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EDITORIAL COMMENT

When Is it Appropriate to Withdraw Cardiac Resynchronization Therapy? Guesses and Evidence*

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In designing clinical trials, investigators consider many factors. The population should have the disease in question and have needs unmet by conventional care that might be improved by intervention. Guessing which clinical variables will identify patients who respond to a therapy, especially when its mechanism of action is uncertain, is hazardous. It would be astonishing if such guesses, and the hypotheses on which they were based, proved to be entirely correct. For cardiac resynchronization therapy (CRT), those planning trials guessed that a QRS duration >120 to 130 ms would identify patients likely to benefit from CRT. This guess turns out to be accurate to within 10 to 20 ms. That ventricular dyssynchrony, measured by imaging, is the key substrate on which CRT acts has, so far, proved a somewhat poorer guess (1).

Recent trials and meta-analyses suggest that it is inappropriate to attempt CRT in patients who have a QRS duration <120 ms and that the benefits of CRT are uncertain when QRS duration is 120 to 140 ms (2,3). However, many patients with a QRS duration <140 ms already have had a CRT device implanted. In this issue of *JACC: Heart Failure*, Sohaib et al. (4) suggest that it may be appropriate to "switch off" CRT in patients with a "short" QRS. They go on to suggest that a randomized controlled trial could be conducted in patients who already have received a CRT device but who have a "short" QRS. This is also a very sensible suggestion. So far, so good. However, there are some problems with their suggestions.

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Sohaib et al. (4) imply that the EchoCRT (Echocardiography Guided Cardiac Resynchronization Therapy) investigators thought that the adverse effects of CRT with a defibrillator compared with an implantable cardioverter defibrillator (ICD) reflected some detrimental aspect of the more complex procedure (3). However, patients in EchoCRT were randomized only after successful CRT device implantation. Sometimes, trialists just do not state the obvious when they consider the alternatives implausible. By excluding the possibility that immediate damage caused by switching on CRT explains its adverse effect on outcome in patients with a narrow QRS, Sohaib et al. (4) have confirmed what almost everyone else had already assumed: the problem with CRT in patients with a QRS duration <130 ms is the long-term physiological effects of biventricular pacing.

The title, correctly, asks for deactivation of ventricular pacing in patients with a "narrow" QRS who have had a CRT device implanted. Unfortunately, the authors then stray into the thorny issue of QRS morphology. Experts in the statistical analysis of clinical trials have tried to educate their clinical cousins on the dangers of subgroup analysis. Clinical experts creating guidelines for heart failure generally avoided paying much attention to subgroup analyses, that is, until they were required to make recommendations on CRT; then caution was thrown to the wind and confident pronouncements were made about an interaction between QRS morphology and the effects of CRT. New analyses cast doubt on the importance of QRS morphology for selecting which

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patient should have CRT (2). There is a strong relationship between QRS duration and morphology, and any analysis of one may be confounded by the other. Also, a high proportion of patients with dilated cardiomyopathy will have left bundle branch block (LBBB), and these patients have a better prognosis than patients with left ventricular systolic dysfunction due to ischemic heart disease (5). In observational studies, patients with LBBB who receive CRT will do better, not because they have LBBB but because they have dilated cardiomyopathy rather than ischemic heart disease. However, the reduction in mortality with CRT, in relative terms, is similar regardless of the etiology of LV dysfunction, and therefore the absolute reduction in mortality with CRT tends to be greater in those with ischemic heart disease (6). RAFT (Resynchronization-Defibrillation for Ambulatory Heart Failure Trial) showed no difference in the effect of CRT on time to death or first hospitalization for heart failure among patients with right bundle branch block, although there was an adverse trend in those with shorter QRS duration and nonspecific intraventricular conduction delay (7). MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy) suggested a worse outcome among patients with right bundle branch block morphology, but there were only 6 deaths in the control group; it would be dangerous to conclude anything on such a small number of events (8). An individual-patient data meta-analysis of 5 substantial trials suggested that QRS duration but not morphology was an independent predictor of CRT response (2). Perhaps an individual-patient data meta-analysis including more trials will show a different result, but we should not pre-judge the issue. To draw strong conclusions about the importance of QRS morphology for the prediction of the effects of CRT on the basis of the data published so far seems most unwise. By using a conventional approach to the interpretation of subgroup data, it should be assumed that the benefits of CRT are similar regardless of QRS morphology until proven otherwise. QRS morphology may just be a surrogate measure for QRS duration.

Whether PR prolongation influences the effects of CRT is also uncertain (9). Analyses will be confounded in studies in which the control group received a device because patients with delayed atrioventricular dysfunction will be at greater risk of, potentially deleterious, right ventricular pacing. The authors do not question the use of CRT in patients with atrial fibrillation, reflecting the surprising paucity of data for this group of patients (10). As we do not really know how CRT works (probably in different ways for different patients at different times and circumstances), it is dangerous to assume that CRT works for most patients with atrial fibrillation (1,5). If shortening atrioventricular delay without exacerbating ventricular dyssynchrony is an important mechanism of benefit for CRT, then it will be ineffective in patients with atrial fibrillation.

The authors suggest a trial comparing various programming modes, including, apparently, dual-chamber right atrial/ventricular pacing. This seems unwise. Trials of ICDs suggest that right ventricular pacing, which presumably worsens dyssynchrony, increases morbidity and perhaps mortality. A large, simple trial comparing CRT with backup pacing only, to avoid right ventricular pacing, in patients with a "narrow" QRS regardless of morphology that had all-cause mortality as its primary endpoint would be a good choice. However, what threshold should be chosen to define a narrow QRS? A normal QRS duration is <100 ms. Most would agree that a QRS duration of 100 to 120 ms, although abnormal, is unlikely to benefit from CRT. Once QRS duration is >140 ms, the benefits of CRT are clear, and there is little evidence that QRS morphology matters. Accordingly, a withdrawal trial that included patients with a QRS duration <140 ms or who were in atrial fibrillation would be appropriate. The MUSTIC (MUltisite STimulation In Cardiomyopathies) trials showed, in a double-blind, cross-over trial of patients with advanced heart failure and a QRS duration >150 ms, a remarkable patient preference for CRT (11). Treatment periods were only 3 months. Accordingly, a double-blind withdrawal trial with 3-month treatment periods could stratify patients into 3 groups: 1) clear preference for CRT-on, in which case do not deactivate; 2) clear preference for CRT-off, in which case deactivate; or 3) no clear preference, in which case randomize to long-term on/off.

There are other issues to consider. Patients in the control group of most trials of CRT had an implanted device, either backup pacing or an ICD. As noted earlier, we do not really know why CRT confers benefit; prevention of marked bradycardia might be important for some patients at some times (12). Only studies with a device-free control group, which must therefore be unblinded, can reveal the full effect of CRT on prognosis. Finally, all the analyses shown are done by intention-to-treat, which is a robust but conservative method for determining whether an intervention is effective or not but will be a gross underestimate of the effects of treatment actually delivered when some patients do not receive the intended intervention and some patients in the control group do. In the COMPANION (Comparison of

Medical Therapy, Pacing, and Defibrillation in Heart Failure) trial, 26% of patients assigned to the control group were thought to have crossed over to CRT implantation, and yet these were included in the mortality analysis as though they had not received a device. In CARE-HF (CArdiac Resynchronization-Heart Failure), a per protocol analysis suggests that the effect on mortality may be twice as large as that based on the intention-to-treat analysis (13,14).

Sohaib et al. (4) have raised an important issue and suggested an obvious solution, which the clinical community should act swiftly to address.

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