Right ventricular apical pacing–induced left ventricular dyssynchrony is associated with a subsequent decline in ejection fraction

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BACKGROUND In patients with normal left ventricular (LV) ejection fraction (EF), the interposition of chronic, high-dose right ventricular apical (RVA) pacing may produce late EF decline.

OBJECTIVE To test the hypothesis that LV dyssynchrony, defined echocardiographically and apparent early after interposition of pacing, would be greater in patients who subsequently demonstrated EF decline.

METHODS Ninety-one patients with normal prepacing EF who underwent atrioventricular node ablation and subsequent high-dose RVA pacing were studied. Transthoracic echocardiograms were performed early (median 4 months) and late (median 28 months) after interposition of pacing, with a significant decline in EF between these studies defined as $\geq$5%. Speckle-tracking longitudinal strain analysis of the early echocardiogram was performed to quantify dyssynchrony. In addition to standard dyssynchrony indices, a novel index of apex-to-base mechanical propagation delay (MPD) was used.

RESULTS Multivariable analysis determined that MPD of the septum correlated with a significant decline in EF, independent of all other dyssynchrony, clinical, or pacing variables. A septal MPD value exceeding 50 ms was associated with EF decline at 81% sensitivity and 88% specificity.

CONCLUSIONS Dyssynchrony, in particular septal MPD, measured early after interposition of high-dose RVA pacing predicted a significant late decline in EF in patients who had normal prepacing EF.

KEYWORDS Atrial fibrillation; Dyssynchrony; Echocardiography; Heart failure; Pacemakers

ABBREVIATIONS AV = atrioventricular; **CI** = confidence interval; **EF** = ejection fraction; **GCS** = global circumferential strain; **GLS** = global longitudinal strain; **LV** = left ventricular/ventricle; **MPD** = mechanical propagation delay; **RVA** = right ventricular apical; **S-PW** = septal-to-posterior wall

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Introduction

In patients with diminished baseline left ventricular (LV) ejection fraction (EF) who require interposition of chronic, high-dose ventricular pacing, accumulating evidence supports the clinical superiority of left or biventricular pacing over right ventricular apical (RVA) pacing.[1]

Nevertheless, RVA pacing remains the standard of care for patients who have normal EF. Although most such patients tolerate RVA pacing, a significant minority will experience a later decline in EF. It is thought that mechanical ventricular dyssynchrony induced by pacing plays a role in this phenomenon.[2,3] Our objective was to test the hypothesis that in patients with normal baseline EF, dyssynchrony apparent early after interposition of RVA pacing would be associated with a later decline in EF.

Methods

The analysis was approved by the Institutional Review Board of the University of Pittsburgh Medical Center.

Study cohort

From a consecutive group of patients at a single hospital, 91 patients were retrospectively identified who had undergone atrioventricular (AV) node ablation for refractory persistent or paroxysmal atrial fibrillation and, in tandem, implantation of a pacing system, which included a lead placed in the RVA region (defined using chest radiography). Each patient was documented to have subsequently undergone chronic, high-dose (source of $>$98% of all ventricular beats, based on device diagnostics) ventricular pacing. Inclusion also

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required to have an initial, early transthoracic echocardiogram of sufficient quality performed within 6 months after the procedure and demonstrating an EF $>50\%$, as well as a second, late echocardiogram performed >2 years later. Patients were excluded if they had an intrinsic QRS duration (eg. measured before pacing) exceeding 120 ms, significant valvular heart disease, or pulmonary hypertension or had suffered a major cardiac event (ischemia, infarction, and/or revascularization) between early and late echocardiograms. Medical history and medicines taken during the period between early and late echocardiograms were cataloged.

Pacemaker systems

Commercial pulse generators and leads were used in all patients. For patients with a paroxysmal atrial fibrillation syndrome, dual-chamber (right atrium and RVA) systems were used, whereas for those with persistent or permanent syndromes, ventricle-only systems were used. After a period of 30–90 days wherein some patients were programmed with a greater lower rate limit because of a rapid preablation ventricular response, a lower rate limit of 70 per minute was targeted. Upper rate limits were tailored individually, but were generally in the range of 120–140 per minute. The majority of patients had activity sensing programmed on.

Electrocardiographic analyses

For each patient, standard 12-lead electrocardiograms were analyzed during intrinsic rhythm (just before AV node ablation) and during RVA paced rhythm (early after AV node ablation). QRS duration was calculated by averaging all leads.

Echocardiographic analyses

Analyses were performed in random patient and study order by investigators blinded to clinical and outcome data. An early and a late echocardiogram were analyzed for each patient. From the late echocardiogram, LV end-systolic volume and EF were calculated by using biplane Simpson's rule.[4] From the early echocardiogram, LV volume and EF were calculated, and in addition dyssynchrony analyses were performed as follows: speckle-tracking strain analysis was performed on digital gray scale images (30–40 frames/s) of the standard parasternal short axis as well as the apical 4-chamber, as we have reported previously.[5–8]

Commercial software (2D Cardiac Performance Analysis v1.1.3 TomTec Image Systems, Munich, DE) was used to analyze images, with endocardial and epicardial regions of interest placed and myocardial walls tracked during the entire LV mechanical cycle. Radial strain was evaluated by using the parasternal short-axis view at the level of the papillary muscles. The LV was divided into 6 standard segments—septum, anteroseptum, anterior, lateral, posterior, and inferior—each of which generated a time-strain curve from which time-to-peak strain was measured. Radial septal-to-posterior wall (S-PW) delay between anteroseptal and posterior segments was calculated as described previously.[8] Circumferential strain was evaluated by using the short-axis view, with segments as per radial strain analysis. Global circumferential strain (GCS) was calculated as the average peak strain in all segments. Longitudinal strain was evaluated by using the apical 4-chamber view. Endocardial and epicardial borders were tracked during the cardiac cycle. The LV was divided into 6 standard segments—basal septum, mid-septum, apical septum, basal lateral wall, mid-lateral wall, apical lateral wall—each of which generated a time-strain curve from which time to peak strain from the onset of the QRS complex was measured. Global longitudinal strain (GLS) was calculated as the average peak strain in all segments. All strain data were reported as absolute values.

We calculated apex-to-base dyssynchrony using the 6 segments from the apical 4- chamber view, which we called the mechanical propagation delay (MPD). MPD was the average difference in time to peak strain between adjacent segments and was calculated as follows (Figure 1):

Septal MPD (ms) = [(Mid-septum – Apical septum) + (Basal septum – Mid septum)] ÷ 2

Lateral wall MPD (ms) = [(Mid-lateral – Apical lateral) + (Basal lateral – Mid lateral) ÷ 2

Our laboratory has previously reported reliable intra- and interobserver reproducibility of LV strain dyssynchrony measurements using the speckle-tracking technique.[6,7] Reproducibility of the novel MPD measurements was assessed in 10 randomly selected patients. Intraclass correlation coefficients for intraobserver reproducibility of septal and lateral wall MPD were 0.97 (95% confidence interval [CI] 0.88–0.99) and 0.89 (95% CI 0.63–0.97), respectively. Coefficients for interobserver reproducibility were 0.91 (95% CI 0.71–0.98) and 0.86 (95% CI 0.57–0.96), respectively. Personnel performing the echocardiographic analysis of EF were unaware of strain or dyssynchrony analysis results as well as of the fact whether the echocardiogram was early or late.

Analytical methods

A significant decline in EF between early and late echocardiograms was prospectively defined as a decline of $\geq 5\%$ in EF units because this magnitude of change in EF has been associated with clinical outcomes in our laboratory.[5] Patients were thus divided into 2 groups: (1) no significant EF decline between early and late echocardiograms and (2) significant EF decline between early and late echocardiograms.

Continuous data are presented as mean ± SD unless otherwise specified. Comparisons of continuous variables were performed by using the 2-tailed *t* tests for paired or unpaired data, as appropriate. Comparisons of categorical variables were performed by using the χ^2 or Fisher exact test, as appropriate. Receiver operating characteristic curve analysis was used to identify the best cutoff values for continuous variables predicting a significant decline in EF between early and late echocardiograms. Univariable and multivariable logistic regression was applied to evaluate for independent predictors of decline. Parameters associated with decline