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EDITORIAL COMMENT

Guiding Left Ventricular Lead Positioning and Refining Ability to Predict Response and Nonresponse to Cardiac Resynchronization Therapy Using dP/dt_{max}

Killing 3 Birds With 1 High-Fidelity Wire?*

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Ability to predict response to cardiac resynchronization therapy (CRT) has been one of the challenges in the treatment of heart failure (HF). Although CRT has been associated with significant clinical improvement in large clinical trials (1–3), approximately 30% of the patients do not experience clinical improvement (4). Several factors of CRT nonresponse have been implicated, such as inappropriate left ventricular (LV) lead positioning, the extent and location of scar tissue, lack of LV mechanical dyssynchrony, and inadequate atria-to-ventricle (AV) or ventricle-to-ventricle (VV) optimization. Recent trials demonstrating benefit in patients with New York Heart Association (NYHA) functional class I and II HF (5,6) will likely increase the number of eligible patients for CRT. However, despite advances in treatment, technology, and experience, the ratio of nonresponders still remains at approximately one-third (6). With the expansion of CRT-eligible patients, the absolute number of nonresponders will likely increase, underlining the importance of improving strategies in predicting nonresponse and therefore improving selection for CRT.

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Prediction of response. Several strategies have been developed to improve response to CRT, including better selection of patients, optimal LV lead placement, and optimization of device programming. The characteristics of patients likely to respond to CRT are already well-known (Fig. 1), such as nonischemic dilated cardiomyopathy, wide QRS (≥150 ms), left bundle branch block, low burden of myocardial scar, preserved posterolateral wall function, and placement of LV lead in posterior or lateral position (7). In this issue of the *Journal*, Duckett et al. (8) observed that optimizing LV lead placement with the rise in maximum rate of left ventricular pressure (LV-dP/dt_{max}) was associated with reduction in left ventricular end-systolic volume (LVESV), improvements in NYHA functional class, and quality of life at 6 months. Acute hemodynamic improvement in dP/dt_{max} with optimal LV lead position has been described before (9–11). Duckett et al. (8) for the first time extend these findings to demonstrate the association of optimal coronary vein selection guided by dP/dt_{max} with reversal of remodeling and clinical response.

The patients enrolled in the study by Duckett et al. (8) fulfilled the standard guideline criteria for CRT but also had left bundle branch block, and their mean QRS duration was 160 ± 23 ms. Seventy percent demonstrated an improvement in dP/dt_{max} during LV pacing; and 77% of these patients demonstrated a reduction in LVESV. A ≥10% rise in dP/dt_{max} during LV pacing at the optimal site predicted reduction in LVESV with a 94% sensitivity and 64% specificity. This approach is quite sensitive in predicting the responders but does not seem to provide incremental sensitivity over conventional criteria such as QRS duration. In the study by Duckett et al. (8), QRS duration of >146 ms had a higher (100%), and the echocardiographic measurement of interventricular mechanical delay had a similar (94%) sensitivity to predict response, compared with the ≥10% rise in dP/dt_{max} during LV pacing.

Prediction of nonresponse. Despite our ability to recognize patients with high likelihood of response to CRT well, the major challenge lies in predicting the long-term nonresponse to CRT. In the study by Duckett et al. (8), specificity or the ability of the increase in LV-dP/dt_{max} ≥10% with CRT to detect the nonresponder at 6 months (64%) was not better than the specificity of baseline QRS duration >146 ms (64%) or interventricular mechanical delay ≥40 ms (86%). Baseline QRS >150 ms by itself has been reported to have a higher specificity of 80% in predicting nonresponse to CRT (12). A >11% rise in dP/dt by Duckett et al. (8), however, increased the specificity to 86%, raising the possibility that even a higher cutoff such as ≥15% rise in dP/dt_{max} could further enhance the ability to detect the nonresponder. Interestingly, 26% of the patients who had a ≥10% rise in dP/dt_{max} in this study did not have a reduction in LVESV; thus, by this approach, the false positive rate was

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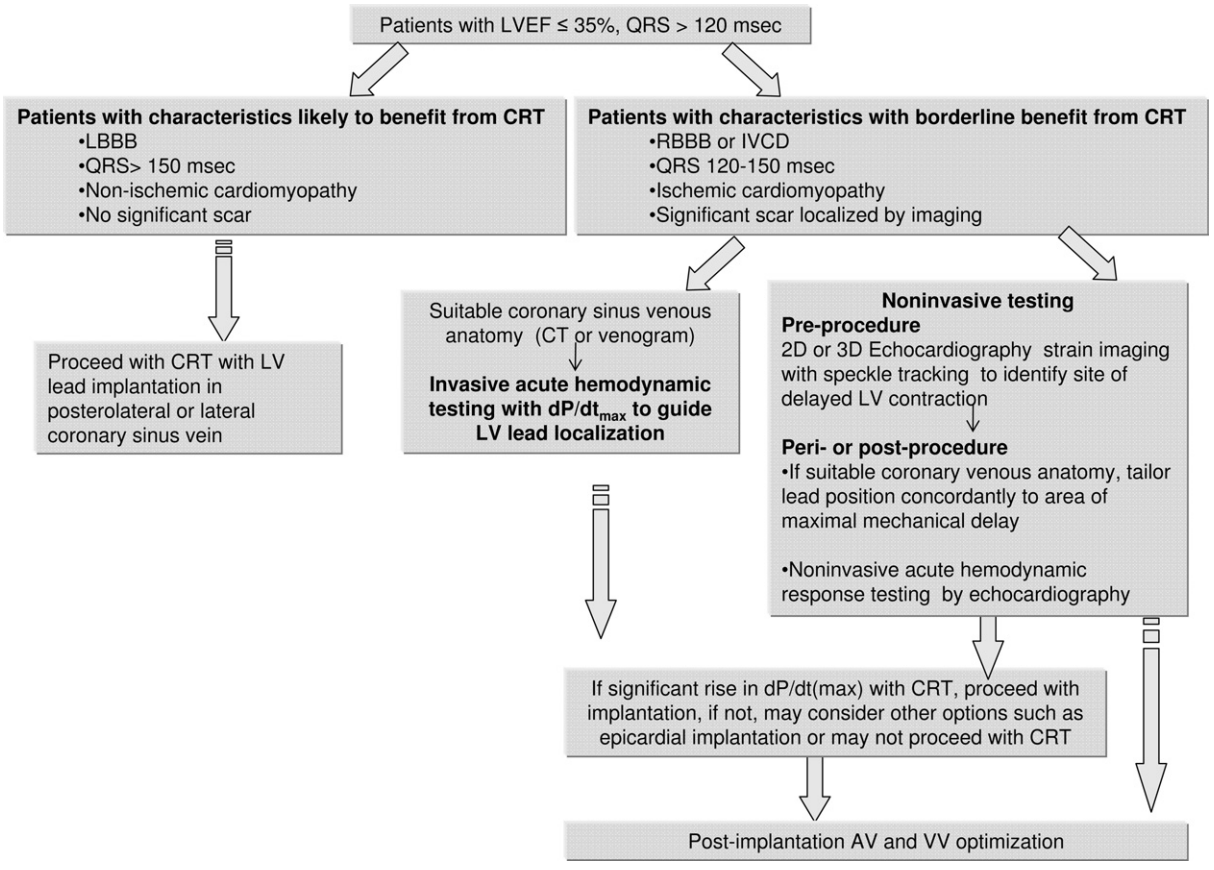

Figure 1 **Proposed Algorithm for Future Studies**

A proposed algorithm for future studies to test whether guided left ventricular (LV) lead localization according to acute hemodynamic response to LV pacing in patients without characteristics likely to benefit from cardiac resynchronization therapy (CRT) would be comparable to a standard implantation approach in patients with characteristics likely to benefit from CRT. 2D = 2-dimensional; 3D = 3-dimensional; AV = atria-to-ventricle; CT = computed tomography; dP/dt_{max} = maximum rate of left ventricular pressure rise; IVCD = intraventricular conduction defect; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; RBBB = right bundle branch block; VV = ventricle-to-ventricle.

not improved when compared with the 30% false positive rate in the historical CRT criteria in the clinical trials (4). One of the very important findings of Duckett et al. (8) was that the false negative rate was only 10% (negative predictive value 90%); thus, if the acute hemodynamic response was absent, it was unlikely that the patient would respond to CRT. More importantly, the approach seemed to provide incremental information on subgroups of patients with characteristics of borderline benefit from CRT, such as narrow QRS or ischemic cardiomyopathy. According to Figure 5 in this study (8), the specificity as well as the sensitivity in the ischemic cardiomyopathy subgroup was close to 100%, emphasizing importance of utility in these patients.

Reversal of remodeling and long-term symptomatic benefit. The magnitude of symptomatic benefit in CRT trials in patients with NYHA functional class III and IV HF is modest and consistent (1–3) with the placebo-subtracted improvement in NYHA functional capacity seen in 15% to 30% of the patients (4). In the study by Duckett et al. (8), most patients had an improvement in NYHA functional class (91%) and quality of life (94%), but only 56% had a reduction in LVESV. Although reversal of remodeling has been shown to correlate with clinical outcomes with CRT (13), as much as 28% of patients have improvement in symptoms without reversal of remodeling (14). Due to the absence of a control group, this raises further questions of whether some of the clinical improvement was attributable to the placebo effect or nonblinding, whether there were benefits of CRT independent of reversal of remodeling, or whether there was a treatment effect other than CRT.

Added procedural risk of optimization of LV lead placement with dP/dt_{max}. The LV lead location is an important factor in achieving response to CRT. Findings of Duckett et al. (8) and others (9–11) strongly support the use of dP/dt_{max} to optimize LV lead placement. This approach unfortunately might be limited by coronary vein anatomy, lead delivery and stability, added risk, and extended duration of the procedure. However, a 3% complication rate of coronary vein dissection and the average procedure time of 138 ± 38 min in

this study were comparable to historical data (1,2,15). In this study, ≥2 coronary sinus veins were present in a majority (91%) of the patients. In other studies, however, approximately 50% of patients had only a single vein, and as many as 20% did not have a feasible vein that reached the LV free wall (16,17). Thus, dP/dt can be helpful to identify the best site for the LV lead in patients with feasible coronary vein anatomy, and the risk of acute hemodynamic testing might be acceptable in patients without the classical features of high likelihood of response (Fig. 1).

Future directions. Unfortunately, the major limitation of the study by Duckett et al. (8) was absence of a control group. Future studies with a risk-stratified approach as depicted in Figure 1 will help clarify whether LV lead localization guided by acute hemodynamic response would be better, compared with a control group with standard approaches. In patients with characteristics of high likelihood of benefit from CRT, the added risk of extra testing with dP/dt might not be warranted. In those without such characteristics, invasive (9–11) or noninvasive (18) testing of acute hemodynamic response during CRT implantation to guide LV lead implantation might be beneficial. Additionally, pre-procedure noninvasive imaging to identify site of delayed LV contraction to tailor lead position (19) might be helpful. Finally, whether a nonresponse to early surrogate testing will identify the chronic nonresponder to CRT, with respect to hard clinical end points, remains to be answered. Without such evidence, it would be difficult to withhold CRT in patients with the standard indications.

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Key Words: acute hemodynamic response ■ cardiac resynchronization therapy ■ heart failure ■ remodeling.