EDITORIAL

Phase analysis of myocardial SPECT to understand mechanisms of disease and therapy

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Right ventricular (RV) pacing is lifesaving in patients with advanced sinus node and atrioventricular node dysfunction. The resultant conduction pattern, however, has been associated with progressive deterioration in left ventricular (LV) function.[1] The pathophysiological basis of this association is attributed to the fact that LV activation originating from the RV apical pacing site proceeds through myocardial rather than specialized conduction tissues, thus causing dyssynchrony.[2] Evidence of this lies in the surface electrocardiogram, which shows a wide left bundle-branch block when the RV is paced. Interestingly, in patients with symptomatic LV systolic dysfunction and wide QRS in whom cardiac resynchronization therapy with biventricular pacing has established prognostic benefit, it is those with widest QRS (>150 ms) LBBB that derive the most consistent benefit, indicating that these patients perhaps have the most severe degrees of LV dyssynchrony.[3] In order to place the origin of LV activation closer to specialized conduction tissue, alternative approaches to RV apical pacing including RV septal and RV outflow tract pacing have been explored.

In this issue of the Journal, Zang et al[4] report on an interesting study exploring the differential effects of RV pacing at the apex vs septum on LV mechanical synchrony assessed by gated single-photon emission computed tomography (SPECT) and LV function at 6 months. Thirty-nine patients, all with indications for permanent pacing, were randomly allocated to one of the two RV pacing sites. Notably, all patients had normal LV systolic function (EF > 60%). The power calculation provided by the authors indicates that this sample size was adequate to demonstrate significant differences between groups in LV dyssynchrony parameters. With >95% RV pacing in both groups, the main findings were that (1) the QRS duration was markedly longer in the apical pacing group, (2) there was a significant difference in one measure of mechanical synchrony (phase standard deviation, PSD) but not the other (phase histogram bandwidth, PHB) between groups at 6 months (worse in the apical pacing group), (3) there was an improvement in measures of LV synchrony from week 1 to 6 months in the septal pacing group, but no change in the apical pacing group, and (4) there was no difference in the LV systolic function or end-systolic volume between the groups at 6 months.

Prior studies have provided considerable evidence of the detrimental effects of RV apical pacing on LV hemodynamics, perfusion, synchrony, structure, and function.[5] Studies cited in the manuscript and others[6] have suggested that LV function and hemodynamics are better preserved in patients with RV septal or outflow tract pacing compared to RV apical pacing, although the findings across such studies have been inconsistent and long-term outcome benefits have not been shown. Thus, the findings of this study by Zang et al are not unexpected. Two specific points are however, noteworthy: First, the patients in this study all had normal LV systolic function, whereas the detrimental effects of RV pacing appear to be most pronounced in patients with abnormal LV systolic function.[7] Second, while the power analysis was performed for the phase analysis parameters, we are not told whether the study was adequately powered to demonstrate a difference in LV ejection fraction and end-systolic volume. Thus, the reader is left to wonder if the lack of evidence of deterioration in LV function may have been due either to the small study sample or short duration of follow-up.

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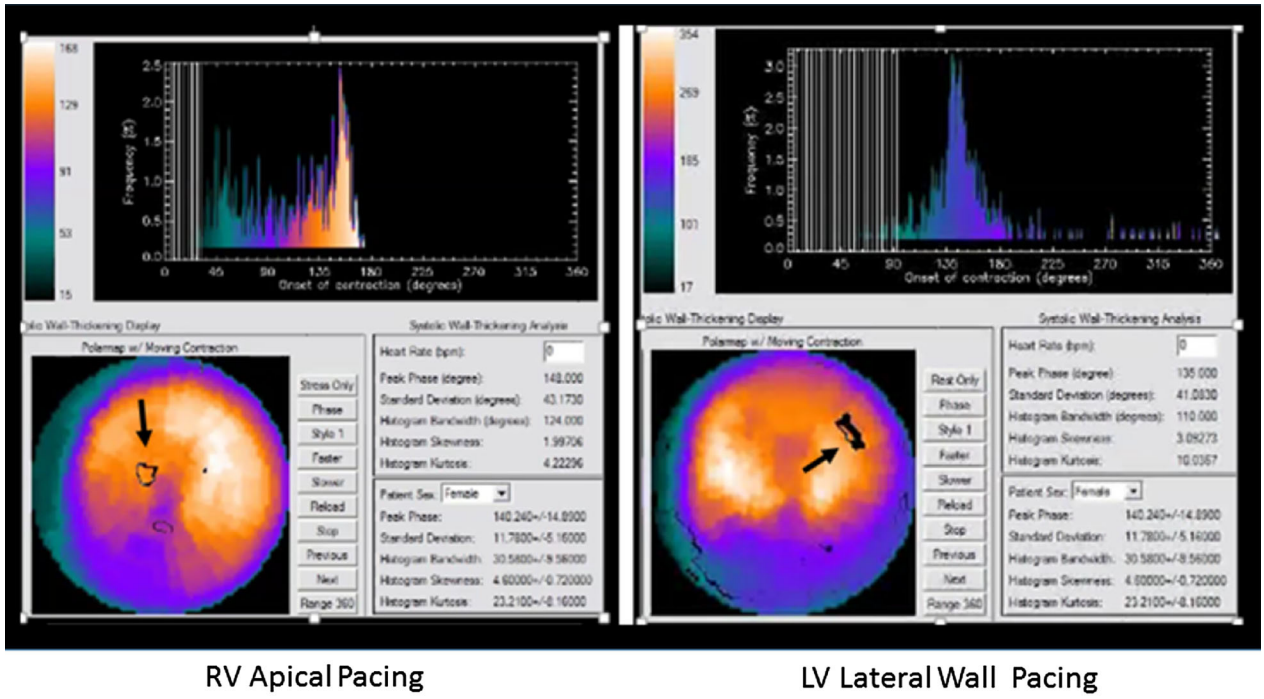

Figure 1. The sequence of LV regional mechanical activation evaluated by phase analysis of myocardial SPECT in a patient with a biventricular pacemaker. The *top panels* show the phase histogram and the *bottom panels* show a perfusion polar map with the region of earliest activation of the LV (*arrow*) superimposed on it. The initial scan (*left panel*) was obtained during RV apical pacing (LV lead turned off), and shows earliest activation of the LV at the apex. A subsequent scan (*right panel*) was performed with LV pacing (RV lead turned off) and shows initial activation in the antero-lateral wall of the LV, corresponding to the position of the LV lead in the coronary sinus. The phase histograms show greater dyssynchrony (wider phase histogram bandwidth) during RV pacing than LV pacing.

What is novel in this study is the approach used for the assessment of LV dyssynchrony. Pioneered by one of the authors of this study, the use of phase analysis of myocardial perfusion SPECT to measure LV dyssynchrony is highly repeatable and widely available.[8] In addition, it facilitates a comprehensive assessment of LV size and function, location and magnitude of myocardial ischemia and scar, LV shape indices, and the specific pattern of LV mechanical activation.[9] While the two parameters used in this study, PSD and PHB, are both validated measures of LV dyssynchrony, it is not known whether differences in the magnitude and pattern of dyssynchrony have variable effects on these parameters, thus explaining the finding of a significant impact of RV apical pacing on PSD but not PHB. In order to better explore mechanisms, it would also have been useful to know the sequence of regional LV mechanical activation with the two RV pacing sites and how they differed in pattern from LV activation during sinus rhythm and native conduction. An imaging modality with high temporal resolution is needed to assess the sequence of regional mechanical activation accurately. Unlike echocardiography or CT where the temporal resolution is easily measured by the pulse repetition frequency and gantry rotation time, respectively, the temporal resolution of SPECT phase analysis is less intuitive to understand. The essential step in the SPECT approach to LV dyssynchrony assessment is the derivation of regional count activity curves which essentially are myocardial thickening curves (based on the partial volume effect).[8] The relatively low temporal fidelity of these curves derived from 8 or 16-bin-gated SPECT studies is improved exponentially by Fourier transformation.

How does one determine the exact temporal resolution of a myocardial thickening curve? Chen et al[10], in an elegant phantom study, reported that phase shifts of 1/64th (or 5.6°) of a cardiac cycle can be resolved by this technique. The example from our laboratory illustrated in Figure 1 shows how the site of initial mechanical activation of the LV differs between RV apical and LV lateral wall pacing in a patient with LV systolic dysfunction and wide QRS who had cardiac resynchronization therapy (CRT) with a biventricular

pacemaker, and can be resolved by phase analysis of SPECT. Thus, in patients with LV dyssynchrony and a prolonged LV activation time (wide QRS), the temporal resolution of the phase analysis approach is sufficient to analyze the sequence of LV activation. However, whether the technique can resolve the timing of regional contraction in patients with normal QRS and LV systolic function remains to be determined.

Phase analysis of myocardial SPECT is now an established approach to LV dyssynchrony assessment. Large, multicenter studies are required to define its role in patient selection for CRT. However, many prior studies have demonstrated its utility in understanding mechanisms.[11-13] The current study is yet another example of how phase analysis of myocardial SPECT can be used to explore mechanisms of disease and therapy.

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