Right Ventricular Function, Pulmonary Pressure Estimation, and Clinical Outcomes in Cardiac Resynchronization Therapy

Patricia Campbell, MB, BCh; Madoka Takeuchi, MS; Mikhail Bourgoun, MD; Amil Shah, MD; Elyse Foster, MD; Mary W. Brown, MS; Ilan Goldenberg, MD; David T. Huang, MD; Scott McNitt, MS; W. Jackson Hall, PhD; Arthur Moss, MD; Marc A. Pfeffer, MD; Scott D. Solomon MD; for the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) Investigators

1 Brigham and Women’s Hospital, Department of Cardiology, Boston, MA
2 University of California at San Francisco, San Francisco, CA
3 University of Rochester Medical Center, Rochester, NY

Correspondence to:
Scott D. Solomon, MD
Cardiovascular Division
Brigham and Women’s Hospital
75 Francis St, Boston, MA 02115
Email ssolomon@rics.bwh.harvard.edu
Phone 857 307 1960
Fax 857 307 1944

DOI: 10.1161/CIRCHEARTFAILURE.112.000127

Journal Subject Codes: [110] Congestive; [120] Pacemaker
Abstract

Background—Right ventricular (RV) function 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 utilized data from the Multicenter Automatic Defibrillator Implantation Trial – Cardiac Resynchronization Therapy trial (MADIT-CRT) to determine whether therapy with CRT is influenced by or affects right ventricular function, and to define the relationship between RV function and outcomes.

Methods and Results—1820 patients were randomly assigned to cardiac resynchronization therapy plus ICD (CRT-D) or ICD-only in a 3:2 ratio. We assessed RV function (RVF) as right ventricular fractional area change (RVFAC) by echocardiography at baseline and after one year of therapy (n=1511 and 1273 respectively). The median RVFAC was 41%, with 10.9% of patients below 35% at baseline. Baseline RVF did not modify the treatment effect of CRT on the primary outcome (interaction p=0.19). Randomization to CRT-D was associated with a greater improvement in RVF (ΔRVFAC 8.1% versus 5.4%, p<0.001) and improvement in RVFAC was related to subsequent outcomes. Every 5-point increase in RVFAC was associated with a 22% reduction in event rates (HR 0.78, 95% CI 0.66-0.92, p=0.003), although this was not independent of the concurrent improvement in LV function. Baseline TR velocity, a measure of pulmonary systolic pressure, was predictive of events in a multivariate analysis (HR 1.86 95% CI 1.24-2.8, p=0.003).

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

Clinical Trial Registration—http://www.clinicaltrials.gov. Unique identifier: NCT01294449.

Key Words: heart failure, right ventricle, cardiac resynchronization therapy
Right ventricular (RV) dysfunction has been associated with worse prognosis in patients with heart failure and left ventricular systolic dysfunction\(^1,2,3,4,5\). Cardiac resynchronization therapy reduces the risk of death and heart failure events in patients with heart failure, low ejection fraction and a wide QRS\(^6,7,8,9,10,11\), in conjunction with improvement in both left ventricular size and function, as well as right ventricular size and function\(^12,13,14,15,16\). In patients with severe heart failure, those with severe right ventricular dysfunction may respond poorly to CRT\(^17,18\). The effect of CRT on RV function and the relationship between RV function and outcomes in patients with mild heart failure is less clear.

The MADIT-CRT trial was designed to test the hypothesis that CRT would reduce death and heart failure events in patients with 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 endpoint of death or heart failure events in patients randomized to the CRT plus implantable cardioverter defibrillator (ICD) group (CRT-D group)\(^11\). We utilized echocardiographic data at baseline and after one-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 RV function (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 US, Canada and Europe from December 2004 – April 2008. Included patients were >21 years of age with mildly symptomatic heart failure (New York Heart Association (NYHA) class I and II if ischemic cardiomyopathy, and NYHA class II if non-ischemic cardiomyopathy), low ejection
fraction (≤30%), as determined by the enrolling site, with a QRS duration of ≥130ms. The
details on inclusion and exclusion criteria and the primary results from the study have been
published previously11–19. 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 40bpm and hysteresis turned off.
Echocardiograms were obtained at baseline prior to device implantation (n=1809) and at
follow up 12 months later (n=626 ICD group, n=752 CRT-D group). Assessment of RVF by
right ventricular fractional area change (RVFAC) was possible in 1511 patients at baseline
(n=610 ICD group, n=901 CRT group), and 1273 at one year follow-up (n=544 ICD group,
n=729 CRT group), with paired data available in 1126 patients. TR velocity was possible in
609 patients at baseline and 576 patients at one-year follow-up. It should be noted that BNP
data was 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 left ventricular (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 (ASE) protocols20, 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}. Tricuspid regurgitant 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 in whom it could not be measured were assessed with chi\textsuperscript{2} for categorical variables and t-tests or ranksum for continuous variables. Similarly, comparisons were made between subgroups above and below two cut-offs of RVF (RVFAC <35\% and \geq35\%, and < and \geq median of 41\%). The treatment effect was compared in the subgroups based on the two cut-offs 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 due to any cause or a non-fatal heart failure event, as adjudicated by an independent endpoints 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 one year and change in RVF from baseline to one year, and the outcomes subsequent to the
one 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 LV ejection fraction and treatment group. The primary event rate subsequent to one year was calculated in each quartile of one 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 left ventricular ejection fraction (LVEF), RVFAC and treatment group, or in a more fully adjusted model that included treatment, age, gender, ischemic status, diabetes, estimated glomerular filtration rate, QRS width, baseline New York Heart Association class, baseline LVEF, and baseline RVFAC. The relationship between TR velocity at one year and outcomes subsequent to the one 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 probability value of <0.05 was considered statistically significant. All analyses were performed at Brigham and Women’s Hospital by the first 2 authors (PC and MT).

Results

Assessment of RVF was possible in 1511 at baseline and 1273 at one year. RVFAC was normally distributed in the MADIT-CRT population at baseline (Figure 1). We divided the population into to those with RVFAC above and below 35% based on the American Society of Echocardiography (ASE) definition for RV dysfunction, and by this definition, 164
patients or 10.9% of the population had evidence of right ventricular 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 one year.

Baseline Characteristics

The baseline characteristics of the population are summarized in Table 1, separated by both RVF cut-offs. Patients with severe RV dysfunction, with an RVFAC <35%, were less likely to be female, 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 BNP.

Baseline Echocardiographic Characteristics

Patients with a lower RVF by either criterion had larger left ventricular (LV) volumes, larger LV dimensions, higher left atrial volumes and lower LV ejection fraction (EF) (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.

RV Function at Baseline and Outcomes

We observed no clear relationship between baseline RVF and outcomes in either treatment group (ICD group HR 1.02, 95% 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 to 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 RV function-treatment interaction (RVFAC above and below 35%, Interaction p=0.346; RVFAC above and below median Interaction, p=0.194).

Change in RV Function from Baseline

The majority of patients had a repeat echo at one 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 LV ejection fraction (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 left atrial volume as previously reported14 (Table 3).

RV Function at One Year and Outcomes

We assessed the relationship between RVF at one year and subsequent primary endpoints, in a landmark type analysis. RVF at one year was better in the CRT group than the ICD group
(Figure 4) and was related to subsequent outcomes in the CRT but not 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). 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 treatment. However, after adjusting for change in LVEF over the same period, RVF 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 since 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 left atrial volume over the same time period.

TR Velocity at Baseline and One Year

Tricuspid regurgitant (TR) velocity, a measure of the gradient between the right ventricle 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 endpoint, 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, gender, ischemic status, diabetes, 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 to an increase of 0.05±0.44 m/s in the ICD-only arm, (p=0.014). TR velocity at one 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.

Discussion

We observed a low prevalence of right ventricular dysfunction, as defined by ASE 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, RV function 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. While RV function itself did not modify the treatment effect of CRT, treatment with CRT was associated with improvement in RV function 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 left atrial volumes. Patients with the best RVF at one year had a lower subsequent event rate, although this improvement was not independent of the observed improvement in left ventricular 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-IV heart failure symptoms treated with CRT. Other small studies have failed to show any improvement in RV function with CRT despite favorable changes to LV function. The REVERSE trial investigators looked at the effect of CRT on longitudinal RV motion as measured by tricuspid annular plane systolic excursion (TAPSE), and found that CRT was not associated with any clinically significant effect on TAPSE or pulmonary arterial pressures, despite significant improvement in LV ejection fraction. The lack of change in RV function as measured by TAPSE 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-D structure of the right ventricle; but it disregards the contribution of the interventricular septum and the RVOT to overall RVF. Using a more global measure of function, right ventricular fractional area change (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 following myocardial infarction\textsuperscript{28, 29}, and in pulmonary embolism\textsuperscript{30}. In most patients who have not been subject to markedly elevated pulmonary pressures, right ventricular function measured by RVFAC serves primarily as an assessment of the right ventricular response to increased afterload, rather than a measure of intrinsic right ventricular contractile function.

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 RVFAC 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 ASE criteria for RV dysfunction\textsuperscript{22}. We observed that baseline tricuspid regurgitant 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 \textsuperscript{>45 mmHg} 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 one 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 right ventricle is a complex geometrical 3-dimensional structure and 2-dimensional echocardiographic assessment using the fractional area change method may not accurately represent true right ventricular function; nevertheless, this method has been shown to correlate well with MRI derived RVEF and has been one of the more robust methods to assess RV function\textsuperscript{20,22,34}. We did not utilize other methods to assess RV function in this analysis. As RVF assessment was available in only 83% of patients at baseline and 70% at one year, we cannot assess the relationship between RVF and outcome in those who did not have these measures. While Doppler transthoracic echocardiographic assessment of TR jet peak velocity has been shown to accurately predict pulmonary arterial systolic pressure 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 RV function was not predictive of outcomes and did not modify the response to CRT treatment. However, patients treated with CRT had greater improvement in RV function and greater reduction in TR velocities than those in the ICD-only arm, regardless of baseline RV function. These changes occurred in parallel with improvement in LV structure and function and left atrial size. Improvements in RV function and TR velocities were predictive of better subsequent outcomes, however, this was not independent of the improvement in left ventricular function, suggesting that improvement in RV function and TR velocities are likely secondary to improvement in LV function in this population.

Sources of Funding

The MADIT-CRT trial was funded by Boston Scientific, through a research grant to the University of Rochester, which in turn provided funding for core laboratories, including the echocardiography core laboratory.

Disclosures

Drs Solomon, Foster and Moss received research support for the conduct of the MADIT-CRT trial from Boston Scientific through a grant given to the University of Rochester. Drs Solomon and Pfeffer served as consultants to Boston Scientific. For all other authors: none.

References


20. 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 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.


Table 1. Baseline Characteristics Using Either Cutoff of RVFAC

<table>
<thead>
<tr>
<th></th>
<th>RVFAC &lt;35%</th>
<th>RVFAC ≥35%</th>
<th>p</th>
<th>RVFAC &lt;41.44%</th>
<th>RVFAC ≥41.44%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>N=164</td>
<td>N=1347</td>
<td></td>
<td>N=758</td>
<td>N=753</td>
<td></td>
</tr>
<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>Female</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></td>
<td>458/60.4%</td>
<td>443/58.9%</td>
<td></td>
</tr>
<tr>
<td>- ICD</td>
<td>61/37.2%</td>
<td>549/40.8%</td>
<td>0.38</td>
<td>300/39.6%</td>
<td>340/41.2%</td>
<td>0.529</td>
</tr>
<tr>
<td>Diabetes</td>
<td>54/32.9%</td>
<td>408/30.3%</td>
<td>0.497</td>
<td>249/32.9%</td>
<td>213/28.3%</td>
<td>0.050</td>
</tr>
<tr>
<td>HTN</td>
<td>100/61%</td>
<td>850/63.2%</td>
<td>0.578</td>
<td>416/62.9%</td>
<td>474/63%</td>
<td>0.951</td>
</tr>
<tr>
<td>Smoking</td>
<td>22/13.7%</td>
<td>153/11.6%</td>
<td>0.431</td>
<td>90/12.1%</td>
<td>85/11.4%</td>
<td>0.687</td>
</tr>
<tr>
<td>MI</td>
<td>77/48.1%</td>
<td>565/43.1%</td>
<td>0.223</td>
<td>322/43.8%</td>
<td>320/43.4%</td>
<td>0.88</td>
</tr>
<tr>
<td>ACEI</td>
<td>132/80.5%</td>
<td>1036/76.9%</td>
<td>0.302</td>
<td>587/77.4%</td>
<td>581/77.2%</td>
<td>0.896</td>
</tr>
<tr>
<td>B Blocker</td>
<td>149/90.9%</td>
<td>1260/93.5%</td>
<td>0.195</td>
<td>700/92.4%</td>
<td>709/94.2%</td>
<td>0.161</td>
</tr>
<tr>
<td>Aldosterone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antagonist</td>
<td>52/31.7%</td>
<td>419/31.1%</td>
<td>0.875</td>
<td>256/33.8%</td>
<td>215/28.6%</td>
<td>0.028</td>
</tr>
<tr>
<td>QRS Duration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(ms)</td>
<td>157.4±19.4</td>
<td>158.1±19.7</td>
<td>0.728</td>
<td>158.4±20.2</td>
<td>157.7±19</td>
<td>0.705</td>
</tr>
<tr>
<td>- LBBB</td>
<td>110/67.1%</td>
<td>953/70.8%</td>
<td>0.323</td>
<td>534/70.5%</td>
<td>529/70.4%</td>
<td>0.965</td>
</tr>
<tr>
<td>- RBBB</td>
<td>29/17.7%</td>
<td>162/12%</td>
<td>0.041</td>
<td>108/14.3%</td>
<td>83/11%</td>
<td>0.061</td>
</tr>
<tr>
<td>- IVCD</td>
<td>24/14.6%</td>
<td>221/16.4%</td>
<td>0.558</td>
<td>108/14.3%</td>
<td>137/18.2%</td>
<td>0.036</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.4±4.8</td>
<td>28.7±5.4</td>
<td>0.041</td>
<td>29.1±5.6</td>
<td>28.4±5.1</td>
<td>0.061</td>
</tr>
<tr>
<td>eGFR (ml/min)</td>
<td>70.4±18.1</td>
<td>70.9±20.3</td>
<td>0.651</td>
<td>70.6±19.8</td>
<td>71.1±20.4</td>
<td>0.552</td>
</tr>
</tbody>
</table>
1.73m2)

| BNP (pg/ml) | 110.7±122.8 | 120.6±155.1 | 0.883 | 131.1±167.2 | 106.8±132 | 0.030 |

Abbreviations: NYHA, New York Heart Association class; CRT-D, cardiac resynchronization therapy with defibrillator; ICD, implantable cardiac defibrillator; HTN, hypertension; MI, myocardial infarction; ACEI, angiotensin converting enzyme inhibitor; B Blocker, beta-adrenergic receptor blocker; LBBB, left bundle branch block; RBBB, right bundle branch block; IVCD, interventricular conduction delay; BMI, body mass index; eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide.
Table 2. Baseline Echocardiographic Characteristics Using Either Cutoff of RVFAC

<table>
<thead>
<tr>
<th></th>
<th>RVFAC ≤35%</th>
<th>RVFAC ≥35%</th>
<th>p</th>
<th>RVFAC ≤41.44%</th>
<th>RVFAC ≥41.44%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>N=164</td>
<td>N=1347</td>
<td></td>
<td>N=758</td>
<td>N=753</td>
<td></td>
</tr>
<tr>
<td>RVFAC (%)</td>
<td>33.4±1.2</td>
<td>43±5</td>
<td>n/a</td>
<td>37.5±2.7</td>
<td>46.5±3.7</td>
<td>n/a</td>
</tr>
<tr>
<td>RVEDA index (cm²/m²)</td>
<td>14.5±1.7</td>
<td>14.2±1.7</td>
<td>0.056</td>
<td>14.3±1.8</td>
<td>14.1±1.7</td>
<td>0.006</td>
</tr>
<tr>
<td>LVEDV index (ml/m²)</td>
<td>128.2±31.4</td>
<td>121.9±26.8</td>
<td>0.023</td>
<td>123.7±29.2</td>
<td>121.5±25.4</td>
<td>0.344</td>
</tr>
<tr>
<td>LVESV index (ml/m²)</td>
<td>95±25.7</td>
<td>86.4±21.4</td>
<td>&lt;0.0001</td>
<td>90±23.7</td>
<td>84.6±19.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>26.3±3.1</td>
<td>29.5±3.3</td>
<td>&lt;0.0001</td>
<td>27.6±3.1</td>
<td>30.7±3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVEDd (cm)</td>
<td>6.66±0.5</td>
<td>6.34±0.5</td>
<td>&lt;0.0001</td>
<td>6.49±0.5</td>
<td>6.25±0.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVESd (cm)</td>
<td>5.71±0.5</td>
<td>5.32±0.5</td>
<td>&lt;0.0001</td>
<td>5.52±0.5</td>
<td>5.21±0.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LA Vol index (ml/m²)</td>
<td>53.3±9.7</td>
<td>45.2±9.4</td>
<td>&lt;0.0001</td>
<td>50.2±9.5</td>
<td>41.8±8.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TR Velocity (m/s)</td>
<td>2.58±0.49</td>
<td>2.5±0.43</td>
<td>0.372</td>
<td>2.53±0.46</td>
<td>2.48±0.42</td>
<td>0.235</td>
</tr>
</tbody>
</table>
Abbreviations: RVFAC, right ventricular fractional area change; RVEDA index, right ventricular end diastolic area indexed to body surface area; LVEDV index, left ventricular end diastolic volume indexed to body surface area; LVEDS index, left ventricular end systolic volume indexed to body surface area; LVEF, left ventricular ejection fraction; LVEDd, left ventricular end diastolic diameter; LVESd, left ventricular end systolic diameter; LA Vol index, left atrial volume indexed to body surface area; TR velocity, tricuspid regurgitant peak velocity.
Table 3. Percentage Change in Echocardiographic Parameters from Baseline, by Treatment Arm, and Correlation Coefficient and $R^2$ Values Between Baseline RVFAC and Other Baseline Echocardiographic Measures

<table>
<thead>
<tr>
<th>Percentage Change in Echocardiographic Parameters from Baseline</th>
<th>CRT-D Group</th>
<th>ICD-Only Group</th>
<th>p</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>LVESV 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>

Abbreviations: RVFAC, right ventricular fractional area change; RVEDA index, right ventricular end diastolic area indexed to body surface area; LVEF, left ventricular ejection fraction; LVEDV index, left ventricular end diastolic volume indexed to body surface area; LVESV index, left ventricular end systolic volume indexed to body surface area; LA Vol index, left atrial volume indexed to body surface area; TR velocity, maximum velocity of the tricuspid regurgitant jet.
Figure Legends

Figure 1. Distribution of right ventricular fractional area change at baseline, and lines demarcating the cutoff of RVFAC used in analysis. 10.9% of the population had RVFAC below 35%. The median RVFAC was 41%. RVFAC, right ventricular fractional area change; ASE, American Society of Echocardiography Guideline Recommendation for cutoff for right ventricular dysfunction, RVFAC <35%; MEDIAN, median for population.

Figure 2. Primary event rate based on baseline right ventricular fractional area change, divided into quartiles of right ventricular fractional area change in the two treatment groups. HF, heart failure; RV, right ventricular.

Figure 3. Change in right ventricular fractional area change from baseline by quartile of change in left ventricular ejection fraction. RVFAC, right ventricular fractional area change; LVEF, left ventricular ejection fraction.

Figure 4. Landmark analysis results, relating right ventricular fractional area change at one year to subsequent primary outcome. HF, heart failure; RV, right ventricular.
Quartiles of Change in LVEF from Baseline per Treatment Arm

-6.79 to 1.62  1.63 to 3.25  3.26 to 5.35  5.37 to 14.15  -11.1 to 8.05  8.06 to 10.91  10.96 to 14.87  14.92 to 25.16

P < 0.0001

P = 0.002

ICD  CRT
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

_Circ Heart Fail._ published online March 22, 2013;
_Circulation: Heart Failure_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circheartfailure.ahajournals.org/content/early/2013/03/22/CIRCHEARTFAILURE.112.000127

**Permissions:** Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation: Heart Failure_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

**Reprints:** Information about reprints can be found online at:
http://www.lww.com/reprints

**Subscriptions:** Information about subscribing to _Circulation: Heart Failure_ is online at:
http://circheartfailure.ahajournals.org//subscriptions/