Myocardial repolarization dispersion and autonomic nerve activity in a canine experimental acute myocardial infarction model

Gianfranco Piccirillo, MD, PhD,* † Federica Moscucci, MD,* Gaetana D’Alessandro, MD,* Matteo Pascucci, MD,* Pietro Rossi, MD, ‡ Seongwook Han, MD, PhD, † Lan S Chen, MD, § Shien-Fong Lin, PhD, † Peng-Sheng Chen, MD, FHIRS, † Damiano Magrì, MD, PhD¶

From the *Dipartimento di Scienze Cardiovascolari, Respiratorie, Nefrologiche, Anestesiologiche e Geriatriche, Policlinico Umberto I, “Sapienza” University of Rome, Rome, Italy, †Krannert Institute of Cardiology, Division of Cardiology, Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana, ‡Dipartimento di Medicina Interna e Specialità Mediche, Policlinico Umberto I, University of Rome, Rome, Italy, §Department of Neurology, Indiana University School of Medicine, Indianapolis, Indiana, and ¶Dipartimento di Medicina Clinica e Molecolare, Azienda Ospedaliera Sant’Andrea, University of Rome, Rome, Italy.

BACKGROUND Evidence from a canine experimental acute myocardial infarction (MI) model shows that until the seventh week after MI, the relationship between stellate ganglion nerve activity (SGNA) and vagal nerve activity (VNA) progressively increases.

OBJECTIVE The purpose of this study was to evaluate how autonomic nervous system activity influences temporal myocardial repolarization dispersion at this period.

METHODS We analyzed autonomic nerve activity as well as QT and RR variability from recordings previously obtained in nine dogs. From a total of 48 short-term ECG segments, 24 recorded before and 24 recorded 7 weeks after experimentally-induced MI, we obtained three indices of temporal myocardial repolarization dispersion: QTe (from Q-wave to T-wave end), QTp (from Q-wave to T-wave peak), and Te (from T-wave peak to T-wave end) variability index (QTeVI, QTpVI, TeVI). We also performed heart rate variability power spectral analysis on the same segments.

RESULTS After MI, all the QT variables increased QTeVI (median [interquartile range]) (from −1.76[0.82] to −1.32[0.68]), QTpVI (from −1.90[1.01] to −1.45[0.78]), and TeVI (from −0.72[0.67] to −0.22[1.00]), whereas all RR spectral indices decreased (P < .001 for all). Distinct circadian rhythms in QT,VI (P < .05), QTpVI (P < .001) and TeVI (P < .05) appeared after MI with circadian variations resembling that of SGNA/VNA. The morning QT,VI and TeVI acrophases approached the SGNA/VNA acrophase. Conversely, the evening QT,VI acrophase coincided with another SGNA/VNA peak. After MI, regression analysis detected a positive relationship between SGNA/VNA and TeVI (R²: 0.077; β: 0.278; p < 0.001).

CONCLUSION Temporal myocardial repolarization dispersion shows a circadian variation after MI reaching its peak at a time when sympathetic is highest and vagal activity lowest.

KEYWORDS Myocardial infarction; Temporal myocardial repolarization dispersion; Sudden cardiac death

ABBREVIATIONS CF = central frequency; CHF = congestive heart failure; HF = high frequency; HRV = heart rate variability; LF = low frequency; LSG = left stellate ganglion; MI = myocardial infarction; SCD = sudden cardiac death; SGNA = stellate ganglion nerve activity; TP = total power; VLF = very low frequency; VNA = vagal nerve activity

Introduction

Mortality from sudden cardiac death (SCD) is notoriously high within the first month after acute myocardial infarction (MI) and remains high in the first 6 months thereafter. Post-MI and congestive heart failure (CHF), its frequent complication, both are conditions characterized by sympathetic hyperactivity, which is so important in triggering potentially life-threatening cardiac arrhythmias that, in selected patients with CHF, some investigators even propose ablating the stellate ganglion. Ample evidence nevertheless shows that
in CHF, vagal activity protects against SCD through its direct antiarrhythmic action mediated by nitric oxide. Accordingly, others suggest intracardiac or extracardiac vagal nerve stimulation as useful therapeutic option devices. A study in an experimental canine acute MI model conducted in recent years in our laboratory showed that left stellate ganglion nerve activity (SGNA) increases immediately after an MI but is concurrently counterbalanced by increased vagal nerve activity (VNA). However, the relationship between these two autonomic variables (SGNA/VNA ratio) tends to increase progressively until it peaks around the seventh week post-MI and its circadian rhythm resembles that described for heart rate variability (HRV). What remains unclear is how autonomic nervous system (ANS) activity influences myocardial repolarization dispersion. This information would help to understand some of the mechanisms underlying SCD after an acute MI and, possibly, to identify patients at highest arrhythmic risk.

In this pathophysiologic study, we reanalyzed autonomic nerve activity and ECG recordings previously obtained from nine dogs and selected one single 5-minute ECG segment hourly during the day, under baseline conditions, and 7 weeks after experimentally induced acute MI. We then performed a short-period HRV power spectral analysis and calculated temporal dispersion in myocardial repolarization.

Materials and methods
Surgical preparation and electrical recording
The data analyzed came from a previous study conducted in nine mongrel male dogs. The methods of electrode placement for nerve recordings have been previously reported. Detailed methods of nerve activity measurements can be found in the report by Han et al. In brief, each dog was implanted with a Data Sciences International (DSI) D70-EEE transmitter with three bipolar recording channels for simultaneous SGNA, VNA, and ECG recordings. One bipolar recording electrode pair was implanted under the left stellate ganglion fascia, another one on the left vagus nerve located above the aortic arch, and the last electrode pair was placed in the subcutaneous chest wall to simulate the ECG orientation in lead I. After 2 weeks to allow the dogs to recover, data for all channels were recorded simultaneously for 7 days. The dogs then underwent the following procedure to induce acute MI: a bolus of unfractionated heparin (3000 UI) and amiodarone (150 mg) were infused before the procedure, and after this procedure amiodarone (150 mg/h) was continuously infused. After left coronary cannulation using a 7Fr Judkins JL guiding catheter, a balloon was inflated for 1 hour to occlude the left anterior descending coronary artery just below the first diagonal branch in six dogs and the left circumflex artery below the second obtuse marginal branch in three dogs. During balloon inflation, the surface ECG showed ST-segment elevation indicating an acute MI. To confirm myocardial necrosis, cardiac troponin I levels were assayed at baseline and 24 hours after this procedure. Left ventriculography was done immediately before the MI was induced. The dogs were allowed to recover for 2 months, and during this time they underwent continuous ambulatory recordings. The animal experiments were approved by the Institutional Animal Care and Use Committee.

Direct measurement of nerve activity
Data were recorded real time at a sampling rate of 1000 samples per second per channel, then analyzed offline. High-pass (50-Hz) filtering was used to reduce the ECG signals from the LSG recording channel, and wavelet filtering was used to eliminate the ECG signals from the vagus nerve recording channels. Most signals recorded from LSG were low-amplitude burst discharge activity. Autonomic nerve activity was integrated over 100 ms and multiplied by the sampling time. The 5-minute integrated nerve activity recording was used to quantify SGNA and VNA, and we calculated QT and RR variability from the simultaneous ECG. Last, we calculated the SGNA/VNA ratio. For each dog we obtained one recording hourly per day at baseline and 7 weeks after MI.

HRV power spectral analysis
Spectral power for HRV was analyzed on 5-minute ECG recording segments and an autoregressive algorithm was used to analyze digitized signals from the ECG recordings (Figure 1). We then determined the following power spectral variables: total power (TP) (total spectral density); high-frequency (HF) component (from 0.15 to 0.40 Hz); low-frequency (LF) component (from 0.04 to 0.15 Hz); and very-low-frequency (VLF) component (below 0.04 Hz) (Figure 2). We also reported (in Hz) the central frequency (CF) and the predominant LF and HF power oscillations.
Temporal myocardial repolarization dispersion and QT-RR coherence

From the respective 5-minute ECG recordings we calculated mean and variance for the following intervals: RR, QT_e (from Q-wave to T-wave end), QT_p (from Q-wave to T-wave peak) and T_e (from T-wave peak to T-wave end) (Figure 1). We then used the original Berger et al formula, which quantifies the magnitude of QT interval fluctuations normalized by both the mean QT duration and the magnitude of the heart rate fluctuations to obtain the three indices for temporal myocardial repolarization dispersion17:

\[ \text{DVI} = \log_{10} \left\{ \frac{\text{(Dvariance)/(Dmean)^2}}{\text{[(RRvariance)/(RRmean)^2]}} \right\} \]

where D = the interval duration of QT_e, QT_p, and T_e (Figures 2 and 3).

The next variable estimated was the coherence function for the RR and the various repolarization intervals. Coherence expresses the power fraction oscillating at a given frequency in either time series and is explained as a linear association between the two signals. The coherence function \( \gamma(f) \) was then computed according to the following formula:

\[ \gamma(f) = \frac{|P_{xy}(f)|^2}{P_{xx}(f)P_{yy}(f)} \]

where \( f \) = frequency, \( P_{xx}(f) \) = spectrum of an RR interval, \( P_{yy}(f) \) = QT_e or QT_p or T_e interval spectrum, and \( P_{xy}(f) \) = cross spectrum. Mean coherences were measured by averaging \( \gamma(f) \) over the frequency bands from 0 to 0.50 Hz.

The coherence function provides a measure between zero and unity in the degree of linear interaction between RR and QT_e or QT_p, or T_e interval oscillations as a function of their frequency. More in general, the QT-RR interval spectral coherence evaluates temporal patterns in oscillating signals and it hypothetically reaches the maximum (unity) when QT and RR interval oscillations proportionally correspond. Although QT-RR interval spectral coherence remains relatively low (<0.400) even under healthy conditions, nevertheless it tends to dramatically decrease further in CHF models (<0.300), a phenomenon thought to reflect a worsening of sinus node function. A single physician (GP) analyzed all digitalized signal recordings.

Statistical analysis

Unless otherwise indicated, all data are expressed as mean ± SD. Data with skewed distribution are given as median and interquartile range (75th percentile–25th percentile). For each dog, 24 recordings (one per hour per day) were obtained at baseline and 7 weeks after acute MI.

Paired t test was used to compare data for normally distributed variables (including RR mean, QT_e mean, QT_p mean, T_e mean, coherence functions, SGNA, and VNA), whereas Wilcoxon test was used to compare non-normally distributed variables (including RR variance, QT_e variance, QT_p variance and T_e variance, QT_e VI, QT_p VI, and T_e VI) at baseline and after MI.

Cosinor tests were used to detect and quantify significant circadian variations and reported the following variable: mesor (m) (value midway between highest and lowest values in the curve), amplitude (amp) (difference between peak and mean wave value), acrophase (ac) (time when the rhythm reached its peak), and trough (th) (time when the rhythm reached its lowest value).

Stepwise multiple regression analysis, using as dependent variables the natural logarithm (ln) SGNA and (ln) VNA, was used to assess the relationship between ANS activity and all the other studied variables at baseline and 7 weeks after MI.

All data were evaluated with the database SPSS-PC+ (SPSS-PC+ Inc, Chicago, IL). \( P \leq .05 \) was considered significant.

Results

Because ECG recordings for three of the nine dogs contained excessive background noise, data were analyzed for only six dogs. Therefore, we analyzed a total of 288 recordings for each dog, 144 obtained at baseline and 144 after MI.

Mean cardiac troponin I values increased from <0.2 ng/mL at baseline to a median value of 85 mg/mL (interquartile range 79 mg/mL) 24 hours after acute MI. When the study ended (2 months after the MI), left ventricular ejection fraction remained statistically unchanged (65% ± 17% vs 53% ± 17%).
Mean values for all QT variables were significantly longer 7 weeks after MI than at baseline: QTc (P < .001), QTp (P < .001), and Te (P < .05) (Table 1). Similarly, all corrected QTc intervals values (QTc Bazett, QTc Tabo, and QTc Van de Water) were longer after MI (P < .001; Table 1). Conversely, RR variance was significantly higher at baseline (P < .001; Table 1). RR mean, QTc, QTp, and Te variance values overlapped in the two study conditions (Table 1).

Similarly, SGNA, VNA, SGNA/VNA, QTc VI, QTp VI, and Te VI values were significantly higher 7 weeks after MI than at baseline (P < .001; Tables 1 and 2). Conversely, no difference was found in coherence between all repolarization variables and RR (Table 2).

TP (P < .001), VLF (P < .001), LF (P < .001), and HF power (P < .001), expressed in absolute power (ln ms²), were significantly lower 7 weeks after MI than at baseline (P < .001; Table 3). LF/HF ratio and LF power, expressed in normalized units, were significantly higher, whereas HF power, expressed in normalized units, was lower 7 weeks after MI than at baseline.

During the 2 days analyzed, SGNA/VNA was significantly higher in the six different hours 7 weeks after MI than in the baseline condition (8:00, 9:00, 12:00, 15:00, 18:00, and 19:00; P < .05; Figure 4). QTc VI reached higher significant values in eight hours per day (0:00, 1:00, 7:00, 8:00, 9:00, 14:00, 16:00, and 18:00; P < .05; Figure 4), QTp VI in seven hours per day (0:00, 4:00, 8:00, 9:00, 12:00, 15:00, and 16:00; P < .05; Figure 4), and Te VI showed higher values only in three hours per day (2:00, 4:00, and 16:00; P < .05; Figure 4). Also, QTc Tabo (P = 0.02) and QTc Van de Water (P = 0.02) showed a circadian rhythmicity when recorded 7 weeks after MI.
During the two study conditions, TP was significantly lower in 11 different hours 7 weeks after MI than in the baseline condition (1:00, 2:00, 3:00, 6:00, 9:00, 11:00, 12:00, 13:00, 14:00, 15:00, 21:00, and 22:00; \( P < .05 \); Figure 5A). Conversely, VLF power was significantly lower in only two hours per day (3:00 and 23:00; \( P < .05 \); Figure 5B); LF power, expressed in absolute power (ln ms\(^2\)), showed lower levels in seven hours per day (2:00 and 12:00, 13:00, 14:00, 17:00, 20:00, and 21:00; \( P < .05 \); Figure 5C), and, HF power showed lower levels in nine hours per day 7 weeks after MI than at baseline (1:00, 2:00, 3:00, 6:00, 12:00, 14:00, 16:00, 21:00, and 22:00; \( P < .05 \); Figure 5D).

TP, VLF and LF power, expressed in absolute power (ln ms\(^2\)), both at baseline and 7 weeks after MI, underwent a circadian variation (TP baseline: \( m = 10.4 \); \( \text{amp} = 0.5 \); ac: 2:00; th: 15:00; \( P = .005 \); TP after MI: \( m = 10.4 \); \( \text{am} = 0.5 \); ac: 2:00; th: 14:00; \( P = .0004 \); VLF power baseline: \( m = 7.8 \); \( \text{amp} = 0.4 \); ac: 3:00; th: 20:00; \( P = .016 \); VLF power after MI: \( m = 7.3 \); \( \text{amp} = 0.4 \); ac: 7:00; th: 23:00; \( P = .023 \); LF power baseline: \( m = 8.4 \); \( \text{amp} = 0.8 \); ac: 2:00; th: 9:00; \( P = .0002 \); LF power after MI: \( m = 7.9 \); \( \text{amp} = 0.6 \); ac: 2:00; th: 20:00; \( P = .0001 \); Figure 5). Conversely, HF power, expressed in absolute values, showed significant circadian variations only 7 weeks after MI (HF power after MI: \( m = 8.5 \); \( \text{amp} = 0.8 \); ac: 2:00; th: 14:00; \( P = .0001 \); Figure 5).

Stepwise multiple regression analysis testing data recorded at baseline detected a small but significant positive relation between ln SGNA/VNA (\( r = 0.187 \); \( R^2 = 0.035 \); \( P < .05 \)) and QTeVI (b: 0.118; se: 0.054; \( \beta = 0.187 \); \( P = .03 \); Figure 6). Conversely, the same analysis testing data recorded after MI detected a significant positive relationship between ln SGNA/VNA (\( r = 0.278 \); \( R^2 = 0.077 \); \( P < .001 \)) and TeVI (b: 0.246; se: 0.072; \( \beta = 0.278 \); \( P = .001 \); Figure 7).

### Discussion

The major finding of this study is that temporal myocardial repolarization dispersion, assessed in terms of QTe VI, QTp VI, and Te VI, increases 7 weeks after dogs undergo experimentally induced acute MI and that only under this condition does a circadian rhythm appear for all three of these QT indices. In particular, we found that Te VI was the QT-derived index that exhibited the best correlation with autonomic nerve activity, as calculated with the SGNA/VNA ratio. Another distinctive but expected finding is that HRV, expressed globally as TP and divided into its three spectral components (VLF, LF, and HF power), diminishes significantly 7 weeks after acute MI.

### Circadian rhythms of temporal dispersion in repolarization and in ANS activity

An important point in designing a pathophysiologic study investigating how the ANS influences myocardial repolarization is the time elapsing between an experimentally induced MI and data recording. Accordingly, we analyzed recordings obtained 7 weeks after experimentally induced MI because our preceding study identified this as the time when the SGNA/VNA ratio reaches its maximum increase.

Our findings in this study indicate that, even though the QT variables we studied partially differ in circadian behavior, temporal myocardial repolarization dispersion displays a circadian rhythm only 7 weeks after MI and is influenced at least in part by ANS activity expressed as the SGNA/VNA ratio. Indeed, under this condition, all these QT indices tend to increase during the day and diminish at night and do so in a circadian pattern similar to that for autonomic nerve activity. The SGNA/VNA ratio peaks between 6:00 and 20:00, as do the three QT indices reflecting temporal dispersion in repolarization, even though their values peak over a slightly wider time range (between 4:00 and 21:00; Figure 4). However, if we consider only QTp VI and Te VI variables, whose circadian rhythms appear strongly only after MI, the overlap between autonomic nerve activity and myocardial repolarization dispersion increases. Accordingly, the QTp VI, Te VI, and SGNA/VNA ratio peak values run

### Table 1  ECG-derived and nerve activity data in the two different study conditions

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline (N = 144 segments)</th>
<th>Seven weeks after myocardial infarction (N = 144 segments)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR mean (ms)</td>
<td>695 ± 137</td>
<td>703 ± 178</td>
<td>.214</td>
</tr>
<tr>
<td>RR variance (ms(^2))</td>
<td>35,559</td>
<td>13,432 (16,512)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>QT(_e) mean (ms)</td>
<td>219 ± 34</td>
<td>253 ± 63</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>QT(_e) variance (ms(^2))</td>
<td>55 (69)</td>
<td>63 (94)</td>
<td>.081</td>
</tr>
<tr>
<td>QT(_f) mean (ms)</td>
<td>160 ± 23</td>
<td>176 ± 24</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>QT(_f) variance (ms(^2))</td>
<td>24 (58)</td>
<td>24 (57)</td>
<td>.387</td>
</tr>
<tr>
<td>T(_e) mean (ms)</td>
<td>54 (24)</td>
<td>56 (34)</td>
<td>.012</td>
</tr>
<tr>
<td>T(_e) variance (ms(^2))</td>
<td>45 (97)</td>
<td>56 (81)</td>
<td>.235</td>
</tr>
<tr>
<td>QT(_fBazett) (ms)</td>
<td>264 ± 33</td>
<td>297 ± 57</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>QT(_fTabo) (ms)</td>
<td>253 ± 32</td>
<td>286 ± 57</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>QT(_f) van de Water (ms)</td>
<td>245 ± 30</td>
<td>276 ± 56</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>SGNA (mV)</td>
<td>9.4 (6.5)</td>
<td>15.4 (16.5)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>VNA (mV)</td>
<td>1.2 (0.9)</td>
<td>1.5 (0.5)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>SGNA/VNA ratio</td>
<td>7.9 (4.1)</td>
<td>9.8 (8.8)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD or median (interquartile range).

SGNA = integrated left stellate ganglion nerve activity; VNA = integrated vagal nerve activity.

### Table 2  QT interval variability index values and related coherence with RR interval in the two different study conditions

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline (N = 144 segments)</th>
<th>Seven weeks after myocardial infarction (N = 144 segments)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QT(_f) VI</td>
<td>-1.76 (0.82)</td>
<td>-1.32 (0.68)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>QTe (_f) → RR ( \rho ) coherence</td>
<td>0.372 ± 0.158</td>
<td>0.367 ± 0.164</td>
<td>.780</td>
</tr>
<tr>
<td>QT(_e) VI</td>
<td>-1.90 (1.01)</td>
<td>-1.45 (0.78)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>QTe (_e) → RR ( \rho ) coherence</td>
<td>0.358 ± 0.104</td>
<td>0.356 ± 0.135</td>
<td>.752</td>
</tr>
<tr>
<td>T(_e) VI</td>
<td>-0.72 (0.67)</td>
<td>-0.22 (1.00)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>T(_e) → RR ( \rho ) coherence</td>
<td>0.287 ± 0.102</td>
<td>0.280 ± 0.103</td>
<td>.549</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD or median (interquartile range).
relatively close to each other (QT\textsubscript{pVI} at 9:00, T\textsubscript{eVI}, at 10:00, and SGNA/VNA ratio at 12:00; Figure 4). Conversely, all the QT variables reach their lowest values at the same time during the night (at 2:00), and SGNA/VNA ratio reaches its trough just an hour earlier. The lowest daily value for all the QT variables also coincides with the acrophase for TP, LF, and HF power, presumably because RR variance belongs to the denominator in the Berger formula (see Methods). Hence, if TP diminishes, the indices for myocardial repolarization dispersion worsen. Whatever the reason, at 7 weeks after MI, the SGNA/VNA ratio and temporal dispersion in myocardial repolarization reach trough levels at almost the same time at night when sympathetic activity is low, whereas vagal activity and HRV are high. Conversely, except for QT\textsubscript{eVI}, the other two QT indices reach values close to the maximum SGNA/VNA ratio from 7:00 to 14:00, precisely when TP, LF, and HF power decline to their lowest levels (Figure 5). Therefore, our experimental findings on circadian rhythms receive strong support from the literature showing that SCD reaches its daily peak incidence when sympathetic activity is high and vagal activity is low.24–27 The QT\textsubscript{eVI} acrophase coinciding with a relatively high SGNA/VNA ratio, around 18:00 (Figure 4), also helps to explain a second reported SCD peak incidence in the afternoon from 15:00 to 19:00.24–27

In conclusion, 7 weeks after MI, two variables reflecting temporal myocardial repolarization dispersion, QT\textsubscript{pVI} and T\textsubscript{eVI}, peak in the morning whereas QT\textsubscript{eVI} peaks in the evening. Why QT\textsubscript{eVI}, a variable that depends on QT\textsubscript{pVI} and on T\textsubscript{eVI}, peaks in nonmorning hours remains a curious

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline (N = 144 segments)</th>
<th>Seven weeks after myocardial infarction (N = 144 segments)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total power (ln ms\textsuperscript{2})</td>
<td>10.3 ± 0.9</td>
<td>9.3 ± 1.1</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Very low frequency (ln ms\textsuperscript{2})</td>
<td>7.8 ± 0.9</td>
<td>7.6 ± 1.2</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Low frequency (ln ms\textsuperscript{2})</td>
<td>8.4 ± 1.1</td>
<td>7.5 ± 1.2</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Low-frequency CF (Hz)</td>
<td>0.112 ± 0.013</td>
<td>0.101 ± 0.012</td>
<td>.650</td>
</tr>
<tr>
<td>High frequency (ln ms\textsuperscript{2})</td>
<td>9.6 ± 1.1</td>
<td>8.4 ± 1.3</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>High-frequency CF (Hz)</td>
<td>0.24 ± 0.07</td>
<td>0.25 ± 0.08</td>
<td>.561</td>
</tr>
<tr>
<td>Low frequency/high frequency</td>
<td>0.3 (0.5)</td>
<td>0.4 (0.7)</td>
<td>.028</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD or median (interquartile range). CF = central frequency.

![Figure 4](https://example.com/figure4.png) **Figure 4** Daytime increase in the three temporal dispersion indices (QT\textsubscript{pVI}, QT\textsubscript{eVI}, and T\textsubscript{eVI}) related to the circadian variation in stellate ganglion nerve activity/vagal nerve activity (SGNA/VNA) 7 weeks after myocardial infarction (MI) (right). Note that SGNA/VNA peak (m = 2.7; amp = 0.4; ac: 10:00; th: 1:00; P = .0001) matched QT\textsubscript{pVI} (m = −1.46; amp = 0.39; ac: 9:00; th: 2:00; P = .0001) and T\textsubscript{eVI} peak (m = −1.18; amp = 0.37; ac: 12:00; th: 2:00; P = .005). In the evening, QT\textsubscript{eVI} peak (m = −1.29; amp = 0.18; ac: 18:00; th: 2:00; P = .0043) corresponded to an evening SGNA/VNA peak.
circadian finding that we find hard to explain. Experimental
evidence nevertheless indicates that QTc circadian variability
could depend on daily functional variability in the transient
outward potassium current (I_{Kto}), whereas other ion currents
fail to exhibit this daily variability. To explain why some
QT-derived variables differ in their circadian behavior, we
conjecture that because the three QT intervals are differently
fluenced from ion channel activities, they might or might
not undergo daily rhythmic variability. Furthermore, given
the incomplete overlap between daily variability in the
SGNA/VNA ratio and in the three temporal myocardial
repolarization dispersion indices, the post-MI circadian
rhythm probably also reflects factors other than the ANS.
For example, the circadian variability for angiotensin II, a
hormone able to modulate various RR spectral components
and inhibit some ion channel activities through the angio-
tensin 1 receptor, resembles the variability we observed
here for myocardial repolarization dispersion (acrophase in
the early morning). Furthermore, it is also true that, besides
the undoubted influence of ANS activity on myocardial
repolarization dispersion, anatomic factors such as fibrosis
and inhomogeneous histologic changes at the border zone of
the infarction play a role in the development of ventricular
arrhythmias.

Figure 5  Significant reduction in all spectral components 7 weeks after myocardial infarction (MI): total power (TP) (A), very-low-frequency (VLF) (B), low-frequency (LF) (C), and high-frequency (HF) (D) power. The spectral RR component behaved in an opposite manner to myocardial repolarization dispersion, being higher at night and lower during the daytime. TP baseline (A): m = 10.4, amp = 0.5, ac: 2:00, th: 15:00; P = .005. TP after MI (A): m = 10.4, amp = 0.5, ac: 2:00, th: 14:00; P = .0004. VLF power baseline (B): m = 7.8, amp = 0.4, acr: 3:00, th: 20:00; P = .016. VLF power after MI (B): m = 7.3, amp = 0.4, ac: 7:00, th: 23:00; P = .023. LF power baseline (C): m = 8.4, amp = 0.8, ac: 2:00, th: 9:00; P = .0002. LF power after MI (C): m = 7.9, amp = 0.6, ac: 2:00, th: 20:00; P = .0001. HF power (D) showed a significant circadian behavior only after MI (HF power after MI: m = 8.5, amp = 0.8, ac: 2:00, th: 14:00; P = .0001).

Figure 6  Linear regression between QTcVI measured on 5-minute ECG recordings and natural logarithm of SGNA/VNA at baseline.
Pathophysiologic meaning of temporal dispersion in myocardial repolarization

All three QT indices we studied, QTc VI, QTp VI, and Tc VI, are noninvasive markers of temporal myocardial repolarization dispersion that increase during CHF17,32 and correlate with SCD.37 In particular, the pathophysiologic meaning of the Tc interval remains controversial. Whereas some consider it a true index of transmural repolarization dispersion,38 others regard it even as a global index of ventricular repolarization dispersion.39–41 Hence, an increased Tc is associated with increased mortality for SCD.42 Experimental and clinical evidence show that this repolarization phase is closely linked to sympathetic activity.14,15,33,42 The small but significant positive relation we found between Tc VI and the SGNA/VNA ratio could support its usefulness because we showed that, after MI, notwithstanding preserved left ventricular ejection fraction, this terminal repolarization phase worsens because of increased sympathetic and reduced vagal activity or both events. Conversely, under baseline conditions temporal dispersion seems to come under the control of autonomic nerve activities. Conversely, under baseline conditions (before MI) they seem uncorrelated. Temporal dispersion in myocardial repolarization seems to worsen during the daytime and improve at night, reflecting daily pathophysiological variations in sympathovagal control. Our preliminary data, albeit limited to an experimental canine model, might help explain some of the mechanisms underlying malignant ventricular arrhythmias after an acute MI. Whether or not our data could be translated in humans to identify post-MI patients at highest risk for SCD warrants confirmation from larger prospective studies.

Study limitations

We analyzed only 5-minute segments hourly rather than data for the 24 hours overall because no software program is yet available for analyzing QT intervals and their subcomponents (QTp and Tc) in an error-free manner over the 24 hours. To eliminate eventual interoperator variability, a single operator checked and measured all ECG intervals directly on the computer screen.

A second possible study limitation is the experimental model used, as the canine model is still debated in evaluating the pathophysiological mechanisms leading to ventricular arrhythmias. Particularly, one of the drawbacks attributed to the canine model in this field is that, given its more predominant vagal activity,46 the occurrence of SCD events is greatly related to vagal overactivity (i.e., severe bradycardia and sinus arrest). However, our research group performed a number of continuous direct recordings of the SGNA and VNA in ambulatory dogs, and we always showed a consistent circadian variation of SGNA and incidence of spontaneous ventricular arrhythmias, including SCD.20,22,23,47 Unfortunately, the present pathophysiological study design allows us to suggest, rather than conclude, a possible link to SCD between the observed changes in ANS activity and myocardial repolarization dispersion. Furthermore, we clearly recognize that our data did not show high correlation values, thus making it difficult to believe that it is possible to predict one parameter from the other (i.e., Tc VI and SGNA/VNA ratio). Nevertheless, this was to be expected mainly because of the small number of recordings and rather scattered data. Furthermore, because sinus node dysfunction has been demonstrated during CHF,19–21 it might result from a partial loss of relationship between SGNA and ECG data.

Conclusion

Two months after experimentally induced acute MI, the circadian rhythm in temporal myocardial repolarization dispersion seems to come under the control of autonomic nerve activities. Conversely, under baseline conditions (before MI) they seem uncorrelated. Temporal dispersion in myocardial repolarization seems to worsen during the daytime and improve at night, reflecting daily pathophysiological variations in sympathovagal control. Our preliminary data, albeit limited to an experimental canine model, might help explain some of the mechanisms underlying malignant ventricular arrhythmias after an acute MI. Whether or not our data could be translated in humans to identify post-MI patients at highest risk for SCD warrants confirmation from larger prospective studies.

References
