CIRCADIAN CHANGES IN THE QT VARIABILITY INDEX IN THE BEAGLE DOG

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SUMMARY

1. QT variability is a non-invasive marker of cardiac repolarization lability and a higher QT variability is associated with sudden death. No data exist as to the circadian fluctuations in QT variability and the QT variability index (QTvi) in the canine. The purpose of the present investigation was to explore QT interval variability over 24 h in the healthy dog.

2. Continuous lead II electrocardiogram and blood pressure data were collected for 24 h from three beagles instrumented with radiotelemetry devices. The mean heart rate (HR), detrended HR variance, mean QT interval and detrended QT variance were calculated from the instantaneous HR and QT time series of 1024 points (256 s), as described previously, and a normalized QTvi was derived.

3. The dog has a diurnal pattern of QTvi similar to healthy humans. Both dogs and humans exhibit a significantly higher QTvi during active waking hours, with more negative values during deep sleep.

4. These findings suggest QTvi may serve as an additional non-invasive tool to assess ventricular repolarization lability in dogs in relation to any conditions or drugs that are known to be associated with increased cardiac mortality.

Key words: circadian, dogs, QT interval variability, QT interval, repolarization.

INTRODUCTION

Recent literature indicates that QT variability serves as a non-invasive marker of cardiac repolarization lability and that a higher QT variability is associated with sudden death.† QT variability is known to be greater in patients with a variety of myocardial disease processes, including dilated cardiomyopathy, congestive heart failure and acute myocardial ischaemia,‡ in patients with anxiety related psychological disorders and in patients treated with drugs that prolong the QT interval. § The QT variability index (QTvi) is an index of QT variability corrected for mean QT interval divided by heart rate (HR) variability corrected for mean HR. An increase in QT variability and a decrease in HR variability make this statistic more sensitive than QT interval or corrected QT interval alone in distinguishing different groups with regard to ventricular repolarization lability. †‡ Previous investigations have examined both short-term changes in QT variability and QT interval variability over 24 h in patients and in healthy controls.

The dog is used routinely in cardiovascular investigations, both because of its physiological similarities to humans and because it is acceptable to regulatory agencies as a model for cardiovascular safety testing. To date, no data exist as to the circadian fluctuations in QT variability and QTvi in the canine. The purpose of the present investigation was to explore QT interval variability over 24 h in the healthy beagle dog.

METHODS

Three male beagle dogs obtained from Marshall Farms (North Rose, NY, USA) and weighing between 8 and 11 kg were instrumented with a lead II configuration electrocardiogram (ECG) and arterial blood pressure telemetry device (Data Sciences International, St Paul, MN, USA), as described previously. †‡ Continuous ECG data were collected for 24 h in the dogs’ normal housing environment (stainless steel cages with a 12 h light/dark cycle: lights on 06.00-18.00 h). The cardiovascular waveforms were sampled and saved to disk at 1000 Hz using a Po-Ne-Mah data-acquisition and analysis system (Gould, Valley View, OH, USA). Five minute segments of ECG were digitized from the beginning of each hour. The ECG data were divided into five epochs over the 24 h period as follows: 07.30–11.30 h, 11.30–16.30 h, 16.30–21.30 h, 21.30–04.30 h and 04.30–07.30 h. A priori, the durations of epochs 1–4 were defined by their containing at least four noise-free segments, a total duration spanning 4–7 h and the first and final epoch encompassing probable waking and sleep, respectively. Owing to dog activity and poor signal quality, epoch 5 only contained three noise-free segments. The results of analyses for each of the four 256 s segments of ECG during epochs 1–4 were averaged.

QT variability

All analyses were conducted on 256 s data segments sampled at 1000 Hz. The QT variability algorithm has been described in detail by Berger et al. †‡ and has been used in previous studies. †‡ Analyses were performed on a PC using Solaris Desktop Unix software (Sunsoft, Mountainview, CA, USA). This system uses a graphical interface of digitized ECG where the time of the R wave is obtained using a peak detection algorithm. The operator provides the program with the beginning and end of the QT wave template. This algorithm finds the QT interval for each beat using the time-stretch model. § If the operator chooses a longer QT template, all the QT intervals will be biased accordingly.
The HR time series was sampled at 4 Hz using the technique of Berger et al. The HR time series free of ventricular premature beats and noise were used. The data were then detrended by using the best-fit line prior to the computation of analyses.

The mean HR (HRm), detrended HR variance (HRV), mean QT interval (QTm) and detrended QT variance (QTv) were calculated from the instantaneous HR and QT time series of 1024 points (256 s).

A normalized QT variability index was calculated as suggested by Berger et al.:

\[ QT_{vi} = \frac{\log_{10}(QTv/QTm^2)}{(HRv/HRm^2)} \]

This index represents the log-ratio between the QT interval and the HR variability, each normalized for the corresponding mean.

**Statistical analyses**

A repeated-measures one-way ANOVA was used for the first four epochs of HR and QT variables. Epoch 5 was excluded from statistical analysis owing to insufficient data. Differences between waking and sleep (epochs 1 and 4) were assessed with a two-tailed t-test. Tests were performed at the \( P \leq 0.05 \) level of significance.

**RESULTS**

Results are presented in Table 1. Mean HR, heart rate variability, QT interval variability and QTvi demonstrated statistically significant diurnal variations across epochs. Mean HR was lowest during epoch 4 (21.30–04.30 h). Heart rate variability was greatest at this time. The mean QT interval was shortest during epoch 1, which had the highest corresponding mean HR. Both the QT variability and the QTvi were greatest during epoch 1 (07.30–11.30 h). Post hoc comparisons of waking and sleep (epochs 1 and 4) revealed significant differences between HRm, HR variability, QT variability and QTvi.

**DISCUSSION**

The dog is used in both cardiovascular safety and physiology investigations. Data indicate that the healthy dog mirrors the circadian variations in HR, QT interval and QT interval variability seen in healthy patients. Lowest mean heart rate in both patients and dogs occur during the early morning, a dark period in these animals’ environment and typically a period of deep sleep. Heart rate variability was also greatest at this time, likely reflecting the presence of sinus arrhythmia in both healthy patients and in the study animals.

This is the first report demonstrating circadian changes in QTvi in the dog. These dogs demonstrate a pattern to QTvi that closely matches that seen in healthy patient controls. Both these dogs and humans exhibit a significantly higher QTvi during active waking hours, with more negative values during night-time and, presumably, deep sleep. Of importance is the relationship between raw QT interval, QT interval variability and QTvi. The epoch of shortest QT interval corresponds to the greatest QT interval variability and QTvi. In this dataset, QTvi indicates an increased level of repolarization lability not indicated by the duration of QT interval alone. These findings suggest QTvi may serve as an additional and potentially more sensitive non-invasive tool to study cardiac repolarization lability in dogs in relation to any conditions or drugs that are known to be associated with increased cardiac mortality. Future studies will focus on the effects of drugs that prolong ventricular repolarization on QT interval variability in healthy dogs.

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**REFERENCES**


