Echocardiography for Cardiac Resynchronization Therapy Selection
Fatally Flawed or Misjudged?

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After the publication of the PROSPECT (Predictors of Response to CRT) trial, the use of echocardiography for the assessment of mechanical dyssynchrony and as a possible aid for selecting patients for cardiac resynchronization therapy has been heavily criticized. Calls have been made to observe the current guidelines and implant according to the entry criteria of recent major trials. However, although this approach is currently to be recommended, the attempt to identify patients who will not receive the benefits of cardiac resynchronization therapy and whose clinical condition may be worsened should continue. Devices are not analogous to drugs: initial costs are higher, complications are significant, and the device cannot readily be withdrawn. Professional resources and the costs to society are high and wasted if devices are implanted inappropriately. Rather that discarding the attempt to identify the most suitable patients pre-operatively, further work is needed to refine the techniques and new clinical trials performed. A combination of methods that include finding the site of latest mechanical activation, myocardial scar localization, and assessing venous anatomy pre-operatively may help to identify those who will not derive any benefit or be potentially worsened. (J Am Coll Cardiol 2009; 53:1960–4) © 2009 by the American College of Cardiology Foundation

Without doubt cardiac resynchronization therapy (CRT) is good treatment for patients with heart failure (1). The benefits of CRT are similar in magnitude to those seen with angiotensin-converting enzyme (ACE) inhibitors and beta-blockers, and they are incremental to the benefits of medical therapy. However, though the implant success rate is about 95%, there are complications: 4.3% of patients develop mechanical problems, and there is a 0.3% to 0.5% risk of death and a 1% to 2% risk of wound or device infection (1). By 11 months, lead problems requiring intervention occur in about 7% of patients. Furthermore, in earlier trials, a consistent feature was that about one-third of the patients did not appear to respond clinically or in terms of echocardiographic measured ventricular volumes (2–4). Indeed, it is a well-recognized clinical observation that CRT does not work in all patients and, indeed, may worsen heart failure in a few. In the recent PROSPECT (Predictors of Response to CRT) trial, the clinical composite response was unchanged in 50% and actually worsened in 16%, 35% had a <15% reduction in left ventricular (LV) end-systolic volume, and in 9%, LV volumes actually increased by more than 15% (5). Therefore, CRT can apparently worsen heart failure in some patients, probably by inducing dyssynchrony where none existed before. It would appear reasonable to try to identify patients more accurately before implantation. One way is to use echocardiography to measure mechanical dyssynchrony, which, theoretically, it is well-suited to do. Subsequently, a large number of studies were performed using various echocardiographic indexes, many of which appeared to be able to predict clinical responders from nonresponders. This approach, however, has been criticized since the publication of the PROSPECT trial (5), and in this issue of the Journal, Hawkins et al. (6) have written another highly critical review of this approach to CRT selection. However, although they claim that the echocardiographic approach to assess mechanical dyssynchrony is fatally flawed, their arguments are weakened by several unsubstantiated comments. For example, they claim that “many clinicians have rejected international guidelines in favor of echocardiographic selection criteria.” The evidence for this allegation is absent, and it is extremely unlikely that any hospital in the U.S. or Europe is deliberately ignoring recommended guidelines and implanting or denying implants on the basis of echocardiographic measurements alone. But a fundamental issue in this debate is whether clinical response matters at all.

Do Nonresponders Matter?

Hawkins et al. (6) state, “Response is itself a flawed dichotomy. All medical therapies present a continuous
spectrum ranging from harm to benefit” and “On the basis of the evidence in populations, we prescribe ACE inhibitors for all patients with heart failure. We do not dwell on selecting which patients will benefit. The arguments apply equally to drugs and devices” (6). But do they? This is wrong on at least 2 counts. First, devices are different from drugs: the up-front costs are higher for the device and the implantation procedure, the initial complications are potentially greater (infection, coronary sinus dissection, and so on), and a device is much more difficult to remove than a drug to stop. Most clinicians would not equate an expensive device with a drug, and this view was recently endorsed in another editorial (7). Second, one of the major developments in current pharmacotherapy is directed at exactly the problem of identifying those patients who are most likely to benefit and least likely to have side effects—so-called “tailored or individualized therapy.” Pharmacogenomics has the same aim. Also, in most major drug trials in heart failure, patients were excluded from entry if they had already experienced an adverse effect with the study drug, which cannot be done with devices.

Hawkins et al. (6) also imply that patients who worsen clinically may still benefit. However, this seems highly unlikely. All of the successful medical therapies in heart failure that have reduced mortality have also shown some degree of improvement in symptoms, LV volumes, and reverse remodeling, as seen with beta-blockers, ACE inhibitors, and aldosterone antagonists (8). Furthermore, the same seems to be true for CRT. Recently Kronberg et al. (9) published long-term follow-up data of 179 patients who had CRT or a CRT defibrillator implanted with a mean left ventricular ejection fraction (LVEF) of 22.5% and a mean QRS duration of 176 ms. Mortality at 5 years was 53%. In both univariate and multivariate analysis, a lack of improvement in New York Heart Association (NYHA) functional class was the strongest predictor of mortality. QRS shortening was unrelated to mortality. Cha et al. (10) from the Mayo Clinic also published their results of 309 patients who received CRT of which 174 returned for follow-up and 127 had repeat echocardiography. The baseline clinical characteristics and survival were similar among those who did or did not return for follow-up. Survival after CRT was associated with a decrease in NYHA functional class (risk ratio: 0.43, p = 0.0004) and an increase in the ejection fraction (risk ratio: 0.94, p = 0.02). Change in ejection fraction and NYHA functional class were correlated, and adjusting for this covariance, a change in NYHA functional class was associated with improved survival. They concluded that patients who experienced improved symptoms, ventricular function, and/or hemodynamics have a better survival after CRT. In a recent study, Ypenburg et al. (11) found that in 302 CRT patients more reverse remodeling resulted in less heart failure hospitalizations and lower mortality during long-term follow-up. The negative responder group had a markedly lower survival rate. These data, therefore, strongly suggest that mortality is related to symptomatic and hemo-
dynamic improvement. It seems highly unlikely that, given all of the other work in heart failure, if a treatment causes symptoms to deteriorate, LV volumes to increase, and ejection fractions to decline it will show a mortality benefit.

The argument, therefore, that trying to identify nonresponders is a worthless exercise appears extreme. To most, common sense suggests that implanting a device into patients who will gain no clinical benefit or are even made worse is not likely to be fruitful or cost-effective. It is interesting that the largest randomized mortality trial of CRT—the CARE-HF (Cardiac Resynchronization Heart Failure) study (12)—has not published so far any data on the percentage of clinical responders or nonresponders, even though NYHA functional class and quality of life were documented in this study. However, analysis of the results shows that all patients were in NYHA functional class III or IV at baseline as required for entry, and by the 18-month follow-up period, 152 patients in the medical therapy group were still in NYHA functional class III/IV, but interestingly, so were 80 patients who received CRT. It is not known whether these patients, whose NYHA functional class did not improve, received any mortality benefit or not. Also there has been no published data on the relation of outcome to changes in NYHA functional class or quality of life. In addition, there is a cost implication of nonresponders. Hawkins et al. (6) state that “Unlike drugs, the majority of the lifetime cost for devices is incurred at implantation. Identifying so-called ‘nonresponders’ is therefore attractive to governments, health services, and other payers.” But the obvious corollary is that identifying nonresponders is probably not attractive to the device industry either, as lower number of devices will be implanted. This obvious converse argument is not heard very often. (All of the clinical trials of CRT, including the PROSPECT trial, have been funded by device companies.) However, the cost of not identifying nonresponders to society as a whole is probably very high.

**What Is the Potential Cost of Nonresponders?**

Left bundle branch block (LBBB) has been the main criteria for selecting patients for CRT as recommended in the guidelines. LBBB, though, is present in about 25% of the general heart failure population (13) and in 35% of patients with more severe LV systolic dysfunction, typical of patients who might be considered for CRT. In Europe, the estimated heart failure prevalence is 2% to 2.5% overall (14). The yearly incidence of heart failure in persons age >55 years is 15 per 1,000 of the population. One in 3 persons age
>55 years will develop heart failure. Currently, up to 14 million people in Europe have heart failure. Therefore, possibly there are 5 million people with heart failure and LBBB in Europe. Of these potential 5 million candidates for CRT (i.e., that have heart failure and LBBB) in Europe, 30% may well turn out to be nonresponders, which is about 1.5 million people. At a conservative estimate of €5,000 per device, this equals €7.5 billion, which could be a complete waste of money. In addition, these 1.5 million nonresponders would have a risk of death at time of implantation of 0.5%, which of 1.5 million nonresponders approximates to 22,500 people. It is possible, therefore, 22,500 people in Europe could die at the time of implantation during a procedure that would have given them no possible clinical benefit in terms of symptoms or functional improvement. On top, we could add in the risk of infection, removal of the system, and coronary dissection complications, which were found in 2.4% of all patients in the CARE-HF study. The figures for the U.S. are likely to be similar although costs will be higher. Therefore, the argument in favor of identifying nonresponders is powerful, not only to prevent unnecessary harm to patients but also because of the considerable waste of financial and medical resources.

### Reasons for Lack of Clinical Response

It is obvious that multiple reasons may account for a poor clinical response, which will vary from individual to individual. These include the lack of correctable mechanical dyssynchrony, a poor lead position (not positioned at the site of latest activation), the presence of a lateral wall myocardial scar, dislodgement, and suboptimal pacemaker settings for interventricular timing and atroventricular intervals. Although Hawkins et al. (6) extol the usefulness of the simple electrocardiogram (ECG), they appear to confuse the effects of electrical and mechanical dyssynchrony. By many measures the ECG is a poor indicator of mechanical dyssynchrony; although a very wide QRS is commonly associated with mechanical dyssynchrony, this is not always the case (15,16), which is not surprising given the very variable nature of activation in LBBB (17). However, there is evidence that CRT is beneficial in those with mechanical dyssynchrony, a poor lead position, and 498 subjects with standard indications for CRT were enrolled. Twelve echocardiographic parameters of dyssynchrony based on both conventional and tissue Doppler methods were evaluated. An improved clinical composite score and a reduction in LV end-systolic volume >15% at 6 months was considered to be a positive response to CRT. The main outcome was that clinical composite score was improved in 69% of 426 patients, and LV end-systolic volume decreased >15% in 56% of 286 patients with paired data. The ability of the 12 echocardiographic parameters to predict either clinical composite score or the LV end-systolic volume responses was poor; sensitivity ranged from 9% to 77% and specificity from 31% to 93%. All of the parameters tested had an area under the receiver-operating characteristics curve of <0.62. In addition, there appeared to be a great variability in analysis of dyssynchrony parameters. After this disappointing result, the use of echocardiography or any method for assessing mechanical dyssynchrony has been largely dismissed for the reasons given by Hawkins et al. (6). Is this response justified based on this trial?

### Analysis of the PROSPECT Trial Results

The interobserver coefficient of variation for dyssynchrony measurements varied from 32% to 72%. The intraoperator coefficient of variation varied from 16% to 24%. Of course this may just reflect the general difficulty of the tissue Doppler imaging (TDI) methodology. However, the variability of interobserver coefficient of variation for the measurement of end-systolic volume was 14.5%. This raises concerns that the problem was more with the quality of
echocardiography in these centers. This was reinforced by the fact that the centers reported the mean LVEF to be 23.6 ± 7% but the core laboratory measured mean LVEF was 29.3 ± 10%; in fact, 20.2% of the subjects had a core laboratory measured LVEF >35% and should not, therefore, have been included in the study according to the entry requirements.

There were further problems with image quality. One-third of the images could not be analyzed even for LV end-systolic volume. In fact, only 286 of 426 patients had the volumes measured. There were no effective measures from the echocardiography core laboratory for echocardiography quality control throughout the study, and this may well have impacted the results of the other centers despite some initial training. Third, there was a problem with multiple echocardiographic machines; 37% of machines were GE manufactured, 50% were Philips, and 12% were Siemens. Forty percent were old machines incapable of acquiring good quality color-coded TDI images, and, unsurprisingly, they failed in the offline analysis. More importantly, all TDI data from the Siemens’ machines were excluded because of suboptimal images. It also needs to be remembered that the previously published data are vendor specific.

Site Selection

Another important factor was that the sites were selected because they were high-volume implantation sites. They were selected, therefore, on their CRT experience, not echocardiographic experience. The availability of the appropriate echocardiography equipment and echocardiographic expertise, TDI and dysynchrony assessment, was apparently overlooked. This study was, of course, funded by a device manufacturer, and the sites were selected by the device company. Echocardiography training was minimal and consisted of 1 day, which clearly would be inadequate for TDI analysis. A learning curve for CRT implantation is well recognized, but there is also a learning curve for echocardiographic assessment of dyssynchrony in both knowledge and techniques. The 3 echocardiography core laboratories were also pre-selected by the manufacturer that sponsored the study. They had a limited track record for publications on TDI. Therefore, is the reported variability for the measurements really reflecting the variability of the technical and analytical skill of the echocardiography centers rather than the measurements per se? However, the variability of the measurements was reported as a failure of echocardiography techniques. TDI patterns are variable and can be difficult to interpret, and, indeed, examples have been shown in recent publications to illustrate the unreliability of TDI. However, by moving the cursor around the ventricle and adding in other techniques such as strain, it can be possible to identify which is the correct systolic peak in the majority of patients.

Thus, the PROSPECT study was a nonrandomized study, which assessed too many echocardiographic parameters, was funded by a device company, and had center selection based on implantation volumes rather than echocardiography track record. Consequently, there must be serious concerns about the quality control of the echocardiography laboratories in these centers. This trial is not sufficient grounds to discard the whole attempt to measure mechanical dysynchrony. Future multicenter trials that attempt to identify nonresponders using echocardiography before implantation need to recognize not only the importance of device implantation training but also that the same standards of expertise and training should apply to the echocardiographic assessment of dyssynchrony with significant periods of hands-on training.

However, without a doubt there are technological and methodological problems with current echocardiography techniques, which Hawkins et al. (6) have thoroughly highlighted, but new echocardiographic developments are occurring. TDI does have limitations: angle dependency, normal segments are affected by tethering from adjacent segments (due to scar or ischemia), and translational movement will impair the effectiveness of TDI techniques (24). Some of these are overcome by strain imaging, and studies are now appearing using speckle tracking, which shows clear superiority, particularly radial strain and torsion can also be evaluated (25–27).

Conclusions

The reality is that not all patients implanted with CRT devices improve and some worsen, and there is an imperative to improve our selection procedures to prevent harm being done. This concept should not be dismissed lightly. However, it is certain that a combination of methodologies will need to be used, with magnetic resonance imaging to identify lateral wall scars, 2-dimensional speckle tracking to find the area of latest mechanical activation, and computed tomography scanning to assess venous anatomy before implantation. New large trials are required to properly test this more targeted approach. This will mean progress for our patients and a more intelligent use of limited medical resources. Unreasonable exhortations to follow current guidelines should not be allowed to stifle developments that may refine those same guidelines for the overall benefit of our patients and society.

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