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Original article

# Electrocardiogram, hemodynamics, and core body temperatures of the normal freely moving laboratory beagle dog by remote radiotelemetry ☆

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**Abstract**

**Introduction:** The objectives of this study were to provide baseline normative values for circadian changes in the time-series data collected over the course of a normal day in laboratory-housed dogs and to assess the relative efficiency of standard correction formulas to correct for the variations in QT intervals and heart rate functions. **Methods:** One hundred and twenty-three beagle dogs (65 M, 58 F) were equipped with radiotelemetry transmitters and continuously monitored, while freely moving in their home cages. Electrocardiograms (ECGs), hemodynamic parameters (diastolic, systolic, and mean arterial pressures) as well as core body temperatures were recorded for 22 h. **Results and discussion:** Blood pressures and core body temperatures demonstrated only very slight variations in their respective values over the 22-h monitoring period. ECGs were measured by a computerized waveform analysis program and quantitative elements reported as RR, PR, QRS, and QT intervals. Little circadian rhythmicity was demonstrated in the ECG intervals. Standard study-specific correction formulas appeared to satisfactorily normalize (i.e., compensate for) the *relationship* between heart rate and QT intervals in these beagle dogs but elevated the values of the QTc as compared to the uncorrected QT intervals. In sharp contrast, a subject-specific correction method based on analysis of covariance produced a more linear function between heart rates and QT intervals and, more importantly, provided QTc values within the normal range of actual, recorded QT interval data.


*Keywords:* Blood pressure; Body temperature; Beagle; Canine; ECG; Electrocardiogram; Hemodynamics; *Canis familiaris*; Methods; Radiotelemetry; QT prolongation

## 1. Introduction

A growing number of preclinical pharmacology studies are being conducted with beagle dogs. Many studies using this strain of dog are drug trials involving safety profiling, as promulgated by the International Commission on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH, 2004), and particularly specific safety pharmacology evaluations. Studies conducted under the guidance of the ICH are designed to discover and characterize the potential adverse cardiovascular effects of biologically active new chemical entities (NCE) that may present as an unintended consequence of exposure (ICH S7A, B).

Remote monitoring of the ECG by radiotelemetry has provided an alternative means of obtaining physiological measurements from awake and freely moving laboratory animals, without introducing either physically or chemically mediated stress or restraint artifacts in the data. It is generally assumed in contemporary pharmacology practice employing in vivo test systems that the quality of physiological measurements, when collected from conscious, freely moving animals, is superior to those obtained under physical or chemical restraint situations that are known to induce large-scale

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deviations from normal homeostasis. Long-term continuous sampling of the physiological endpoint of interest using telemetry protocols that minimize distortions due to stressful or noxious environments is now commonplace in many laboratories. Moreover, there has been explicit acknowledgement in ICH and other regional regulatory drug safety testing guidelines that conditions present during routine telemetric monitoring may most closely approximate the normal physiological state of the animal, and therefore safety endpoints evaluated under such conditions may consequently demonstrate the greatest predictive validity to outcomes of similar testing in human beings.

There are a number of advantages to the use of remote radio-monitoring in preclinical safety pharmacology: (1) telemetry-enabled observation provides the most humane method for monitoring physiologic endpoints in conscious, freely moving laboratory animals, eliminating the stress related to the use of restraint; (2) in the intervening decades since its inception, remote radiotelemetry has become more affordable and reliable, and now easy-to-use commercial products are readily available for monitoring a variety of physiological signals; (3) indwelling sensors for monitoring flow or pressure are usually more accurate and reliable than alternate non-invasive methods, such as transcutaneous laser-Doppler devices, tail cuff blood pressure monitors, etc.; and (4) biotelemetry allows for automated, high temporal resolution, continuous, and long-term data collection via computer, for days, weeks, or months, without any special animal care or maintenance. When used in tandem with remote video monitoring, radiotelemetry can be used to the exclusion of any direct human contact for prolonged periods of time so as to minimize this additional source of interference with physiologically normal baselines. The minimization of human contact during recording intervals can greatly augment the readability, as well as the reliability, of the data derived from emotional animals, whose physiological parameters demonstrate significant synchronous changes with such contact. One of the most important features of radiotelemetry, however, is the reduction of animal use by 60% to 70% in single dose studies (van Acker et al., 1996) and by more than 90% in multiple dose or repeat studies (Kinter, 1996; Kramer & Kinter, 2003).

The ECG in beagle dogs has been previously described as demonstrating normal sinus arrhythmias. The irregularity in the ECG appears to be secondary to fluctuations in vagal tone associated with the respiratory cycle (Tilley & Goodwin, 2001). Significant differences are found in the ECG waveform measurements when the dog is assessed in the sitting position when compared to sternal recumbency or lateral recumbency. Coleman and Robson (2005) suggest that reference range values for right lateral recumbency are not valid for ECGs obtained in the sitting position or sternal recumbency (Coleman & Robson, 2005).

The present study was a one-year retrospective examination of 123 kennel-raised beagle dogs (65 males, 58 females) surgically implanted with remote cardiovascular and hemodynamic radiotelemetry physiologic transducers. Remote monitoring of each dog's baseline ECG, blood pressures (diastolic, systolic, and mean arterial), and body temperature values were collected for 22 consecutive hours prior to any test initiation. The purposes of this study were four-fold: (1) to expand and supplement current knowledge on circadian stability of the serially and continuously sampled baseline ECG, blood pressures, and core body temperatures for clinically normal, kennel-born and reared, freely moving dogs within a laboratory setting; (2) to define the circadian characteristics of the ECG waveforms (RR, PR, QRS, QT, and QTc intervals) collected in individually housed laboratory beagle dogs; (3) to examine the relative usefulness of a number of correction formulas applied to normalize QT interval and heart rate functions in dogs; and (4) to compare these findings with a recent and similar report from this group using cynomolgus monkeys (Gauvin, Tilley, Smith, & Baird, 2005).

## 2. Methods

### 2.1. Regulatory guidelines

All procedures, data review, collection, and analysis were conducted on equipment and software validated in accordance with the Standard Operating Procedures of MPI Research, Inc. (Mattawan, MI), and/or the United States Food and Drug Administration (FDA) Good Laboratory Practice Regulations, 21 CFR Part 58. Data presented were reviewed by the Quality Assurance Unit of MPI Research.

### 2.2. Subjects

Sixty-five male and 58 female kennel-bred beagle dogs (*Canis familiaris*), approximately 5–8 months of age, were purchased from Covance Research Products Inc. (Portage, MI) or Marshall Farms (North Rose, NY) and placed in stainless steel double-wide cages according to MPI Research Standard Operating Procedures. Following the testing facility's standard operating procedures, complete physical, immunological, electrocardiographic, and hematological screening was used to verify the general well-being and good health of each dog. In full accordance and strict adherence to the National Institutes of Health, U.S. Department of Agriculture, U.S. Food and Drug Administration, and AAALAC guidelines, the dogs were approved to undergo surgical procedures to implant the radiotelemetry device. All experimental protocols and procedures were performed following approval of the MPI Research Institutional Animal Care and Use Committee. Baseline recordings occurred approximately 1 month following arrival (2-week acclimation, 2-week post-surgery recovery). Dogs were approximately 6 to 9 months of age when the baseline parameters reported in this study were monitored. The body weights were approximately 5.5 to 8 kg for male dogs and 5.0 to 7.5 kg for female dogs during the monitoring period.

### 2.3. Surgical implantations

Both the surgical placement of the radiotelemetry devices and post-surgical care were conducted by the veterinary team