# Autonomic nerve activity and the short-term variability of the $T_{peak}$-$T_{end}$ interval in dogs with pacing-induced heart failure

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**BACKGROUND** In congestive heart failure (CHF), autonomic nervous system (ANS) activity is known to modulate arrhythmic risk through its effects on myocardial repolarization. An increased interval between the peak and the end of the T wave ($T_{peak}$-$T_{end}$) has been reported to increase the incidence of sudden cardiac death. However, the ANS influence on the $T_{peak}$-$T_{end}$ interval remains unclear.

**OBJECTIVE** We directly measured ANS nerve activity in ambulatory dogs with pacing-induced CHF to test the hypothesis that ANS activity modulates the $T_{peak}$-$T_{end}$ variability index ($T_{peak}$-$T_{end}$VI), the short-term variability of the $T_{peak}$-$T_{end}$ interval obtained on 30 beats ($T_{peak}$-$T_{end}STV_{30}$), and the short-term variability of the $T_{peak}$-$T_{end}$ interval obtained on 5-minute ECG recording ($T_{peak}$-$T_{end}STV_T$).

**METHODS** By using data previously recorded in 6 ambulatory dogs before and after pacing-induced CHF, we assessed ANS activity recorded with an implanted radiotransmitter that monitored integrated left stellate ganglion nervous activity (iSGNA), integrated vagus nerve activity (iVNA), and electrocardiogram (ECG). We selected for analysis 36 segments recorded at baseline and 36 after pacing-induced CHF with similar iSGNA.

**RESULTS** During CHF, $T_{peak}$-$T_{end}STV_{30}$ ($P < .001$) and $T_{peak}$-$T_{end}STV_T$ ($P < .05$) were significantly higher than those at baseline. The multiple linear mixed regression analysis disclosed a significant positive correlation between iSGNA and $T_{peak}$-$T_{end}STV_T$ (baseline: $\beta$ 2.92, $P < .001$; CHF: $\beta$ 1.13, $P < .001$) and a significant negative correlation between iVNA and $T_{peak}$-$T_{end}STV_T$ (baseline: $\beta$ −6.74, $P < .001$; CHF: $\beta$ −1.42, $P < .001$).

**CONCLUSIONS** In a canine model of pacing-induced CHF, iSGNA correlates positively while iVNA correlates negatively with $T_{peak}$-$T_{end}STV_T$. These findings suggest that SGNA increases while VNA decreases the dispersion of ventricular repolarization in ambulatory dogs with CHF.

**KEYWORDS** Chronic heart failure; QT variability; Autonomic nervous system; Sudden cardiac death

**ABBREVIATIONS** **ANS** = autonomic nervous system; **APD** = action potential duration; **CHF** = congestive heart failure; **ECG** = electrocardiogram; **iSGNA** = integrated left stellate ganglion; **iVNA** = integrated vagus nerve activity; **$QT_{end}$** = Q wave to the end of the T wave; **$QT_{end}$VI** = $QT_{end}$ variability index; **$QT_{peak}$** = Q wave to the apex of the T wave; **SCD** = sudden cardiac death; **STV** = short-term variability; **$T_{peak}$-$T_{end}$** = difference between $QT_{end}$ and $QT_{peak}$; **$T_{peak}$-$T_{end}$STV30** = short-term variability of the $T_{peak}$-$T_{end}$ interval obtained on 30 beats; **$T_{peak}$-$T_{end}$STVT** = short-term variability of the Tpeak-Tend interval obtained on the total 5-minute ECG recording

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## Introduction

An increased temporal dispersion of myocardial repolarization, as assessed noninvasively by QT interval variability analysis, is known to be able to predict arrhythmic risk, particularly in patients with congestive heart failure (CHF).[1–7] In a previous study, conducted in a canine model of tachycardia pacing-induced CHF, we provided evidence about a positive correlation between sympathetic nerve activity directly measured in left stellate ganglion and $QT_{end}$

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variability index ($QT_{end}VI$),[8] a noninvasive marker of temporal dispersion of myocardial repolarization closely related to sudden cardiac death (SCD). However, it is unclear which part of the $QT_{end}$ interval is modulated by the sympathetic tone. Growing evidence now tends to suggest that the $T_{peak}$-$T_{end}$ interval and its derived indices are markers of SCD risk and that these markers are more sensitive than those obtained from the whole $QT_{end}$ interval. Indeed, an increase in the $T_{peak}$-$T_{end}$ interval has been found to be independently associated with SCD events in a large community-based study,[9] and just few years ago, others in our research group demonstrated that sympathetic nerve activation was able to induce malignant ventricular arrhythmias by means of $T_{peak}$-$T_{end}$ interval prolongation in an experimental canine model of SCD.[10] Furthermore, an increase in this interval during epinephrine infusion unmasks latent mutation carriers with LQT1 form of congenital long QT syndrome.[11] To the best of our knowledge, what is still lacking is direct evidence documenting possible relationship between autonomic nervous system (ANS) activity and the last part of myocardial repolarization phase, namely, that explored by the $T_{peak}$-$T_{end}$ interval. Therefore, we reanalyzed surface electrocardiographic (ECG) and direct nerve recordings data obtained in a canine model of tachycardia pacing-induced CHF[8,12] to investigate the differential effects of ANS activity on QT interval segments and their derived variability indices. Our analysis specifically focused on the possible relationship of integrated left stellate ganglion (iSGNA) and integrated vagus nerve activity (iVNA) with the $T_{peak}$-$T_{end}$ variability index ($T_{peak}$-$T_{end}VI$), calculated as $T_{peak}$-$T_{end}$ variance normalized for the variance of RR; the short-term variability of the $T_{peak}$-$T_{end}$ interval obtained on 30 beats ($T_{peak}$-$T_{end}STV_{30}$); and the short-term variability of the $T_{peak}$-$T_{end}$ interval obtained on the total 5-minute ECG recording ($T_{peak}$-$T_{end}STV_T$) (see formula in Methods).[13–16]

## Methods

### Surgical preparation and electrical recording

The data analyzed came from a previous study conducted in 6 female dogs.[8,17] The surgical procedures and the temporal relationship between cardiac arrhythmia and ANS activity are reported in detail elsewhere.[12,18] Briefly, a high-frequency pacing lead was implanted in the right ventricular apex and connected to an Itrel neurostimulator (Medtronic, Minneapolis, MN) in a subcutaneous pocket. We then implanted a Data Sciences International D70-EEE transmitter with 3 bipolar recording channels for simultaneous recording of SGNA, VNA from the left thoracic vagal nerve located above the aortic arch, and subcutaneous ECG. After implantation, the Itrel stimulator was initially turned off for 2 weeks to allow the dogs to recover from surgery and to allow us obtain baseline recordings. The stimulator was then programmed to pace at 150 beats/min for 3 days, at 200 beats/min for 3 days, and then at 250 beats/min for 3 weeks to induce CHF. The pacemaker was then turned off to allow an additional 2 weeks of ambulatory monitoring and recording during CHF. All CHF data were recorded within the first week. The animal experiments were approved by the Institutional Animal Care and Use Committee of Cedars-Sinai Medical Center, Los Angeles, CA.

### Direct measurement of ANS

Data were recorded real time at a sampling rate of 1000 samples per second per channel and then analyzed off-line. The software used has been described elsewhere.[12,18] In brief, to analyze long-term trends in the large segmented data files effectively, a custom-designed program was developed by using Labview software to automatically import, filter, and analyze the Data Sciences International transmitter data for ANS activities and heart rates. The software determined the activation cycle lengths (RR intervals) automatically derived from ECG, based on a Hilbert transform algorithm.[19] Integrated data from iSGNA and iVNA were high-pass (200 Hz) filtered and rectified over a fixed time segment. Because RR intervals shorter than 200 ms were usually due to either ectopic beats, artifacts, or rhythm disturbances, they were removed and excluded from analysis. To assess ANS activity in greater detail, we selected 5-minute ECG epochs at baseline and after pacing-induced CHF for each dog. The epochs were selected because they contain similarly known iSGNA values over that 5-minute time segment. Overall, we compared 36 ECG recording epochs at baseline with 36 ECG recording epochs after pacing-induced CHF, all with similar sympathetic nerve activity.

### QT variability and QT-RR coherence

From the respective 5-minute ECG recordings, we calculated mean and variance for the following intervals: RR, $QT_{end}$ (measured from the Q wave to the end of the T wave), $QT_{peak}$ (measured from the Q wave to the apex of the T wave), $T_{peak}$-$T_{end}$ (difference between $QT_{end}$ and $QT_{peak}$) (Figures 1 and 2). We then used the original Berger et al[1] formula:

$$DVI = \log_{10}\{[(D\ variance)/(D\ mean)^2]/[(RR\ variance)/(RR\ mean)^2]\}$$

where D is the duration of $QT_{end}$, $QT_{peak}$, $T_{peak}$-$T_{end}$ intervals. Finally, we obtained the following 3 indices of temporal myocardial dispersion: $QT_{end}VI$, $QT_{peak}VI$, and $T_{peak}$-$T_{end}VI$ (Figure 2).

The same 5-minute ECG segments were analyzed with autoregressive power spectral[17,20–22] and cross-spectral analysis.[1,8] The next variable estimated was the coherence function for the RR and QT intervals. Coherence expresses the fraction of power at a given frequency in either time series and is explained as a linear transformation of the other, thus providing an index of a linear association between the 2 signals.[1,8] The coherence function $\gamma(f)$ was then computed according to the following formula:

$$\gamma(f)\frac{|P_{xy}(f)|^2}{P_{xx}(f)P_{yy}(f)}$$