

# CONTROVERSIES IN ARRHYTHMIA AND ELECTROPHYSIOLOGY

## QRS Duration Criteria to Select Patients for Cardiac Resynchronization Therapy

### *CRT Should Be Reserved for a QRS Duration $\geq 150$ ms: Pro*

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Cardiac resynchronization therapy (CRT) is now a major therapeutic tool in the management of patients with systolic heart failure. In several small- and large-scale studies, CRT led to statistically significant improvements in cardiac performance, promoted reverse remodeling, and reduced adverse clinical events, including death in patient populations with heart failure and prolonged QRS durations.<sup>1-4</sup> However, soon after these studies were completed and guidelines were written, it was recognized that these statistically very significant benefits, observed at the level of study cohorts, did not translate into clinical improvement in many individual patients receiving CRT according to the enrollment criteria of these previous studies, that is, symptomatic systolic heart failure with a QRS duration usually greater than 120 ms. Postapproval studies showed that one third to one half of patients receiving this treatment based on the guidelines do not respond to this treatment.<sup>5,6</sup>

#### **Response by Guglin and Curtis on p 442**

Treatment guidelines initially recommended CRT in patients with systolic heart failure with New York Heart Association (NYHA) III or IV symptoms and a QRS duration  $>120$  ms<sup>7-10</sup> and were extrapolated from the patient enrollment criteria of the 2 early major CRT trials.<sup>11,12</sup> Given the well-documented lack of response in a sizable fraction of patients who met these guideline criteria for CRT, cardiologists had to contend with a large group of CRT nonresponders, which led to the creation of special nonresponder clinics in some institutions.<sup>13</sup> This type of approach primarily focused on an attempt to optimize

the device settings echocardiographically after device implant when there was lack of a clinical improvement. However, lack of benefit from CRT has other causes, including a lack of a suitable electromechanical substrate. Therefore, patients may not derive any benefit no matter what type of device settings are used, and they may not even be appropriate candidates for this therapy. Can such patients be identified before a potentially futile implant? Indeed, careful examination of the early pilot studies with surrogate end points, 2 large-scale trials with hard outcomes (ie, Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure [COMPANION]<sup>11</sup> and Cardiac Resynchronization-Heart Failure [CARE-HF]<sup>12</sup>), and subsequent clinical trials designed to widen the indications for CRT (such as RETHINQ [Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS], Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy [MADIT-CRT], and RAFT [Resynchronization-Defibrillation for Ambulatory Heart Failure Trial]) provides valuable insight into the identification of patients who will not benefit from CRT. Subgroup analyses of all these trials suggest that patients with a QRS duration  $<150$  ms do not get any hemodynamic, echocardiographic, symptomatic, or survival benefit with CRT.

#### **Evidence From Studies With Surrogate End Points**

The lack of benefit of CRT in patients with heart failure with QRS durations  $<150$  ms has been observed in a multitude of

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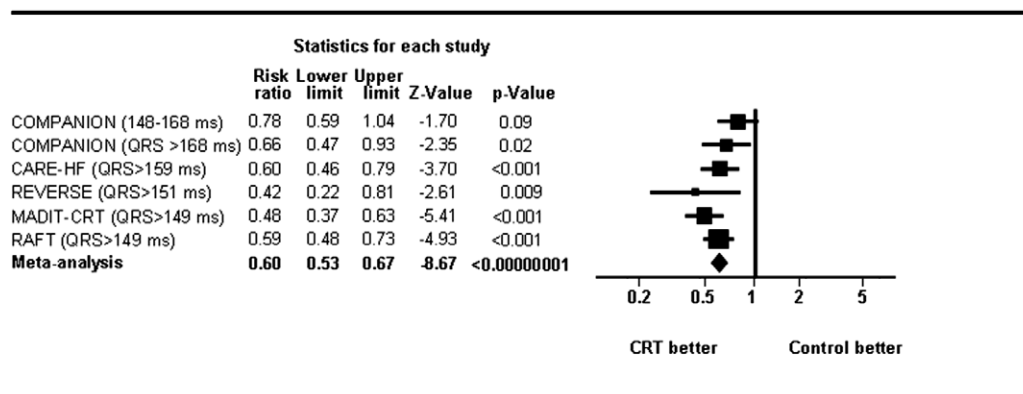
hemodynamic and echocardiographic studies, as well as in studies using cardiopulmonary stress test and quality of life measures. Auricchio et al<sup>1</sup> first observed that when the QRS duration was <150 ms biventricular pacing did not improve either the maximum left ventricular pressure derivative (LV+dP/dt) or the aortic pulse pressure, whereas those patients with longer QRS intervals had improvements in both parameters. Nelson et al<sup>14</sup> reproduced these findings a year later. Another very recent study confirms that LV+dP/dt increases significantly only in those patients with a QRS duration >150 ms.<sup>15</sup> In a randomized study, Auricchio et al<sup>16</sup> also showed that peak oxygen consumption ( $V_{O_2}$ ) and  $V_{O_2}$  at anaerobic threshold did not improve with LV pacing in patients with QRS durations between 120 and 150 ms. In contrast, both of these parameters improved significantly in patients with a QRS duration >150 ms. Similarly, 6-min walk distance and quality-of-life scores improved only in patients with a QRS duration >150 ms. With echocardiography, the REsynchronization reVERses Remodeling in Systolic left vEntricular dysfunction (REVERSE) study investigators showed that there was no reverse remodeling with CRT in patients with a QRS duration  $\leq$ 151 ms, contrasting with the significant reverse remodeling in those with longer QRS durations.<sup>2,17</sup> Finally, in an echocardiographic substudy of the PROSPECT (Predictors of Response to CRT) trial, responders to CRT had significantly longer QRS durations.<sup>6</sup>

### Evidence From Studies With Clinical End Points and Their Meta-Analysis

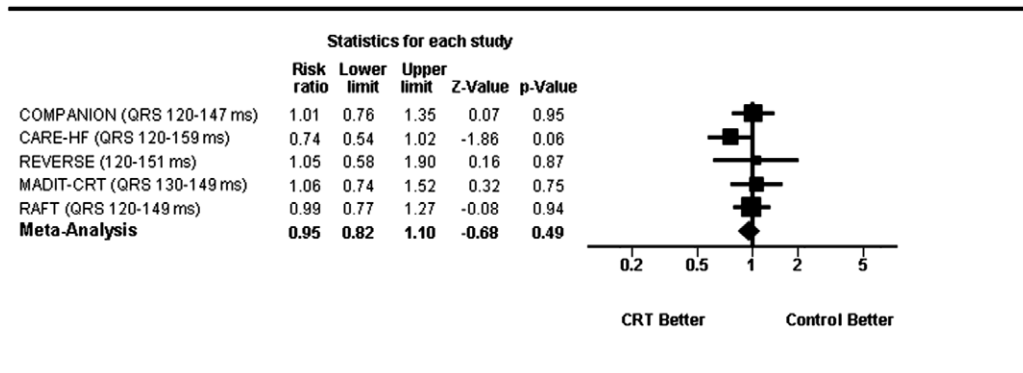
To date a total of 5 large-scale randomized clinical trials, enrolling a total of 5813 patients, reported the main outcome results for clinical events according to QRS duration at baseline. These trials include the COMPANION, CARE-HF, REVERSE, MADIT-CRT, and RAFT trials. A meta-analysis recently examined the clinical event reduction in these clinical trials according to baseline QRS duration.<sup>18</sup> All of these trials reported statistically significant reductions in their composite clinical events (always including death and heart

failure hospitalizations) in patients with a QRS duration of approximately  $\geq$ 150 ms. On meta-analysis, there was a highly statistically significant 40% reduction in composite clinical events with CRT as compared with no-CRT ( $I^2=32.1\%$ ;  $P<0.001$ ; Figure 1). In striking contrast, there was no statistically significant reduction in composite clinical events in any of these 5 clinical trials in the subgroups with a QRS duration of approximately <150 ms (Figure 2). On combined analysis, the meta-analytic risk ratio was 0.95 ( $P=0.49$ ), ruling out even a 20% risk reduction with 95% confidence ( $I^2=0\%$ ; 95% CI, 0.82–1.10). A meta-regression analysis examining the relationship between QRS duration as a ranked-variable and the clinical benefit of CRT (ie, the risk ratio) shows a tight correlation between the two ( $P<0.001$ ; Figure 3). In conclusion, this meta-analysis extends previous observations of lack of benefit on surrogate measures in patients with a QRS duration <150 ms to the lack of reduction in clinical events, including death and hospitalizations in such patients in the setting of randomized controlled clinical trials. In addition, other commonly implicated reasons for nonresponse, such as ischemic cardiomyopathy, do not seem to be as important a determinant for lack of clinical event reduction. For example, among the randomized controlled clinical trials included in this meta-analysis, namely CARE-HF, MADIT-CRT, and RAFT, all showed statistically significant clinical event reduction with CRT in ischemic cardiomyopathy; in COMPANION, there was an analogous strong trend for clinical benefit in patients with ischemic systolic heart failure.

The meta-analysis about lack of benefit in those with moderately prolonged QRS durations reignited a candid discussion about the appropriateness of the treatment guidelines within the journal publishing the article,<sup>19,20</sup> in the electrophysiology and cardiology community,<sup>21</sup> in the regulatory agency<sup>22</sup> as well as in the lay press.<sup>23,24</sup> In light of the findings of the study, an editorial by Stevenson<sup>19</sup> suggested that relying only on the primary end point while interpreting a series of positive clinical trials can be dangerous. Attention to certain subgroups that



**Figure 1.** Effect of cardiac resynchronization therapy (CRT) on composite clinical events in patients with severely prolonged QRS interval (ie, mostly >150 ms). CARE-HF indicates Cardiac Resynchronization-Heart Failure; COMPANION, Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure; MADIT-CRT, Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy; RAFT, Resynchronization-Defibrillation for Ambulatory Heart Failure Trial; and REVERSE, REsynchronization reVERses Remodeling in Systolic left vEntricular dysfunction. From Sipahi et al.<sup>18</sup>



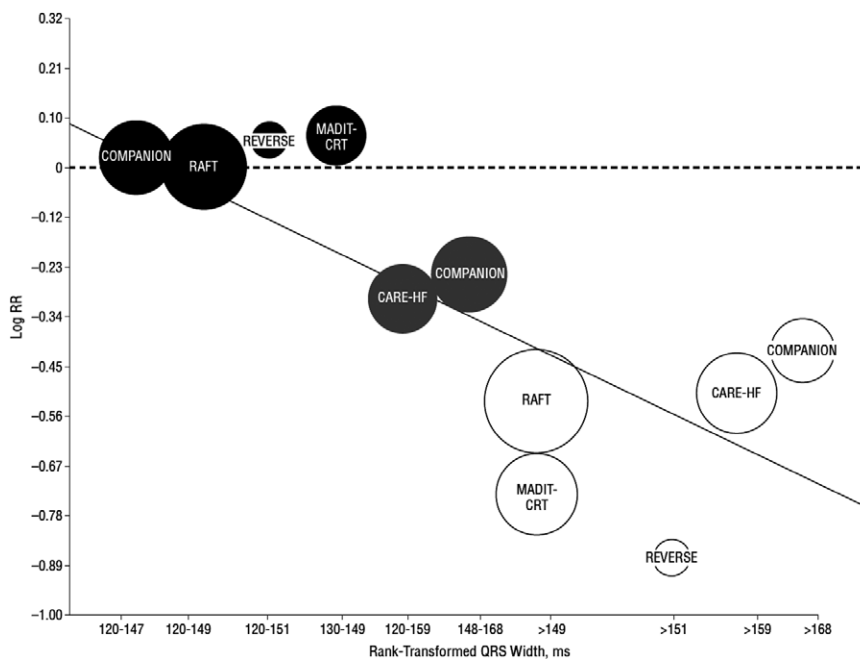
**Figure 2.** Effect of cardiac resynchronization therapy (CRT) on composite clinical events in patients with moderately prolonged QRS interval (ie, mostly <150 ms). CARE-HF indicates Cardiac Resynchronization-Heart Failure; COMPANION, Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure; MADIT-CRT, Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy; RAFT, Resynchronization-Defibrillation for Ambulatory Heart Failure Trial; and REVERSE, REsynchronization reVERses Remodeling in Systolic left vEntricular dysfunction. From Sipahi et al.<sup>18</sup>

consistently show lack of benefit can provide crucial information while shaping treatment guidelines.<sup>19</sup>

### Reaction of the Food and Drug Administration to the Meta-Analysis

On the publication of this meta-analysis, the representatives of the Food and Drug Administration (FDA) from the Center

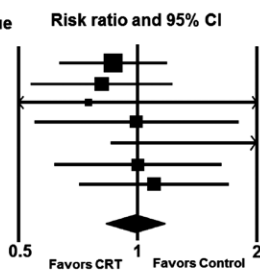
for Devices and Radiological Health and Office of Device Evaluation sent a letter to the editor.<sup>22</sup> They pointed out that QRS morphology may be more important for predicting response to CRT. They stated that in an analysis of the MADIT-CRT trial, there was no benefit in patients with nonleft bundle-branch block (LBBB) morphology receiving CRT and suggested additional analyses examining the



**Figure 3.** Relationship between baseline QRS duration and the effect of cardiac resynchronization therapy on composite clinical events. Each circle represents a QRS subgroup within a trial. The sizes of the circles are proportional to the sample size of each subgroup. The dashed line corresponds to a log risk ratio of 0 (ie, risk ratio of 1.00), where there is no net benefit or harm. The further the circles are below the 0 line, the larger the clinical benefit. There was a high statistically significant relationship between the QRS duration and the log risk ratio ( $P=0.00018$ ). Accordingly, groups with QRS ranges below 150 ms did not benefit from CRT (black circles, log odds ratio  $\approx 0$ ). Clinical benefit started to appear when cases with a QRS duration >150 ms were included (grey circles) and became more prominent with increasing QRS width (white circles). CARE-HF indicates Cardiac Resynchronization-Heart Failure; COMPANION, Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure; MADIT-CRT, Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy; RAFT, Resynchronization-Defibrillation for Ambulatory Heart Failure Trial; REVERSE, REsynchronization reVERses Remodeling in Systolic left vEntricular dysfunction; and RR, risk ratio. From Sipahi et al.<sup>18</sup>



Study name	Risk Ratio	Lower Limit	Upper Limit	Z-Value	p-Value
COMPANION - Non-LBBB	0.86	0.63	1.17	-0.96	0.34
CARE-HF - RBBB	0.81	0.54	1.22	-0.99	0.32
CARE-HF - IVCD	0.75	0.24	2.33	-0.50	0.62
MADIT-CRT - RBBB	0.99	0.55	1.79	-0.03	0.97
MADIT-CRT - IVCD	1.44	0.88	2.36	1.45	0.15
RAFT - RBBB	1.00	0.62	1.62	0.00	1.00
RAFT - IVCD	1.10	0.71	1.69	0.43	0.67
<b>Meta Analysis</b>	<b>0.97</b>	<b>0.82</b>	<b>1.15</b>	<b>-0.32</b>	<b>0.75</b>



**Figure 4.** Effect of cardiac resynchronization therapy (CRT) on composite clinical events in patients with non-LBBB morphology. CARE-HF indicates Cardiac Resynchronization-Heart Failure; IVCD, intraventricular conduction delay; LBBB, left bundle-branch block; CI, confidence interval; COMPANION, Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure; MADIT-CRT, Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy; RAFT, Resynchronization-Defibrillation for Ambulatory Heart Failure Trial; RBBB, right bundle-branch block; and REVERSE, REsynchronization reVERses Remodeling in Systolic left vEntricular dysfunction. Modified from Sipahi et al.<sup>28</sup>

interactions between QRS duration, morphology, and CRT benefit. Unfortunately, independent investigators have not had access to the individual patient data held by the sponsors to perform these analyses. To date, such an analysis has been limited to MADIT-CRT by regulatory agencies, and the FDA did not examine the lack of benefit according to QRS duration or morphology before or after approval of CRT. Subsequently, CRT devices have been approved for all patients with systolic heart failure with NYHA III and IV symptoms with a QRS duration >120 ms without any attention to the degree of QRS prolongation or QRS morphology.

In this context, recently performed computerized simulations demonstrate that development of LBBB almost always leads to a severe prolongation of QRS duration, and it has been suggested that the traditional QRS cutoff of >120 ms for defining LBBB is too low and has to be increased substantially.<sup>25</sup> As it can be predicted from these observations, patients with LBBB and those with a QRS duration >150 ms overlap greatly. For example, 77% of patients with LBBB in MADIT-CRT trial also had a QRS duration >150 ms. On the other hand, only 11% of the MADIT-CRT population had a non-LBBB QRS morphology with a duration above 150 ms.<sup>26</sup> Given the close relationship between LBBB and severe QRS prolongation and the different pathways of depolarization in the non-LBBB conduction abnormalities, it makes physiological sense for only the patients with LBBB to respond to CRT. This pathophysiology should therefore be independent of functional class as confirmed by recent trials of patients with NYHA I and II symptoms, such as those included in MADIT-CRT trial, and the original cohorts of patients with NYHA III and IV symptoms included in the earlier trials.

### QRS Duration or QRS Morphology or Both?

It has long been suspected that, in addition to the duration of the QRS wave, the type of conduction abnormality causing the QRS prolongation could be an important determinant of response to CRT.<sup>27</sup> Although examination of the interactions of QRS duration, morphology, and CRT benefit requires individual patient-level data, a trial-level meta-analysis examining CRT benefit according to QRS morphology has been published.<sup>28</sup> This meta-analysis included the same clinical trials as the original QRS duration meta-analysis with the exception of REVERSE (which did not provide outcome data according to QRS morphology and therefore could not be included). This

analysis showed that patients with either right bundle-branch block (RBBB) or intraventricular conduction delay (IVCD) did not receive any clinical benefit from CRT ( $n=1232$ ,  $P=0.0$ ; risk ratio [RR] for composite primary outcome = 0.97 [95% CI, 0.82–1.15];  $P=0.75$ ) ruling out a 20% risk reduction in this group of patients (Figure 4). Conversely, patients with LBBB received significant benefit ( $n=3949$ ;  $P=72.7\%$ ; RR=0.64 [95% CI, 0.52–0.77];  $P=0.00001$ ). This is not an unexpected finding because heart failure with RBBB or IVCD is physiologically different from that with LBBB.<sup>29,30</sup> Investigators have shown that LV activation times are at best only minimally prolonged in RBBB.<sup>31</sup> Therefore, it is understandable that biventricular pacing in an attempt to synchronize contraction of the left ventricle does not improve outcomes in patients with RBBB. Although IVCD seems to be the second most common conduction abnormality after LBBB in patients with LV systolic dysfunction, the change in LV activation times in the setting of IVCD has not been examined systematically. Nevertheless, in the meta-analysis, there was no evidence of benefit of current CRT systems in patients with RBBB ( $n=424$ ; RR=0.91 [95% CI, 0.69–1.20];  $P=0.49$ ) or IVCD ( $n=525$ ; RR=1.19 [95% CI, 0.87–1.63];  $P=0.28$ ), when examined separately.<sup>28</sup> On the other hand, the highly significant risk reduction in patients with LBBB, when examined as a whole, suggests that CRT implantation in some patients with LBBB and a QRS duration <150 ms may be appropriate.

### Reaction of the Heart Failure Society of America: Updated Guidelines

After the publication of these findings, the Heart Failure Society of America revised its treatment guidelines for CRT (Table).<sup>32</sup> The Heart Failure Society of America uses 4 levels of strength in its guideline recommendations. These include “is recommended,” indicating that the therapy should be part of routine care and exceptions minimized; “should be considered,” indicating that the majority of patients should receive the intervention; “may be considered,” indicating that patient individualization is needed in the application of therapy; and “is not recommended.” Importantly, biventricular pacing therapy is now recommended with strength of evidence A only for patients in sinus rhythm with a widened QRS interval ( $\geq 150$  ms) not attributable to RBBB and LV ejection fraction ( $<35\%$ ) who have NYHA II or III symptoms despite optimal medical therapy. Greater clarity to these





**Table. Indications for Cardiac Resynchronization Therapy: 2011 Update From the Heart Failure Society of America Guideline Committee**

2010 Guideline	Summary of Change for Updated Guidelines
Biventricular pacing therapy is recommended for patients in sinus rhythm with a widened QRS interval ( $\geq 120$ ms) and severe LV systolic dysfunction LVEF ( $< 35\%$ ) who have persistent moderate to severe HF (NYHA III) despite optimal medical therapy (strength of evidence A)	Change QRS to $\geq 150$ , add not due to right bundle-branch block, add NYHA II
Selected ambulatory NYHA IV patients in sinus rhythm with QRS $\geq 120$ ms and LV systolic dysfunction may be considered for biventricular pacing therapy (strength of evidence B)	Change QRS to $\geq 150$ ms  New Recommendation: CRT may be considered for patients with a QRS interval of $\geq 120$ to $< 150$ ms and severe LV systolic dysfunction (LVEF $\leq 35\%$ ) who have persistent mild to severe HF (NYHA functional class II to ambulatory class IV) despite optimal medical therapy (strength of evidence B)
Biventricular pacing therapy may be considered for patients with atrial fibrillation with a widened QRS interval ( $\geq 120$ ms) and severe LV systolic dysfunction LVEF ( $\geq 35\%$ ) who have persistent moderate to severe HF (NYHA III) despite optimal medical therapy (strength of evidence B)	Expand to include NYHA II
In patients with reduced LVEF who require chronic pacing and in whom frequent ventricular pacing is expected, biventricular pacing may be considered (strength of evidence C)	No change

recommendations with respect to other subgroups would be provided by an individual patient-level meta-analysis of existing trials examining the interactions of QRS duration and morphology as well as new trials testing the usefulness of echo criteria of dyssynchrony in patients with a QRS duration between 120 and 150 ms and non-LBBB conduction abnormalities.

In conclusion, the current data do not support the implantation of CRT in patients with heart failure with only moderately prolonged QRS durations and QRS morphologies other than LBBB. Considering the cost, invasiveness, and morbidity (eg, infections) of CRT, we do not think empirical CRT implantation in patients with QRS duration  $< 150$  ms to see what might happen is justified.

## Disclosures

None.

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KEY WORDS: cardiac resynchronization therapy ■ ECG ■ heart failure ■ pacemaker

## Response to Ilke Sipahi, MD, FACC, and James C. Fang, MD, FACC

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The article by Sipahi and Fang adds little to their argument from a previously published meta-analysis,<sup>1</sup> which was flawed by a categorical division of continuous QRS width into values over and under 150 ms. Meanwhile, several studies have been published since we submitted our viewpoint, and they confirm our stance that QRS duration should be approached as a continuous variable or divided into more categories.

Dupont et al<sup>2</sup> demonstrated that all patients with left bundle-branch block (LBBB) had a significant increase in left ventricular ejection fraction after cardiac resynchronization therapy. The increment was  $12\pm 12\%$  in those with a QRS duration  $\geq 150$  ms ( $21\pm 8\%$  to  $32\pm 13\%$ ) and  $8\pm 10\%$  in those with a QRS duration  $< 150$  ms ( $23\pm 8\%$  to  $32\pm 13\%$ ). The difference in response between the groups was not significant. Anyone who works with patients with heart failure knows that the difference between a left ventricular ejection fraction of 20% and 30% can be critical in terms of morbidity, mortality, and quality of life. Not surprisingly, mean New York Heart Association functional class improved similarly in both groups, from 2.9 to 2.0. Moreover, 13 out of 85 patients with LBBB and a QRS duration  $< 150$  ms seemed to be super-responders. The authors also showed that QRS morphology, namely LBBB, is more important than QRS duration for deriving benefits from cardiac resynchronization therapy. If the opinion of our opponents became official policy, all these advantages would be denied to unfortunate patients with LBBB and systolic dysfunction, whose QRS does not happen to be wide enough by their definition.

Sipahi and Fang cite the study by Ploux et al,<sup>3</sup> who analyzed the acute hemodynamic response to biventricular pacing in patients with heart failure with narrow, moderately prolonged, and severely prolonged QRS durations. Our opponents rightfully state that invasive left ventricular dP/dt measurements revealed a significant response in patients with a QRS duration  $\geq 150$  ms and no significant response in patients with a QRS duration  $< 150$  ms. However, when we look at the numbers, 11 patients with a moderately prolonged QRS had an increase in dP/dt by  $4.4\pm 6.9\%$ ;  $P=0.06$ . Of course, we would all like to see a  $P$  value of  $\leq 0.05$ , but honestly, for these 11 patients, a  $P$  value of 0.06 is not to be dismissed lightly. It indicates only a 6% chance that this increase in left ventricular contractility was unrelated to resynchronization.

Finally, and most convincingly, in the analysis of the REsynchronization reVERses Remodeling in Systolic left vEntricular dysfunction (REVERSE) trial, Gold et al<sup>4</sup> showed that both morphological (decrease in left ventricular size) and clinical benefits from cardiac resynchronization therapy increased progressively with each 10 ms increment in QRS duration, starting at about 120 ms.

If we are looking for a magical number in a resynchronization saga, it is 120 ms, demarcating complete LBBB from normal conduction. In a person with LBBB and systolic dysfunction, cardiac resynchronization should be viewed as an important tool for prolonging survival and improving quality of life.

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