigned to CRT-D therapy versus ICD-only therapy in a 3:2 ratio. In the ICD-only group, the pacing mode was programmed as VVI for single chamber units and DDI for dual chamber units, both with lower rates set to 40 beats per minute and hysteresis turned off. Echocardiograms were obtained at baseline before device implantation (n=1809) and at follow-up 12 months later (n=626 ICD group; n=752 CRT-D group). Assessment of RVF by RV fractional area change (RVFAC) was possible in 1511 patients at baseline (n=610 ICD group; n=901 CRT group) and 1273 at 1-year follow-up (n=544 ICD group; n=729 CRT group), with paired data available in 1126 patients. Tricuspid regurgitant (TR) velocity was possible in 609 patients at baseline and 576 patients at 1-year follow-up. It should be noted that B-type natriuretic peptide data were available in only 1197 patients, all of whom were from US sites.

**Echocardiographic Measures**

Echocardiograms were sent on digital media storage or on videotape to Brigham and Women’s Hospital, where LV, RV, and left atrial (LA) measurements were made by a single technician at the echocardiographic core laboratory according to established American Society of Echocardiography protocols.\textsuperscript{20,21} LV volumes were measured by Simpson’s method of discs in the apical 4-chamber and 2-chamber views, and averaged. LV ejection fractions (LVEF) were calculated accordingly. LA volumes were measured by Simpson’s method of discs in the apical 4-chamber view. RVFAC was calculated as the difference in RV diastolic and systolic areas, divided by the diastolic area, in the apical 4-chamber view.\textsuperscript{22} TR velocities were measured according to standard protocols. Maximum peak TR velocity was measured from the view where continuous wave Doppler velocity reading was highest. Patients with undetectable, inadequate, or difficult to visualize envelopes of TR were excluded from the analysis. Approximately 70% of MADIT-CRT studies were digital. For videotape studies, these were initially digitized to digital loops, and all studies were subsequently analyzed in the same manner. To estimate the amount of pacing of the RV in the ICD-only group, device interrogation analysis was performed on a random sample of 90 ICD-only patients.

**Statistical Analyses**

Differences in baseline characteristics between those patients in whom RVFAC could be measured and those patients in whom it could not be measured were assessed with \(\chi^2\) test for categorical variables and \(t\) tests or ranksum for continuous variables. Similarly, comparisons were made between subgroups above and below 2 cutoffs of RVF (RVFAC <35% and \(\geq 35\%\), and median of 41% and >41%). The treatment effect was compared in the subgroups based on the 2 cutoffs for RVF described above, and the interaction between subgroup and treatment effect with respect to outcomes was assessed.

The primary outcome of the trial was a composite outcome of death attributable to any cause or a nonfatal heart failure event, as adjudicated by an independent end points committee unaware of treatment assignment. The relationship between baseline RVF and outcomes was assessed using an unadjusted Cox proportional hazards model. The primary event rate was calculated in each quartile of baseline RVF in each treatment group. The relationship between RVF at 1 year and change in RVF from baseline to 1 year, and the outcomes subsequent to the 1-year echocardiogram were assessed in a landmark type analysis using the Cox proportional hazards model, adjusted for treatment status and further adjusted for change in LVEF and treatment group. The primary event rate subsequent to 1 year was calculated in each quartile of 1-year RVF in each treatment group.

The relationship between baseline TR velocity and outcomes was assessed using a Cox proportional hazards model, initially unadjusted, then either adjusted for baseline LVEF, RVFAC, and treatment group, or in a more fully adjusted model that included treatment, age, sex, ischemic status, diabetes mellitus, estimated glomerular filtration rate, QRS width, baseline NYHA class, baseline LVEF, and baseline RVFAC. The relationship between TR velocity at 1 year and outcomes subsequent to the 1-year echocardiogram was assessed in a landmark type analysis using the Cox proportional hazards model, adjusting for treatment, change in LVEF, and change in RVF.

All analyses were performed using STATA version 11 (Stata Corporation, College Station, TX). For all analyses, a \(P\) value of <0.05 was considered statistically significant. All analyses were performed at Brigham and Women’s Hospital by the first 2 authors (P.C. and M.T.).

**Results**

Assessment of RVF was possible in 1511 at baseline and 1273 at 1 year. RVFAC was normally distributed in the MADIT-CRT population at baseline (Figure 1). We divided the population into those with RVFAC above and below 35% based on the American Society of Echocardiography definition for RV dysfunction,\textsuperscript{22} and by this definition, 164 patients or 10.9%...
of the population had evidence of RV dysfunction. Because the majority of patients had an RVF within the normal range, we also divided the population above and below the median RVFAC of 41%.

The 298 patients who did not have RVF assessed at baseline differed minimally from those who had RVF assessed, although they were more likely to have had a history of ventricular arrhythmia (10.9% versus 6.5%; P=0.007) and had higher diastolic blood pressure at baseline (72.8±10.5 versus 71.3±10.3; P=0.021).

Assessment of TR velocities was possible in 609 patients at baseline (40.3%) and 576 (45.2%) at 1 year.

Baseline Echocardiographic Characteristics
Patients with a lower RVF by either criterion had larger LV volumes, larger LV dimensions, higher LA volumes, and lower LVEF (Table 2). Random interrogation of devices in patients treated with ICD-only revealed that for patients with single chamber units, 83% had no RV pacing, 15% had ≤5% RV pacing, and only 2% had >5% RV pacing. Of those with dual chamber units, 87% had no RV pacing, 7% had ≤5% RV pacing, and 6% had >5% RV pacing.

RVF at Baseline and Outcomes
We observed no clear relationship between baseline RVF and outcomes in either treatment group (ICD group: hazard ratio [HR], 1.02; 95% confidence interval [CI], 0.98–1.04; P=0.736 and CRT group: HR, 0.98; 95% CI, 0.95–1.02; P=0.313), although the primary event rates were substantially lower in the patients receiving CRT compared with those treated with ICD-only (Figure 2). To examine whether RVF modified the treatment effect of CRT, we assessed for interaction between baseline RVF and treatment effect on outcome and observed no evidence of a baseline RVF-treatment interaction (RVFAC above and below 35%; interaction P=0.346; RVFAC above and below median; interaction P=0.194).

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**Baseline Characteristics**

Table 1 shows the baseline characteristics of the population, separated by both RVF cutoffs. Patients with severe RV dysfunction, with an RVFAC <35%, were less likely to be women, more likely to have a higher body mass index and more likely to have right bundle-branch block. Those with RVFAC less than the median (≤41%) were more likely to be treated with an aldosterone antagonist, were less likely to have interventricular conduction delay, and had higher baseline B-type natriuretic peptide.

**Table 1. Baseline Characteristics Using Either Cutoff of Right Ventricular Fractional Area Change**

<table>
<thead>
<tr>
<th></th>
<th>RVFAC &lt;35% (n=164)</th>
<th>RVFAC ≥35% (n=1347)</th>
<th>P Value</th>
<th>RVFAC &lt;41.4% (n=758)</th>
<th>RVFAC ≥41.4% (n=753)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>65.4±10.4</td>
<td>64.5±10.8</td>
<td>0.31</td>
<td>64.6±11</td>
<td>64.5±10.4</td>
<td>0.862</td>
</tr>
<tr>
<td>Women</td>
<td>25/15.3%</td>
<td>358/26.6%</td>
<td>0.002</td>
<td>182/24%</td>
<td>201/26.7%</td>
<td>0.231</td>
</tr>
<tr>
<td>White</td>
<td>150/92.6%</td>
<td>1207/90%</td>
<td>0.755</td>
<td>680/90.1%</td>
<td>677/90.5%</td>
<td>0.844</td>
</tr>
<tr>
<td>Ischemic</td>
<td>97/59.2%</td>
<td>726/53.9%</td>
<td>0.203</td>
<td>416/54.9%</td>
<td>407/54.1%</td>
<td>0.746</td>
</tr>
<tr>
<td>NYHA II</td>
<td>133/81.1%</td>
<td>1165/86.5%</td>
<td>0.061</td>
<td>654/86.3%</td>
<td>644/85.5%</td>
<td>0.673</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRT-D</td>
<td>103/62.8%</td>
<td>798/59.2%</td>
<td>0.38</td>
<td>300/39.6%</td>
<td>310/41.2%</td>
<td>0.529</td>
</tr>
<tr>
<td>ICD</td>
<td>61/37.2%</td>
<td>549/40.8%</td>
<td>0.497</td>
<td>249/32.9%</td>
<td>213/28.3%</td>
<td>0.050</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>54/32.9%</td>
<td>408/30.3%</td>
<td>0.578</td>
<td>476/62.9%</td>
<td>474/63%</td>
<td>0.951</td>
</tr>
<tr>
<td>HTN</td>
<td>100/61%</td>
<td>850/63.2%</td>
<td>0.431</td>
<td>90/12.1%</td>
<td>85/11.4%</td>
<td>0.687</td>
</tr>
<tr>
<td>Smoking</td>
<td>22/13.7%</td>
<td>153/11.6%</td>
<td>0.223</td>
<td>322/43.8%</td>
<td>320/43.4%</td>
<td>0.88</td>
</tr>
<tr>
<td>MI</td>
<td>77/48.1%</td>
<td>565/43.1%</td>
<td>0.302</td>
<td>587/77.4%</td>
<td>581/77.2%</td>
<td>0.896</td>
</tr>
<tr>
<td>ACEI</td>
<td>132/80.5%</td>
<td>1036/76.9%</td>
<td>0.015</td>
<td>700/92.4%</td>
<td>709/94.2%</td>
<td>0.161</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>149/90.9%</td>
<td>1260/93.5%</td>
<td>0.087</td>
<td>256/33.8%</td>
<td>215/28.6%</td>
<td>0.028</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>52/31.7%</td>
<td>419/31.1%</td>
<td>0.875</td>
<td>157.4±19.4</td>
<td>158.1±17.9</td>
<td>0.728</td>
</tr>
<tr>
<td>QRS duration, m/s</td>
<td>157.4±19.4</td>
<td>158.1±17.9</td>
<td>0.323</td>
<td>157.7±19</td>
<td>157.4±20.2</td>
<td>0.705</td>
</tr>
<tr>
<td>LBBB</td>
<td>110/67.1%</td>
<td>953/70.8%</td>
<td>0.041</td>
<td>108/14.3%</td>
<td>83/11%</td>
<td>0.061</td>
</tr>
<tr>
<td>RBBB</td>
<td>29/17.7%</td>
<td>162/12%</td>
<td>0.058</td>
<td>108/14.3%</td>
<td>137/18.2%</td>
<td>0.036</td>
</tr>
<tr>
<td>IVCD</td>
<td>24/14.6%</td>
<td>221/16.4%</td>
<td>0.041</td>
<td>28.7±5.4</td>
<td>28.4±5.1</td>
<td>0.061</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29.4±4.8</td>
<td>28.7±5.4</td>
<td>0.651</td>
<td>106.8±132</td>
<td>0.030</td>
<td></td>
</tr>
</tbody>
</table>

ACEI indicates angiotensin-converting enzyme inhibitor; β-Blocker, β-adrenergic receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; CRT-D, cardiac resynchronization therapy with defibrillator; eGFR, estimated glomerular filtration rate; HTN, hypertension; ICD, implantable cardiac defibrillator; IVCD, interventricular conduction delay; LBBB, left bundle-branch block; MI, myocardial infarction; NYHA, New York Heart Association class; RBBB, right bundle-branch block; RVFAC, right ventricular fractional area change.
Change in RVF from Baseline

The majority of patients had a repeat echo at 1 year, and RVF assessment was possible in 1273 patients. RVF improved to a greater extent in the CRT group than in the ICD group with an absolute change from baseline in RVFAC of 8.1±5.5% versus 5.4±4.8% (P<0.001). This improvement occurred in parallel with changes in LVEF (Figure 3); for each increasing quartile of improvement in LVEF, RVFAC improvement similarly increased. The improvement also occurred in parallel with changes in LV end-diastolic volume index, LV end-systolic volume index, and LA volume as previously reported (Table 3).

RVF at 1 Year and Outcomes

We assessed the relationship between RVF at 1 year and subsequent primary end points, in a landmark type analysis. RVF at 1 year was better in the CRT group than in the ICD group and was related to subsequent outcomes in the CRT but not in the ICD group (CRT group; HR, 0.92; 95% CI, 0.88–0.98; P=0.005; ICD group; HR, 0.98; 95% CI, 0.93–1.03; P=0.48; interaction P=0.078; Figure 4). Each 5% absolute increase in RVFAC from baseline was associated with a 28% reduction in risk of the primary outcome, after adjusting for baseline RVF (HR, 0.72; 95% CI, 0.59–0.87; P=0.001). This association remained after adjusting for change in LVEF during the same period, but was no longer an independent predictor of outcome (HR, 0.97; 95% CI, 0.76–1.25; P=0.828). We report adjustment for LVEF because it is a measure that is easily comprehended and obtained; however, change in RVF was similarly no longer an independent predictor after adjusting for change in LV end-diastolic volume, LV end-systolic volume, and LA volume during the same time period.

TR Velocity at Baseline and 1 Year

TR velocity, a measure of the gradient between the RV and the right atrium and an indirect measure of pulmonary pressures, was similar at baseline in those randomized to CRT-D or to ICD-only (Table 2). Baseline TR velocity was predictive of the primary end point, even after adjusting for treatment group, baseline LVEF, and baseline RVFAC (HR, 2.01; 95% CI, 1.35–2.99; P=0.001), and in a more fully adjusting model adjusting for treatment, age, sex, ischemic status, diabetes mellitus, status, estimated glomerular filtration rate, QRS width, NYHA class, baseline LVEF, and baseline RVFAC (HR, 1.86; 95% CI, 1.24–2.8; P=0.003); there was no interaction between baseline TR velocity and treatment effect on outcome (P=0.596). In 576 patients with repeat TR velocity measures, TR velocity decreased by −0.07±0.49 m/s in the CRT-D arm compared with an increase of 0.05±0.44 m/s in the ICD-only arm, (P=0.014). TR velocity at 1 year was predictive of subsequent events, irrespective of treatment arm (ICD group: HR, 1.93; 95% CI, 1.04–3.58; P=0.036; CRT group: HR, 3.48; 95% CI, 1.45–8.32; P=0.005). However, when adjusted for change in LVEF and RVF, it was no longer predictive of events.

<table>
<thead>
<tr>
<th>Table 2. Baseline Echocardiographic Characteristics Using Either Cutoff of Right Ventricular Fractional Area Change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RVFAC &lt;35%</strong></td>
</tr>
<tr>
<td>(n=164)</td>
</tr>
<tr>
<td>RVFAC, %</td>
</tr>
<tr>
<td>RVEDA index, cm²/m²</td>
</tr>
<tr>
<td>LVEDV index, ml/m²</td>
</tr>
<tr>
<td>LVESV index, ml/m²</td>
</tr>
<tr>
<td>LVEF, %</td>
</tr>
<tr>
<td>LVEDd, cm</td>
</tr>
<tr>
<td>LVEDs, cm</td>
</tr>
<tr>
<td>LA vol index, ml/m²</td>
</tr>
<tr>
<td>TR velocity, m/s</td>
</tr>
</tbody>
</table>

LA vol index indicates left atrial volume indexed to body surface area; LVEDd, left ventricular end-diastolic diameter; LVEDS index, left ventricular end-systolic volume indexed to body surface area; LVEDV index, left ventricular end-diastolic volume indexed to body surface area; LVEF, left ventricular ejection fraction; LVESeqd, left ventricular end-systolic diameter; RVEDA index, right ventricular end-diastolic area indexed to body surface area; RVFAC, right ventricular fractional area change; and TR velocity, tricuspid regurgitant peak velocity.

Figure 2. Primary event rate based on baseline right ventricular (RV) fractional area change, divided into quartiles of right ventricular fractional area change in the 2 treatment groups. CRT indicates cardiac resynchronization therapy; HF, heart failure; and ICD, implantable cardioverter defibrillator.
Discussion

We observed a low prevalence of RV dysfunction, as defined by American Society of Echocardiography criteria as an RVFAC of <35%, in MADIT-CRT patients with mild heart failure being randomized to CRT-D or ICD-only therapy. In contrast to other studies, RVF at baseline was not related to outcomes in this population, perhaps related to the low prevalence of RV dysfunction in this cohort of NYHA class I and II heart failure patients. Although RVF itself did not modify the treatment effect of CRT, treatment with CRT was associated with improvement in RVF and a reduction in TR velocity, a measure of pulmonary pressures, which occurred in parallel with improvements in LV volumes and ejection fraction, as well as LA volumes. Patients with the best RVF at 1 year had a lower subsequent event rate, although this improvement was not independent of the observed improvement in LV function.

Reduction in pulmonary artery pressure with concomitant reverse remodeling of the RV has been demonstrated in some small studies of patients with NYHA class III and IV heart failure symptoms treated with CRT. Other small studies have failed to show any improvement in RVF with CRT, despite favorable changes to LV function. The Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) Trial Investigators looked at the effect of CRT on longitudinal RV motion as measured by tricuspid annular plane systolic excursion and found that CRT was not associated with any clinically significant effect on tricuspid annular plane systolic excursion or pulmonary arterial pressures, despite significant improvement in LVEF. The lack of change in RVF as measured by tricuspid annular plane systolic excursion in the REVERSE Trial may reflect the inherent limitations of this measure. Assessment using this technique is restricted to longitudinal motion of the RV free wall and it assumes that the displacement of this segment represents the function of the complex 3-dimensional (3D) structure of the RV, but it disregards the contribution of the interventricular septum and the right ventricular outflow tract to overall RVF. Using a more global measure of function, RVFAC, we found significant improvement in RVF in patients treated with CRT in parallel with improvement in LV size and function, as well as pulmonary pressures (Table 3). This measure of RVF has been shown to be predictive of outcomes in patients with heart failure after myocardial infarction and in pulmonary embolism. In most patients who have not been subject to markedly elevated pulmonary pressures, RVF measured by RVFAC serves primarily as an assessment of the RV response to increased afterload, rather than a measure of intrinsic RV contractile function.

Table 3. Percentage Change in Echocardiographic Parameters from Baseline, by Treatment Arm, and Correlation Coefficient and $R^2$ Values Between Baseline Right Ventricular Fractional Area Change and Other Baseline Echocardiographic Measures

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CRT-D Group</th>
<th>ICD-Only Group</th>
<th>P Value</th>
<th>Correlation Coefficient</th>
<th>$R^2$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVFAC</td>
<td>20.6±17.6</td>
<td>14±13.2</td>
<td>&lt;0.001</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>RVEDA index</td>
<td>−9±5.6</td>
<td>−3.9±4.4</td>
<td>&lt;0.001</td>
<td>−0.11</td>
<td>0.013</td>
</tr>
<tr>
<td>LVEF</td>
<td>38±18.7</td>
<td>12.2±11.6</td>
<td>&lt;0.001</td>
<td>0.93</td>
<td>0.329</td>
</tr>
<tr>
<td>LVEDV index</td>
<td>−20.7±11.5</td>
<td>−6±5.7</td>
<td>&lt;0.001</td>
<td>−0.02</td>
<td>0.01</td>
</tr>
<tr>
<td>LVEVS index</td>
<td>−32.3±15.3</td>
<td>−10.2±8.9</td>
<td>&lt;0.001</td>
<td>−0.05</td>
<td>0.039</td>
</tr>
<tr>
<td>LA vol index</td>
<td>−26.5±6.4</td>
<td>−9.9±8.1</td>
<td>&lt;0.001</td>
<td>−0.29</td>
<td>0.264</td>
</tr>
<tr>
<td>TR velocity</td>
<td>−0.9±18.4</td>
<td>3.2±18.1</td>
<td>0.065</td>
<td>−0.01</td>
<td>0.008</td>
</tr>
</tbody>
</table>

LA vol index, left atrial volume indexed to body surface area; LVEDS index, left ventricular end-systolic volume indexed to body surface area; LVEDV index, left ventricular end-diastolic volume indexed to body surface area; LVEF, left ventricular ejection fraction; RVEDA index, right ventricular end-diastolic area indexed to body surface area; RVFAC, right ventricular fractional area change; and TR velocity, maximum velocity of the tricuspid regurgitant jet.
Patients with worse RVF receiving CRT have worse response to CRT\textsuperscript{17,27,31} and have worse outcomes.\textsuperscript{16} One possible explanation for this is that patients with significant RV dysfunction may be too sick to benefit from CRT. In this cohort of patients with mild heart failure, we have demonstrated a significant improvement in RVF\textsubscript{AC} with CRT regardless of baseline RVF. This may be explained at least partially by the fact that overall RVF in this population was well preserved, with just 10.9\% meeting American Society of Echocardiography criteria for RV dysfunction.\textsuperscript{22}

We observed that baseline TR velocity, itself reflective of pulmonary pressures, was related to outcomes independent of baseline LVEF and RVF. Pulmonary arterial pressures have proven prognostic value in patients with heart failure, where pulmonary arterial systolic pressures of >45 mm Hg are generally associated with worse prognosis.\textsuperscript{32,33} Patients in the MADIT-CRT population, however, had TR velocities suggestive of much lower pulmonary pressures; nevertheless, TR velocity remained prognostically important. Lower TR velocity at 1 year was associated with improved outcomes, but was not independent of the improvement in LVEF and RVF, suggesting that these improvements may indeed occur in response to profound improvements in LV function and size that occur as a result of CRT.

A number of limitations of our analysis should be noted. Because of the large sample size, some of the differences between patients with higher and lower FAC measures were statistically significant, although clinically relatively trivial. The RV is a complex geometric 3D structure, and 2D echocardiographic assessment using the fractional area change method may not accurately represent true RVF; nevertheless, this method has been shown to correlate well with MRI-derived RVEF and has been one of the more robust methods to assess RVF.\textsuperscript{20,22,24} We did not use other methods to assess RVF in this analysis. As RVF assessment was available in only 83\% of patients at baseline and 70\% at 1 year, we cannot assess the relationship between RVF and outcome in those who did not have these measures. Although Doppler transthoracic echocardiographic assessment of TR jet peak velocity has been shown to predict pulmonary arterial systolic pressure accurately as observed by invasive measures,\textsuperscript{35,36} it is a technique with inherent potential limitations. Measurement of peak TR jet velocity requires an adequate TR envelope, which is frequently not possible or inadequate, especially in patients without clinically significant TR. This limitation led to exclusion of TR velocity data from a large number of patients in this study. Finally, overall RVF in the MADIT-CRT cohort was generally preserved, and the relationship between RVF and outcome in a population with more severely symptomatic heart failure will likely differ from what we observed in MADIT-CRT.

In summary, in patients in the MADIT-CRT cohort with mild symptoms of heart failure baseline RVF was not predictive of outcomes and did not modify the response to CRT treatment. However, patients treated with CRT had greater improvement in RVF and greater reduction in TR velocities than those in the ICD-only arm, regardless of baseline RVF. These changes occurred in parallel with improvement in LV structure and function and LA size. Improvements in RVF and TR velocities were predictive of better subsequent outcomes; however, this was not independent of the improvement in LV function, suggesting that improvement in RVF and TR velocities is likely secondary to improvement in LV function in this population.

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**References**

6. Saxon LA, De Marco T, Schafer J, Chatterjee K, Kumar UN, Foster E; VIGOR Congestive Heart Failure Investigators. Effects of long-term...
20. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shawe OB, 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.
Right ventricular function (RVF) is a known predictor of adverse outcome in patients with heart failure. We assessed RVF at baseline and follow-up in patients being randomized to cardiac resynchronization therapy or implantable cardioverter defibrillator only in the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy Trial. Although baseline RVF was well preserved in this relatively low-risk New York Heart Association class I and II population and was not itself a predictor of outcome, RVF did improve with cardiac resynchronization therapy and those patients with the best right ventricular function at 1 year had the best subsequent outcomes. These data suggest that right ventricular function may be a marker for cardiac resynchronization therapy response, and improvement in RVF may identify a group of patients who will have lowest subsequent event rates after cardiac resynchronization therapy.
Right Ventricular Function, Pulmonary Pressure Estimation, and Clinical Outcomes in Cardiac Resynchronization Therapy
Patricia Campbell, Madoka Takeuchi, Mikhail Bourgoun, Amil Shah, Elyse Foster, Mary W. Brown, Ilan Goldenberg, David T. Huang, Scott McNitt, W. Jackson Hall, Arthur Moss, Marc A. Pfeffer and Scott D. Solomon

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