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Endocardial and Epicardial Repolarization Alternans in Human Cardiomyopathy

Evidence for Spatiotemporal Heterogeneity and Correlation With Body Surface T-Wave Alternans

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Objectives The aim of this study was to define the spatiotemporal distribution of intracardiac alternans and its relationship to body surface alternans in humans.

Background Spatial heterogeneity of alternans exists in the animal heart owing to nonuniform calcium cycling and restitution kinetics. Patients with cardiomyopathy manifest similar myocardial substrate, which might influence the distribution of intracardiac alternans and its projection onto the body surface.

Methods Repolarization alternans was simultaneously measured from unipolar electrograms in the right ventricular endocardium, left ventricular (LV) epicardium, and the surface electrocardiogram in patients with cardiomyopathy ($n = 14$, LV ejection fraction 29 ± 2%) during atrial pacing at cycle length (CL) 800, 600, and 500 ms. Alternans was determined from the entire JT interval as well as the early, mid, and late JT interval with spectral analysis.

Results Alternans was not uniformly distributed within the heart, with alternating and nonalternating myocardial segments lying adjacent to one another. A greater number of epicardial sites exhibited alternans than endocardial sites at CL 600 ms. Temporal heterogeneity in alternans was present along the JT interval, and apical segments had proportionately less alternans in the late JT interval than mid or basal segments, resulting in apicobasal alternans heterogeneity in late JT interval. Discordant alternans was seen in 5 patients confined to the epicardium. Patients with surface alternans had a greater proportion of intracardiac sites with alternans when compared with those patients without surface alternans.

Conclusions Spatiotemporal heterogeneity and discordant alternans are evident in patients with cardiomyopathy. Greater spatial distribution of intracardiac alternans is associated with measurable body surface alternans. (J Am Coll Cardiol 2007;49:338–46) © 2007 by the American College of Cardiology Foundation

Repolarization alternans describes the beat-to-beat alternation in the shape or amplitude of the ST segment and T wave. In humans, repolarization alternans has been well characterized from the body surface and it has been shown to exhibit heart rate dependency (1), phase reversal (2), and temporal heterogeneity along the JT interval (3). Body surface T-wave alternans (TWA) predicts total mortality and nonfatal ventricular arrhythmias in patients with cardiomyopathy and is emerging as an important prognostic marker in this clinical setting (4,5). However, the origin of body surface TWA within the human heart has not been well defined. A limited number of reports have measured intracardiac alternans with spectral analysis of the unipolar JT interval recorded from a single ventricular site (6,7). These studies provide little information about the regional distribution of intracardiac alternans and its relationship to body surface TWA.

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The spatial distribution of alternans is not uniform in the animal heart (8,9). In particular, arrhythmogenic repolarization gradients can develop during discordant alternans where anatomically distinct myocardial segments alternate out of phase from one another (10). Important mechanisms driving this spatial heterogeneity include nonuniform intracellular calcium cycling (8,11) and restitution kinetics (12).

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In humans, abnormalities in intracellular calcium cycling exist in diseased myocardial segments (13), and restitution kinetics have been shown to exhibit regional heterogeneity (14), which might provide the substrate for nonuniform alternans. The temporal distribution of alternans might also vary with disease states. In an animal model of ischemia, alternans is apparent in the first half of the T wave (15), whereas in patients with myocardial substrate for ventricular arrhythmias, alternans is seen later during repolarization (3).

Therefore, we hypothesized that the spatial and temporal distribution of intracardiac alternans would not be uniform in patients with cardiomyopathy. We further hypothesized that the spatial distribution of intracardiac alternans would influence the measurement of surface TWA. To test this hypothesis, the spatial and temporal distribution of repolarization alternans was measured along the JT interval from multiple sites in the anteroseptal right ventricular (RV) endocardium and left ventricular (LV) epicardium where wall motion abnormalities were present, indicating myocardial disease. Spectral analysis of the unipolar JT interval at each recording site was used to detect regional intracardiac alternans, which was then correlated with body surface TWA.

Abbreviations and Acronyms

CL = cycle length
ECG = electrocardiogram
EF = ejection fraction
H = high voltage (intracardiac recording of beat-to-beat fluctuations)
L = low voltage (intracardiac recording of beat-to-beat fluctuations)
LV = left ventricle/ventricular
RV = right ventricle/ventricular
TWA = T-wave alternans

Methods

Study patients. Consecutive patients with cardiomyopathy, defined as an LV ejection fraction (EF) ≤40%, and wall motion abnormalities in the anterior wall, septum, or apex were included in the study. Left ventricular function was assessed by gated blood pool nuclear imaging (multiple gate acquisition scan [MUGA]) within 6 months of enrollment. Patients were excluded if there was a history of myocardial infarction or unstable angina in the past 3 months, decompensated congestive heart failure, uncontrolled hypertension, sustained ventricular arrhythmias, or amiodarone therapy within 3 months. All patients underwent clinical electrophysiology testing for evaluation of syncope or risk stratification for prophylactic defibrillator implantation. The study was approved by the Research Ethics Board of University Health Network and Mount Sinai Hospital, and all patients gave written, informed consent.

Intracardiac recording and pacing protocol. The clinical electrophysiology study was performed in the postabsorptive state, and beta-blockers and antiarrhythmic drugs were held for 5 half lives. The research protocol commenced 30 min after the clinical electrophysiology study. Ten unipolar recordings from the RV endocardium were obtained with a 10-pole catheter (Livewire, St. Jude Medical Diagnostic Division Inc., Minnetonka, Minnesota) placed along the anteroseptal RV endocardium. Sixteen unipolar recordings from the LV epicardium were obtained from a 16-pole catheter (Pathfinder, Cardima, Freemont, California) advanced down the great cardiac vein onto the anteroseptal LV epicardium as previously described by our group (16). Both catheters have electrode pairs with 2-mm interelectrode spacing, and adjacent electrode pairs are separated by a distance of 5 mm for the Livewire and 6 mm for the Pathfinder.

Constant right atrial pacing was performed with a quadripolar catheter (Biosense Webster, Diamond Bar, California) at cycle lengths (CL) of 800, 600, and 500 ms for 2 to 4 min at each CL. During atrial pacing, simultaneous surface 12-lead electrocardiograms (ECGs) and intracardiac unipolar electrograms were recorded at a sampling rate of 1,000 Hz on a Prucka workstation (GE Medical Systems, Milwaukee, Wisconsin). The unipolar electrograms were recorded with a bandpass filter of 0.05 to 500 Hz, and Wilson central terminal provided a reference.

Repolarization alternans. Intracardiac repolarization alternans and body surface TWA were measured from unipolar electrograms and surface ECGs, respectively, with custom interactive software written in Matlab (MathWorks, Inc., Natick, Massachusetts). The last available sequence of 64 contiguous beats without ectopics, fusion beats, or loss of capture was selected for analysis of both intracardiac and body surface alternans. After QRS complex detection, baseline wander was removed by subtracting an interpolated cubic spline. The QRS complex alignment was refined by maximizing the dot product to an averaged QRS complex template (17). A 2-dimensional matrix was constructed with 64 rows corresponding to the 64 beats and n columns, where n represented the number of time points in the JT interval. Fast Fourier Transform was applied to unwindowed voltage series column-wise to generate power spectra for each time point, which were then summed to generate an aggregate power spectrum. The spectral magnitude at a frequency of 0.5 cycles/beat represents the alternans magnitude ($P_{0.5}$). The noise band was defined as the 10 preceding spectral points (0.33 to 0.48 cycles/beat) (17). The mean amplitude in this interval was the mean noise (μ_{noise}) and the SD of noise was σ_{noise}. The magnitude of alternans was measured by V_{alt} and k value (18):

$$V_{alt} = \sqrt{\{(P_{0.5} - \mu_{noise})/\text{JT duration}\}}$$

$$k = (P_{0.5} - \mu_{noise})/\sigma_{noise}$$

The presence of significant alternans at each intracardiac recording site was determined on the basis of a k value ≥3, indicating an alternans magnitude exceeding the mean noise level by more than 3 SDs (6,19). The V_{alt} was not considered in the definition of significant intracardiac alternans because there is no clinically validated threshold that

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