Interplay Between Right Ventricular Function and Cardiac Resynchronization Therapy

An Analysis of the CARE-HF Trial (Cardiac Resynchronization–Heart Failure)

Thibaud Damy, MD, PhD,*†‡ Stefano Ghio, MD, PhD,§ Alan S. Rigby, PhD,||
Luc Hittinger, MD, PhD,†‡ Sandra Jacobs, MD, PhD,¶ Francisco Leyva, MD,#
Juan F. Delgado, MD, PhD,** Jean-Claude Daubert, MD, PhD,†† Daniel Gras, MD,‡‡
Luigi Tavazzi, MD, PhD,§§ John G. F. Cleland, MD, PhD,||||

Créteil, Rennes, and Nantes, France; Pavia and Cotignola, Italy; Kingston-upon-Hull and Sutton Coldfield, United Kingdom; Maastricht, the Netherlands; and Madrid, Spain

Objectives
The aim of this study was to investigate the impact of cardiac resynchronization therapy (CRT) on right ventricular (RV) function and the influence of RV dysfunction on the echocardiographic and clinical response to CRT among patients enrolled in the CARE-HF (Cardiac Resynchronization-Heart Failure) trial.

Background
Cardiac resynchronization therapy prolongs survival in appropriately selected patients with heart failure but the benefit might be diminished in patients with RV dysfunction.

Methods
Of 813 patients enrolled in the CARE-HF study, 688 had tricuspid plane systolic excursion (TAPSE) measured at baseline, and 345 of these were assigned to CRT. Their median (interquartile range) age was 66 (58 to 71) years, left ventricular (LV) ejection fraction was 24% (21% to 28%), and TAPSE was 19 (16 to 22) mm. Baseline LV function and size and QRS duration were similar among TAPSE tertiles, but those in the worst tertile (TAPSE < 17.4 mm) were more likely to have ischemic heart disease.

Results
Overall, CRT improved LV but not RV structure and function with little evidence of an interaction with TAPSE. During a median (interquartile range) follow-up of 748 (582 to 950) days, 213 deaths occurred. Patients with lower TAPSE had a higher mortality, regardless of assigned treatment (p < 0.001). Greater inter-ventricular mechanical delay, New York Heart Association functional class, mitral regurgitation, and N-terminal pro–B-type natriuretic peptide, lower TAPSE, and assignment to the control group were independently associated with higher mortality. Reduction in mortality with CRT was similar in each tertile of TAPSE.

Conclusions
Right ventricular dysfunction is a powerful determinant of prognosis among candidates for CRT, regardless of treatment assigned, but did not diminish the prognostic benefits of CRT among patients enrolled in the CARE-HF trial. (Care-HF Cardiac Resynchronization in Heart Failure; NCT00170300) (J Am Coll Cardiol 2013;61:2153–60) © 2013 by the American College of Cardiology Foundation

Right ventricular (RV) dysfunction indicates a poor prognosis in patients with heart failure (1,2). Cardiac resynchronization therapy (CRT) improves left ventricular (LV) function, symptoms, and prognosis in patients with symp-
ever, observational studies measure outcome with but not the response to an intervention. A control group is required to distinguish treatment effects from the natural history of the disease (11). A post-hoc analysis of the REVERSE (Re-VERsion in Systolic left vEntricular dysfunction) trial, including 450 patients with chronic heart failure and mild symptoms, suggested that those with RV dysfunction (tricuspid annular plane systolic excursion [TAPSE] ≤14 mm) had a diminished response to CRT (n = 61), with less reverse LV remodelling and a poorer symptomatic response (12).

We investigated the impact of CRT on RV function and the influence of RV dysfunction on the echocardiographic and clinical response to CRT among patients enrolled in the CARE-HF (Cardiac Resynchronization—Heart Failure) trial (13).

**Methods**

The CARE-HF trial was a randomized trial of 813 patients (3) who had symptoms of heart failure despite guideline-indicated treatment who were in sinus rhythm and had LV systolic dysfunction and dilation and markers of cardiac dyssynchrony.

This analysis is based on 688 patients (85% of all patients in the CARE-HF trial) who had a measurement of lateral wall TAPSE at baseline by M-mode (13). In addition to TAPSE, echocardiographic measurements included: LV end-diastolic and end-systolic volumes, left ventricular ejection fraction (LVEF), RV end-diastolic area and end-systolic area, RV fractional shortening area, mitral regurgitation and tricuspid regurgitation (TR) by measuring the area of the jet divided by the area of the right atrium on color flow Doppler and trans-tricuspid gradient pressure. Echocardiography was repeated at 3, 9, and 18 months.

**Statistical methods.** Continuous data were summarized by the median (25th/75th) percentiles; categorical data were summarized by percentages. An analysis of variance model was used to look at the trend for continuous variables; the chi-squared test was used to look for trend for categorical variables (Tables 1 and 2). Data are shown by tertile of TAPSE. The primary outcome measure of the CARE-HF trial was all-cause mortality or an unplanned hospital stay for a major cardiovascular event. All-cause mortality was the principal secondary endpoint and the primary endpoint of an extension phase (3).

Survival curves were constructed with the Kaplan-Meier method; univariate and multivariate Cox regression modeling were performed to assess the independent impact of TAPSE on clinical outcome (14,15). We explored whether the inclusion of 3 additional covariates—TAPSE, TR jet/right atrial diastolic area, and TR pressure gradient—added prognostic value to previous models (14,15). Both baseline and 3-month post-implant values were considered. Where the proportional hazards assumption was violated, Cox models with time-dependent effects were considered. Over-fitting and goodness-of-fit was also addressed. Missing values at 3 months were imputed from baseline values to preserve the integrity of randomization.

**Results**

The maximum and minimum values for TAPSE in each tertile were 5.5 to 17.3 mm, 17.4 to 21.1 mm, and 21.2 to 33.4 mm, respectively; 93 patients had values ≤14 mm. Patients in the lowest tertile of TAPSE were more often men, were twice as likely to have ischemic heart disease (IHD), and had evidence of more severe heart failure (Table 1).

Cardiac resynchronization therapy reduced LV end-systolic and end-diastolic volumes and increased LVEF within 3 months of implantation, with evidence of further benefit by 9 months, which was sustained at 18 months (16). Mitral regurgitation was reduced by 3 months, and the effect was sustained (Table 2). Overall, CRT did not improve RV structure and function. The effects of CRT on LV structure and function and mitral regurgitation and the lack of effect on RV structure and function were broadly similar across tertiles of TAPSE, although patients in the worst tertile had a slightly greater reduction in RVES area and TR gradient (Table 2). Results for RV structure and function were similar when patients were divided according to the presence or absence of IHD (Fig. 1).

Among patients with a TAPSE measurement, 329 reached the primary endpoint (T1 = 145, T2 = 99, T3 = 85), and 213 died (Fig. 2). The median (interquartile range) follow-up, censored for death, was 748 days (58 to 950) days. A higher TAPSE at baseline was associated with a lower risk of the primary outcome (chi-square log-rank test: 27.1; p < 0.001) and better survival (chi-square log-rank test: 12.4; p < 0.001), regardless of treatment assigned. However, the effect of CRT on outcome was similar across tertiles of TAPSE (Figs. 2A and 2B). Analysis confined to the 93 patients with a TAPSE ≤14 mm also showed similar improvement in outcome, both for the primary endpoint (hazard ratio: 0.57, 95% confidence interval: 0.34 to 0.94, p = 0.029) and all-cause mortality (hazard ratio: 0.62, 95% confidence interval: 0.34 to 1.11, p = 0.11). Patients with worse TAPSE were more likely to die of heart failure. Caution should be applied to interpretation of CRT effects on mode of death in subgroups, due to the small number of events (Fig. 2B).

Adding measures of RV function to a published multivariable model (14) eliminated IHD as a predictor of mortality, replacing it with TAPSE measured at 3 months.
after randomization (Table 3). The following variables, as in the original published model, remained independently associated with higher all-cause mortality: less interventricular mechanical delay at baseline; New York Heart Association functional class IV at baseline; assignment to the control group; more severe mitral regurgitation at 3 months; and NYHA functional class IV at baseline. Although a marker of a worse overall prognosis, RV dysfunction was not an important determinant of the effects of CRT on LV structure or function and that the severity of RV dysfunction is a weak determinant of the effects of CRT on LV structure or function. Although a marker of a worse overall prognosis, RV dysfunction was not an important determinant of the effects of CRT on LV structure or function.

### Discussion

This analysis shows that CRT has little effect on RV function and that the severity of RV dysfunction is a weak determinant of the effects of CRT on LV structure or function. Although a marker of a worse overall prognosis, RV dysfunction was not an important determinant of the relative benefits of CRT.

As far as we are aware, this is the first study to investigate the effect of CRT on RV function in a randomized...
### Table 2: Changes in Quality of Life and Cardiac Function Between Baseline and 9 Months

<table>
<thead>
<tr>
<th>TAPSE Tertiles</th>
<th>CRT</th>
<th>Medical</th>
<th>CRT</th>
<th>Medical</th>
<th>CRT</th>
<th>Medical</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>T1</td>
<td>T2</td>
<td>T3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number with paired results</td>
<td>89</td>
<td>75</td>
<td>94</td>
<td>92</td>
<td>85</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>LVEDV (ml)</td>
<td>–27 (–67 to –3)</td>
<td>–1 (–29 to 15)</td>
<td>–59 (–98 to –22)</td>
<td>–11 (–39 to 7)</td>
<td>–49 (–107 to –6)</td>
<td>–6 (–38 to 16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>4 (1.3 to 9.2)</td>
<td>0.9 (–0.9 to 3.2)</td>
<td>5.6 (1.1 to 10.8)</td>
<td>1 (–1.7 to 3.7)</td>
<td>6.2(1.6 to 11.9)</td>
<td>1.2 (–0.7 to 4.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RA diastolic area, cm²</td>
<td>–4.8 (–8.4 to 1.8)</td>
<td>–3.7 (–7.1 to 2.2)</td>
<td>–3.8 (–7.7 to 0.6)</td>
<td>–1.9 (–7.0 to 1.7)</td>
<td>–5.2 (–9.2 to 0.7)</td>
<td>–2.4 (–3.7 to 0.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>MR jet area (%)</td>
<td>–4 (–13 to –2)</td>
<td>0 (–11 to 9)</td>
<td>–4 (–14 to 1)</td>
<td>0 (–9 to 5)</td>
<td>–3 (–9 to 3)</td>
<td>2 (–3 to 10)</td>
<td>0.001</td>
</tr>
<tr>
<td>IVMD (ms)</td>
<td>–24 (–41 to –4)</td>
<td>0 (–17 to 15)</td>
<td>–21 (–38 to –9)</td>
<td>–5 (–21 to 10)</td>
<td>–24 (–40 to –2)</td>
<td>1 (–9 to 13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TAPSE (mm)</td>
<td>1.1 (–0.1 to 3.7)</td>
<td>1.4 (–0.7 to 4.1)</td>
<td>0.4 (–1 to 3.6)</td>
<td>0.8 (–1.1 to 2.8)</td>
<td>–1.0 (–3.5 to 0.1)</td>
<td>–2.1 (–3.6 to 0.8)</td>
<td>0.50</td>
</tr>
<tr>
<td>RVES area (cm²)</td>
<td>–2.9 (–6.4 to 0.7)</td>
<td>–1.0 (–4.4 to 1.9)</td>
<td>–0.4 (–4 to 0.5)</td>
<td>–1.0 (–2.8 to 0.7)</td>
<td>–0.8 (–2.5 to 1.7)</td>
<td>–1.0 (–2.8 to 0.3)</td>
<td>0.38</td>
</tr>
<tr>
<td>RV fractional shortening area (%)</td>
<td>6 (1 to 15)</td>
<td>5 (0 to 13)</td>
<td>4 (–4 to 11)</td>
<td>3 (–3 to 8)</td>
<td>–1 (–11 to 5)</td>
<td>3 (–3 to 13)</td>
<td>0.38</td>
</tr>
<tr>
<td>Paired TR jet</td>
<td>41 (46%)</td>
<td>60 (80%)</td>
<td>45 (48%)</td>
<td>46 (50%)</td>
<td>47 (55%)</td>
<td>61 (66%)</td>
<td></td>
</tr>
<tr>
<td>TR jet area (cm²)</td>
<td>–0.6 (–2.3 to 0.8)</td>
<td>–0.5 (–2.2 to 0.9)</td>
<td>–0.4 (–1.3 to 1.4)</td>
<td>–0.4 (–1.7 to 0.3)</td>
<td>0.1 (–1.2 to 1.1)</td>
<td>–0.1 (–1.1 to 0.5)</td>
<td>0.41</td>
</tr>
<tr>
<td>RA diastolic area (cm³)</td>
<td>–0.9 (–7.7 to 1.4)</td>
<td>–1.3 (–4.3 to 0.9)</td>
<td>–0.9 (–3.9 to 1.9)</td>
<td>–0.6 (–4.7 to 1.2)</td>
<td>–0.5 (–2.5 to 1.4)</td>
<td>–1.1 (–3.8 to 1)</td>
<td>0.56</td>
</tr>
<tr>
<td>TR jet area/RA area (cm²)</td>
<td>–4.5 (–14.9 to 5.6)</td>
<td>–1.3 (–11.5 to 9.1)</td>
<td>–2.2 (–9.2 to 11.7)</td>
<td>–0.8 (–14.3 to 4.8)</td>
<td>3.8 (–4.2 to 12)</td>
<td>2.8 (–13.4 to 10.8)</td>
<td>0.32</td>
</tr>
<tr>
<td>Paired TR gradient</td>
<td>29 (33%)</td>
<td>28 (37%)</td>
<td>32 (34%)</td>
<td>16 (17%)</td>
<td>22 (26%)</td>
<td>20 (22%)</td>
<td></td>
</tr>
<tr>
<td>TR gradient, mm Hg</td>
<td>–8 (–11.7 to –3.4)</td>
<td>–1.6 (–10.5 to 6.3)</td>
<td>–0.4 (–5.6 to 3.7)</td>
<td>–2.8 (–6.1 to 2.8)</td>
<td>0 (–9.2 to 2.7)</td>
<td>–5.1 (–7.5 to –1.5)</td>
<td>0.42</td>
</tr>
</tbody>
</table>

*p for interaction between CRT and TAPSE level from an analysis of variance model combining TAPSE levels 2/3.

CRT = cardiac resynchronization therapy; other abbreviations as in Table 1.
controlled trial. Cardiac resynchronization therapy might be expected to improve RV function by lowering left atrial and pulmonary artery pressures due to improvements in LV function and mitral regurgitation (19–22). However, pacing leads might interfere with tricuspid valve function and RV apical pacing might impair RV function (23). However, we identified no substantial improvement in right heart function with CRT when compared with pharmacological therapy alone, in contrast to several (7,19), but not all (24), observational studies, although we might have missed subtle changes that can be measured by newer echocardiographic techniques, such as tissue Doppler or RV strain (24,25).

At baseline, LV systolic dysfunction was similar across tertiles of TAPSE, but those with worse TAPSE had more severe mitral regurgitation, higher pulmonary artery pressure, more severe TR and higher plasma concentration of N-terminal pro–B-type natriuretic peptide. The extent to which RV dysfunction reflects pulmonary hypertension or intrinsic RV dysfunction is uncertain and likely to vary over time and among individual patients (26). However, the high prevalence of IHD in patients with worse TAPSE suggests that RV ischemic damage might be common (7,19–22, 24–26). Poor baseline RV function was associated with a trend to smaller improvements in LV function in response to CRT, consistent with a previous report (12). However, this trend was accounted for by the high prevalence of IHD in patients with RV dysfunction. Patients with IHD are more likely to have myocardial scar, which will impair the beneficial remodeling response to both pharmacological interventions and CRT (27,28).

There is growing evidence, reinforced by this analysis, that RV rather than LV dysfunction might be the more important determinant of prognosis (1,26). Both lower TAPSE and higher TR gradient estimated at baseline were associated with an adverse prognosis, and this relationship

**Figure 1** Effects of CRT

Effects (between baseline and 9 months) of cardiac resynchronization therapy (CRT) compared with a control group on tricuspid annular plane systolic excursion (TAPSE) (A), tricuspid regurgitation gradient (TRG) (B), right ventricular end-diastolic area (RVED) (C), right ventricular (RV) fractional shortening area (D), left ventricular end-diastolic volume (LVEDV) (E), and left ventricular end-systolic volume (LVESV) (F) in patients in the lowest compared with the 2 highest tertiles (T) of TAPSE according to the presence or absence of ischemic heart disease (IHD).
was strengthened when re-estimated at 3 months after randomization. Interestingly, after measures of RV dysfunction were added to the prognostic model, the presence of IHD was no longer an independent predictor of outcome. This could also reflect the importance of RV damage due to ischemia (29). Whether, RV dysfunction or etiology is the more important driver of an adverse prognosis is uncertain. The strong statistical association between worse TAPSE and higher prevalence of IHD suggests that one might just be a surrogate for the other in such models.

Several observational (6,10) studies have suggested that patients with RV dysfunction receive less prognostic benefit from CRT. The problem with observational studies is that they are unable to distinguish between outcome with treatment and response to it (11). This analysis confirms
previous reports showing that, in patients who receive CRT, those with poor RV function will have a worse outcome. However, the change in prognosis (i.e., the response to treatment) is similar in patients with and without RV dysfunction. This contradicts assertions that CRT is ineffective in patients with substantial RV dysfunction (6,10). Whether the severity of RV dysfunction should influence the choice between CRT and CRT with defibrillator is uncertain. Patients with RV dysfunction are more likely to die of heart failure rather than suddenly. However, sudden death still represents a substantial proportion of deaths in patients with RV dysfunction, which might be reduced by implantation of CRT with defibrillator.

**Study limitations.** The current hypothesis was not defined prior to conducting the study. Ideally, the results should be confirmed in a prospective trial of patients with both RV and LV dysfunction, but it is not clear whether this would receive ethical clearance. Alternatively, data might be available from another randomized trial that could be analyzed retrospectively. A study of the size and duration of the CARE-HF trial is unlikely to have missed substantial effects of CRT on RV function but more modern imaging technologies might identify subtler effects. On the other hand, the study was not adequately powered to investigate the effects of CRT on outcomes, such as mode of death in subgroups of patients.

**Conclusions**

Right ventricular dysfunction is a powerful determinant of prognosis among candidates for CRT, regardless of treatment assigned, but does not diminish the prognostic benefits of CRT among patients enrolled in the CARE-HF trial.

These data illustrate the difference between “outcome with” and “response to” CRT, urging caution in the interpretation of observational data, and might help clinicians make appropriate clinical choices for their patients.

### Table 3

<table>
<thead>
<tr>
<th>Variables</th>
<th>HR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA functional class IV</td>
<td>2.16 (1.28–3.63)</td>
<td>0.004</td>
</tr>
<tr>
<td>NT-proBNP, 3 months (pg/ml)*</td>
<td>1.62 (1.41–1.86)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MR, 3 months (cm²)*</td>
<td>1.01 (1.00–1.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IVMD (ms)</td>
<td>0.98 (0.98–0.99)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRT</td>
<td>0.57 (0.53–0.60)</td>
<td>0.04</td>
</tr>
<tr>
<td>TAPSE, 3 months (mm)*</td>
<td>0.58 (0.40–0.84)</td>
<td>0.004</td>
</tr>
<tr>
<td>TAPSE (mm)* by tertile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>0.76 (0.56–1.04)</td>
<td>0.09</td>
</tr>
<tr>
<td>T3</td>
<td>0.69 (0.50–0.97)</td>
<td>0.03</td>
</tr>
<tr>
<td>Missing</td>
<td>0.97 (0.59–1.58)</td>
<td>0.91</td>
</tr>
</tbody>
</table>

NT-proBNP transformed by natural logarithms. *3-month values imputed by last observation carried forward where baseline data missing. The TAPSE by tertile replaced TAPSE continuous (mm), adjusting for same covariates. Hazard ratio (HR) for missing TAPSE gives an indication of bias. Q = quartile; other abbreviations as in Table 1.

### References


Key Words: chronic heart failure, prognosis, resynchronization, right ventricle.