Over 20 years ago, Cazeau et al. (1) described a 54-year-old man with left bundle branch block (LBBB) and class IV congestive heart failure who responded remarkably to 4-chamber pacing (1). Six weeks of cardiac resynchronization therapy (CRT) delivered by standard right-sided endocardial pacing coupled with left atrial and left ventricular (LV) epicardial pacing resulted in a 17-kg diuresis and improvement from New York Heart Association functional class IV to II symptoms. Would that it were always so easy.

In the 2 decades since that original report, both the promises and the limitations of CRT have become clearer. Large randomized clinical trials have established that, in appropriate patients, CRT significantly reduces morbidity and mortality (2–4). However, a persistent level of nonresponse remains in 25% to 50% of patients (5). There are a host of correctable reasons for nonresponse (6), but there will always be a cohort of patients whose anatomy (e.g., absence of a coronary sinus [CS], diffuse posterolateral scar tissue) precludes effective epicardial LV pacing. What is more, even for an individual “responder,” one wonders if the potential response could be greater than that achieved. Physiological ventricular activation in the setting of intact His-Purkinje conduction proceeds in a carefully orchestrated pattern, with early activation of LV tissue along the interventricular septum, followed by rapid distal ventricular activation in an endocardial-to-epicardial direction. In the setting of typical LBBB, activation of the LV is delayed, often with a line of blockage resulting in a U-shaped pattern of ventricular activation (7). Conventional CRT has focused pacing regions of latest activation at the epicardial posterolateral LV. LV pacing from the epicardial surface has advantages, but they are clearly advantages of expediency (e.g., ease of access, avoidance of risk of systemic thromboembolism) rather than physiology.

LV endocardial pacing to deliver CRT therapy is attractive, then, for 2 reasons: it can overcome constraints of CS anatomy and potentially augment CRT response. Morgan et al. (8) recently reported results from the ALSYNC (ALternate Site Cardiac ResYNChronization) investigation, a study of LV endocardial pacing achieved by lead placement antegrade across the mitral valve. Pacing was achieved in nearly 90% of patients, and the response to CRT appeared robust. There were 5 patients who experienced a cerebrovascular accident (despite anticoagulation), however, reinforcing the thromboembolic risk associated with lead placement in the LV cavity.

Recently, Mafi-Rad et al. (9) described a means of achieving LV endocardial pacing by placing a transvenous lead through the interventricular septum, thereby avoiding risk of thromboembolism. It is in that context that Rademakers et al. (10) introduce the current investigation in which the electromechanical effects of LV endocardial pacing are examined and compared with those of conventional CRT.

In this issue of JACC: Clinical Electrophysiology, Rademakers et al. (10) studied 13 dogs with LBBB (7 with superimposed myocardial infarction [MI]) and 12 CRT patients (7 nonresponders, 5 with LV lead issues including dislodgement or phrenic stimulation) referred for LV endocardial pacing. In canine

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subjects, electromechanical response to CRT was assessed by multielectrode epicardial bands and by pressure catheter measurement. Four pacing configurations were assessed: right ventricular (RV) apex-LV epicardium (conventional CRT); RV apex-LV septum endocardium (plunge electrode); LV septum endocardium; and RV apex-LV septum-LV epicardium. All pacing configurations, compared with baseline RA pacing, “reduced total activation time and QRS duration to a similar amount.” RV-lateral epicardial LV pacing reduced QRS duration by 17%, whereas RV-LV septal endocardial pacing reduced QRS duration by 20%. The mechanical consequences of all 4 pacing modes were similar, with “all pacing modes increase[ing] LVdP/dtmax by $\sim 15\%$.”

In the clinical studies, patients were paced in 3 configurations: RV apex-LV septum; RV apex-LV lateral endocardium; and RV apex-LV lateral epicardium (conventional CRT). As was the case with the canine model, all configurations of CRT improved LV mechanical function comparably (by 10% to 15% over baseline). In 6 of the 12 patients studied, RV/LV septal pacing resulted in the highest LV dP/dtmax achieved. Electrical mapping data or QRS analysis in the human subjects is not available. All studies, both in canine and in human subjects, were acute only.

What, then, to make of these data, which seem to turn the long-held dogma of pacing at sites of latest LV activation on its head? How can pacing at a site of early electrical activation (i.e., the LV surface of the ventricular septum) yield electromechanical results comparable to those of conventional CRT? The answer may lie in global LV activation times. In the canine data, pacing in any configuration studied resulted in global activation that was significantly more rapid than baseline LBBB (with or without superimposed MI). This rapid activation may have been achieved differently (colliding septal and lateral wave fronts, versus a single right-to-left sweep of activation), but in all cases, the LV was activated within 40 to 60 ms, contrasted with 80 ms at baseline. How this rapid electrical activation was achieved is not addressed in the current study, although different possibilities (penetration of the His-Purkinje system versus rapid myocyte-myocyte endocardial conduction) are mentioned in the Discussion.

The mechanism matters, and given the expertise of Rademakers et al. at detailing electrical activation patterns and mechanism, there is something of a lost opportunity here (although I am sure further studies will be forthcoming). We are told in the canine component of the study that “all CRT conditions reduced asynchrony of activation, even to some extent in the infarcted region,” but there is nothing about patterns or depth of fibrosis that might allow for conclusions about how rapid endocardial activation was achieved. Does pacing toward the apex blunt response to LV endocardial pacing? Are there issues of anisotropy, pacing site/scar relationship, or other factors that influence the effectiveness of endocardial activation? The human data presented also leave significant questions unanswered. Little is offered in terms of how electrical activation translated into mechanical response; and we are to be encouraged by the fact that acute mechanical responses were equivalent among the different pacing modalities? This was, after all, a population in which 7 of 12 patients were nonresponders to conventional CRT, suggesting that “equivalence” to conventional CRT here may not be an entirely positive descriptor.

Despite the circumscribed aspects of this investigation, there is every reason to believe that the results put forth by Rademakers et al. (10) are of real clinical significance. Hyde et al. (11) recently published a model of CRT delivery allowing for stepwise evaluation of different pacing sites and myocardial components, including structural characteristics and rapid endocardial conduction. They found that recruitment of rapidly conducting LV endocardial tissue explained the increased response to CRT seen (in modeling) with endocardial pacing. I think the study by Rademakers et al. (10) is exciting, and although it has some acknowledged limitations, nevertheless, it is among the first tentative steps in a new direction. Investigations of LV endocardial pacing have largely presented the concept as a fallback measure, a strategy reserved for situations in which conventional CRT is impossible due to anatomic constraints. Increasingly, however, there are lines of evidence suggesting that more physiological reproduction of ventricular activation may have distinct electromechanical benefits. Data from the study by Rademakers et al. (10) seem to fit within that new approach to CRT, where activation of the LV endocardium first is to be sought after, not settled for.

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