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The Effect of Atenolol on QT Interval in Instrumented Beagle Dogs

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Abstract

In cardiology, the QT interval is a measurement of the heart's electrical cycle between the start of the Q-wave and end of the T-wave in electrocardiogram (ECG). Assessment of the QT interval is of clinical importance because prolongation of repolarization may be associated with malignant ventricular arrhythmias and sudden cardiac death. Atenolol, a beta-blocker, is an effective anti-hypertensive agent that its protective effect may reduce the QT interval in some patients. However, the data of atenolol in animals or patients with long-QT syndrome are limited. The goal of this paper was to evaluate the effect of atenolol on QT interval in beagle dogs. Two experiments conducted by the Health and Environmental Sciences Institute were used for the evaluation. In two Latin-square studies, beagles were given varying levels of atenolol on separating dosing days and their ECGs were measured telemetrically. As QT interval is correlated with heart rate, we investigated the relationship between heart rate and QT interval using the vehicle control group animals. In addition to QTcF, QT interval corrected based on Fridericia's formula, QTcP, which was based on the study population, and QTcI, which was derived from each individual animal, were evaluated. QTcF, QTcP, and QTcI were analyzed for each dose group at each time point compared to the vehicle. The analyses suggest that atenolol does not affect QT interval in beagle dogs.

Keywords: QT Interval; Heart rate; Atenolol; Beagle dog; Latin square design.

Introduction

In cardiology, the QT interval is a measurement of the heart's electrical cycle between the start of the Q-wave and end of the T-wave as seen on electrocardiograms (Figure 1). It measures the time interval between depolarization and repolarization of the ventricles in the heart's electrical cycle. The QT interval, when corrected for heart rate (QTc), is useful for detecting congenital and acquired heart diseases that can lead to fatal arrhythmias [1]. Long-QT syndrome is a notable example that is characterized by chronic lengthening of the QT interval which can result in fainting, seizures, and ventricular fibrillation. This disease can be inherited or acquired when taking drugs that inadvertently block cardiac potassium channels. In extreme cases, long-QT syndrome can lead to Torsades des Pointes, a potentially fatal type of ventricular tachycardia.

As there is currently no drug approved for patients with long-QT syndrome, most treatment options have been limited to beta-blockers, therapeutic anti-hypertension drugs. Beta-blockers inhibit the binding of norepinephrine and adrenaline nerves, which subsequently lowers heart rate and reduces the risk for heart disease [2]. Atenolol, a beta-1 adrenergic receptor blocker, is a prescription drug used in treating patients with cardiovascular disease and lowering blood pressure [3]. Since its introduction in 1976, it has replaced propranolol in treating hypertension and has seen widespread use

throughout the world. Adrenergic nerves stimulate the cardiac function and regulate cardiac outputs. Atenolol blocks specific receptor adrenergic nerves, decreasing cardiac stimulation. This allows the heart to beat at a slower rate, reducing the blood flow through arteries and decreasing blood pressure. Atenolol has also been used as an off-label treatment for long-QT syndrome [4,5].

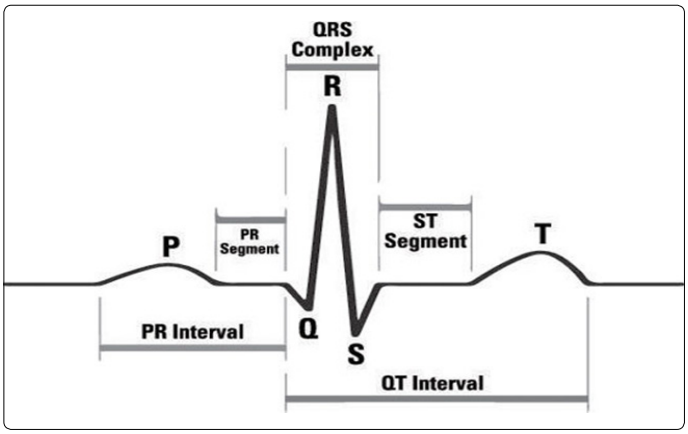

Figure 1. An ECG of the heart displaying the QT interval, from the start of the Q-wave and end of the T-wave.

Though atenolol has been frequently prescribed, there is a lack of conclusive data on its efficacy on the QT interval. We hypothesize that atenolol is an effective treatment for long-QT syndrome. To test this, we used animal data based on experiments conducted from two different laboratories. Each laboratory used eight beagle dogs in their experiment. The data, courtesy of Health and Environmental Sciences Institute, was taken continuously from each of the eight dogs using cardiac telemetry, with a small device implanted in the dog's heart, allowing researchers to monitor various aspects of each dog's heart function over a period of twenty-four hours [6]. The implants transmitted data continuously, and averaged data of ten-minute intervals for twenty-four hours was made available to the public. As each experiment was conducted using a double 4 × 4 Latin-square design, data was organized by dosing group, vehicle control, low-dose, medium-dose, and high-dose of atenolol. Each animal was administered to a different dose group on four separate dosing days.

While other measurements of cardiac function and ECG were collected, our primary interest was the length of the QT and RR intervals, which has not been published previously. The RR interval is the length between one peak of an ECG wave and the peak of the next wave. The RR interval is inversely related to heart rate; in fact, RR in millisecond is equal to 60*1000 divided by heart rate in beats per minute. The QT interval can be affected directly by a drug or indirectly by the drug induced heart rate change, making it difficult to accurately measure the drug's direct effects on the QT interval (See figure 2) for an illustration. Therefore, the QT interval is often corrected for the change in heart rate or RR, denoted by QTc or corrected QT interval [7]. Frederica's correction formula, known as QTcF, is commonly used in human and is calculated using a correction constant of 1/3 to account for the length of the QT interval compared to the RR interval, i.e., $QTcF = \frac{QT}{(RR)^{1/3}}$. However, Frederica's formula was derived from human it may not be suitable for beagle dogs. In this paper, we attempted to derive and compare appropriate formulas for correcting the QT interval in beagle dogs. Treatment effects of atenolol were statistically evaluated using two-sided t-test for each dose level at each time point.

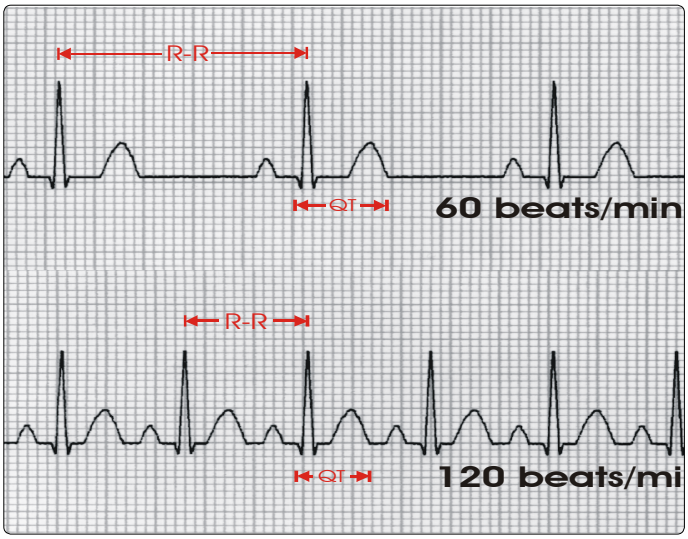

Figure 2. An illustration of QT and RR relationship under two different heart rate scenarios.

The layout of this paper is as follows. In Methods section, we describe the experimental designs, data collection, and methods to conduct the statistical analysis. We also discuss the statistical models to identify an appropriate heart rate correction formula for QT interval in beagle dogs. In Results section, we evaluate and summarize the performance of various heart rate correction formulas. The statistical analyses of atenolol effects on these QTc intervals are summarized. Discussion and concluding remarks are given in one section.

Methods

Experimental design

The data was obtained from studies performed by two independent laboratories through Health and Environmental Sciences Institute [6]. The ECG data has not been published previously. Beagle dogs from Lab 1 were sourced from Marshall Farms, and Covance Research Products provided beagle dogs for Lab 2. All beagle dogs were examined to confirm their health and suitability according to local procedure. Each laboratory used DSI Physiotel™ D70-PCTP telemetry instrumentation. The telemetry system was surgically implanted into dogs under general anesthesia under procedures approved by each laboratory's local internal review board. All animals were given sufficient recovery time from surgery prior to the beginning of the study. Each study was conducted using eight beagle dogs, all males, given three different doses of atenolol as well as a vehicle on four different dosing days with a minimum 72-hour washout period in between. This was done using a double 4 × 4 double Latin square design. Atenolol was administered orally, with deionized water as vehicle control. Group 1 administered vehicle control, Group 2 (low dose) 0.3 mg/kg, Group 3 (medium dose) 1 mg/kg, and Group 4 (high dose) 3 mg/kg of atenolol. See table 1 for an illustration of the design from Lab 2.

	Animal ID							
	8369	8370	8371	8372	8373	8374	8375	8376
Day 1	3	2	1	4	1	2	4	3
Day 2	1	3	4	2	2	4	3	1
Day 3	2	4	3	1	4	3	1	2
Day 4	4	1	2	3	3	1	2	4

Table 1. Groups 1-4 represent vehicle control, low dose, medium dose, and high dose of atenolol, respectively. Animals 8369-8372 forms a 4 × 4 Latin square and animals 8373-8376 forms another 4 × 4 Latin square. On each dosing day, each of the eight animals was administered a vehicle control or a dose of atenolol.

QT Correction for heart rate

Digital ECG signals were continuously acquired from at least one hour prior to dosing through 24 hours post dose on each dosing day. Derived data were calculated for every cardiac cycle and the results were collapsed into 10-minute mean values available for analysis. In order to investigate the relationship between QT and RR without the influence of treatment effect, we used only vehicle control group. Luo et al. [8] shows that the relationship may be linear on a logarithm-scale. Using only the vehicle control group data in each study, the relationship between log (QT) and log (RR) were plotted for each animal. A least-squares regression line was estimated using the following model,

$\log(QT)=a+c\log(RR)+e$,

where e was assumed to follow a Normal distribution. The line's slope estimate $\hat{c}$ and its standard error were summarized. The slope estimate $\hat{c}$ is also known as the correction factor because if we let the intercept estimate $\hat{a}$=log (QTcF), then from the above equation

$$\hat{a} = \log(QT) - \hat{c}\log(RR) = \log\left(\frac{QT}{RR^{\hat{c}}}\right)$$

And hence

$$QTc = \frac{QT}{(RR)^{\hat{c}}}$$

Fridericia estimated that a factor of $\hat{c}$=1/3 is adequate in human. To confirm that Fridericia's correction factor of 1/3 was adequate in beagle dogs, a 95% confidence interval for the slope was derived for each animal. If the 95% confidence interval did not contain 1/3, then Fridericia's formula may not be adequate for beagle dogs. The slope estimates were averaged to derive the study-specific QT interval correction factor. The QTcP was calculated using the following formula: $= \frac{QT}{(RR)^{p}}$, where p is the average of the slope estimates from all animals in each study. The QTcI was calculated using $\mathrm{QTCI} = \frac{QT}{(RR)^{c_i}}$, where c_i is the slope estimate of i-the animal in each study. QTcP is the QT interval corrected with the population slope factor, and QTcI is the QT interval corrected with an individual's slope factor. The QTcP takes a more universal, applicable approach to the QT rate-correction; the QTcI is more individualized and animal-specific.

Statistical analysis

For each of the QTcF, QTcP, and QTcI interval, data were collapsed into hourly averages for each dog. The hourly intervals were derived based on the averages of six of the 10-minute mean values, resulting a baseline at time 0 (pre-dosing) and 24 hourly time points post-dosing. The purpose of this process was to reduce the amount of ambient noise from the background and hence reduce the unaccountable variability of the measurements.

For each post-dosing hourly time point, changes from baseline were derived for each animal in each dose group. Treatment effects of low dose, medium dose, and high dose of atenolol on QTcF, QTcP, or QTcI were compared to the control. For each QTc, a two-sided t-test with a significance level of 0.05 was employed for the comparison between each treatment group versus control. No multiplicity adjustment was made [9]. The p-values generated by the t-test were plotted against 0.05 for each treatment group.

Results

The data sets from Health an Environmental Sciences Institute contain QT, QTcF, and RR in 10-minute interval for 24 hours. Following the process of converting 10-minute intervals into hourly intervals as described in Statistical analysis section, figure 3 displays the derived hourly averaged QTcF over the 24-hour period for each of eight animals in lab 2 with different treatment groups. Preliminary analysis shows that there might not be any atenolol treatment effects over time. The QTcF seems to be similar across all treatment groups. This may indicate that atenolol does not have an effect on the QT interval in beagle dogs, or that Frederica's correction formula is unfit for the QT interval in beagle dogs.

Figure 4 shows the vehicle control animal QT-RR relationship on a log-log scale along with the least-squares regression line for each animal. The slope estimate and its confidence interval for each animal are summarized in table 2, revealing that none of the intervals covers 1/3. This suggests that Fridericia's correction factor is unsuitable for use in the correction of the QT interval in these two studies. Furthermore, the average of slope estimates in is 0.29 for Lab 1 and 0.23 for Lab 2, indicating that the Fridericia's formula may be over-correcting for the RR changes. The estimates of 0.29 and 0.23 are used to derive QTcP for animals in Lab 1 and Lab 2, respectively. The slope estimates listed in table 2 are used to derive QTcI for each animal.

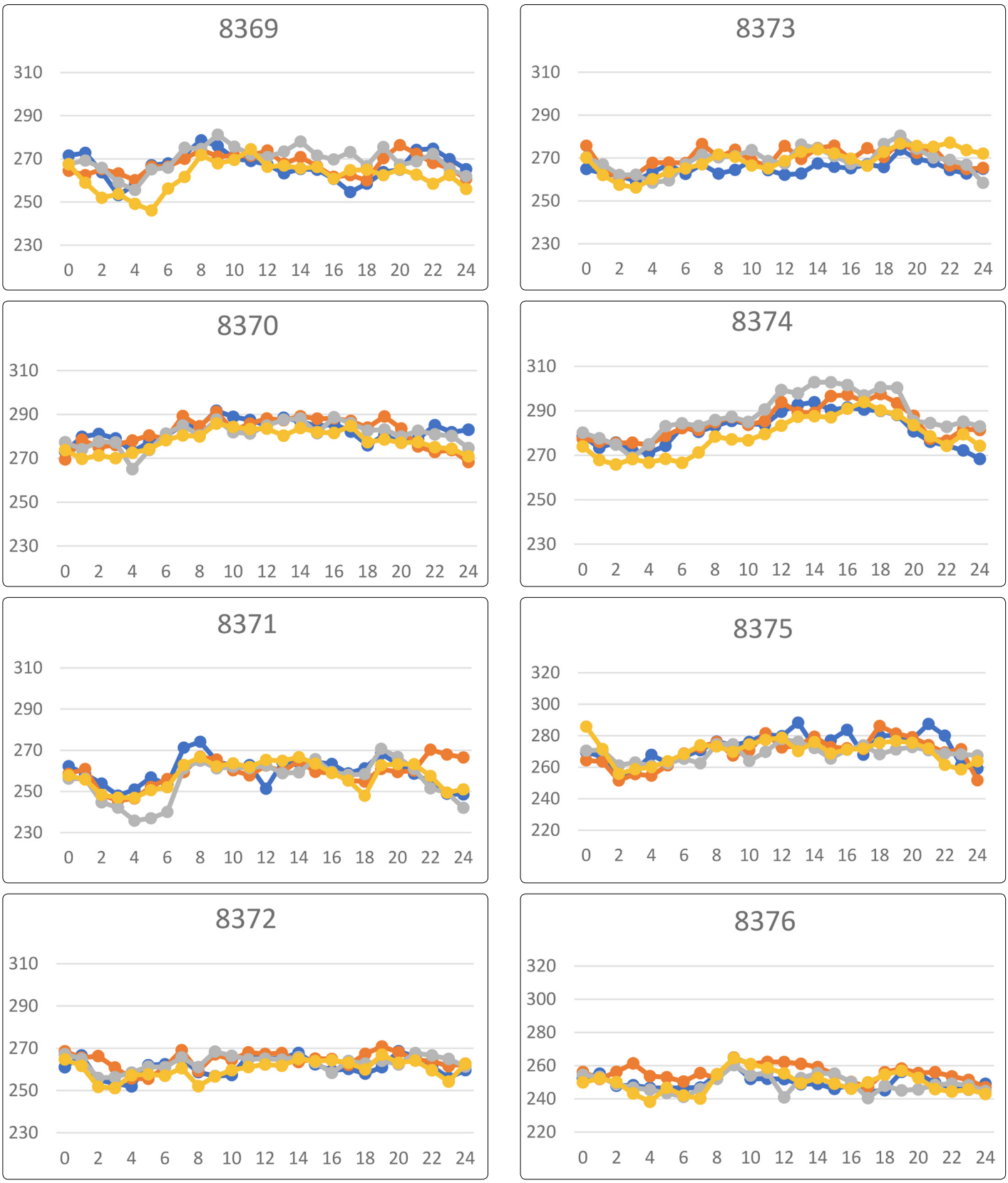

Figure 3. Hourly QTcFof each animal on different treatment groups in Lab 2.

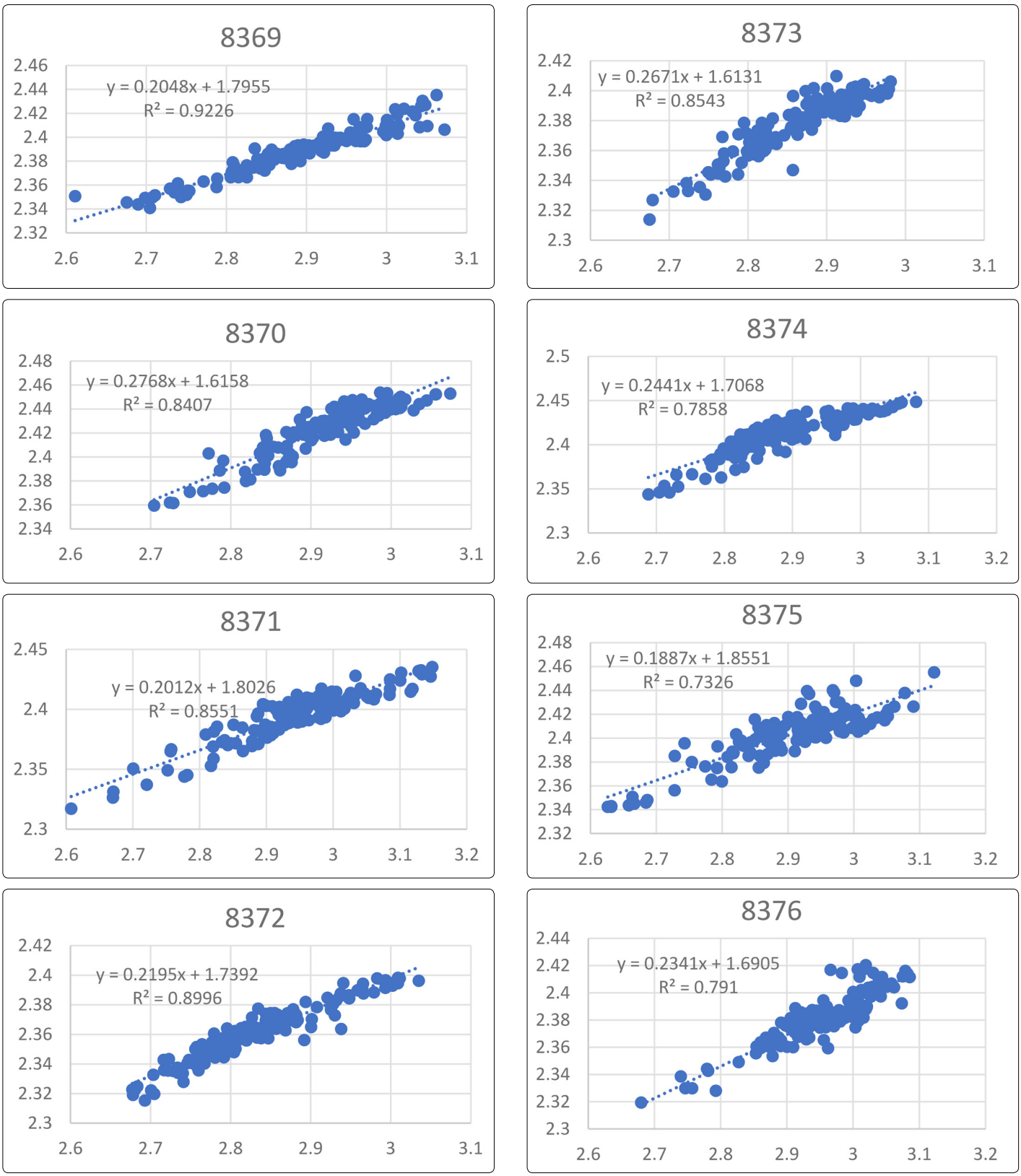

Figure 4. QT-RR relationship on log-log scale for each animal in Lab 2.

Table 2. Summary of slope estimates and their 95% confidence intervals from QT-RR plots.

Lab 1 Animal	**360**	**888**	**1859**	**4152**	**4217**	**4563**	**5897**	**6741**
Slope	.271	.212	.301	.273	.354	.211	.350	.413
95% C.I.	0.271 ± 0.013	0.212 ± 0.017	0.301 ± 0.018	0.273 ± 0.016	0.354 ± 0.015	0.211 ± 0.012	0.350 ± 0.014	0.413 ± 0.018
95% C.I. covers 1/3?	No	No	No	No	No	No	No	No
Lab 2 Animal	**8369**	**8370**	**8371**	**8372**	**8373**	**8374**	**8375**	**8376**
Slope	.205	.277	.201	.220	.267	.244	.189	.234
95% C.I.	0.205 ± 0.010	0.277 ± 0.020	0.201 ± 0.014	0.219 ± 0.012	0.267 ± 0.018	0.244 ± 0.021	0.189 ± 0.019	0.234 ± 0.020
95% C.I. Covers 1/3?	No	No	No	No	No	No	No	No

Figure 5 shows the changes from baseline for QTcF, QTcP, and QTcI from both Lab 1 and Lab 2. While there appears to be some difference in time profile between Lab 1, where most changes are negative, and Lab 2, where most changes are positive, the treatment group difference within each study is minimal. In addition, QTc changes from baseline over time appear to be consistent among QTcF, QTcP, and QTcI in Lab 1. For Lab 2, the longitudinal QTcF changes from baseline are different from QTcP and QTcI, where small increases are observed during the initial hours after dosing. It is noted that none of the change from baseline is above 10 ms, an area of potential clinical concern [1,9].

Figure 5. Changes from baseline of hourly QTcF, QTcP, ad QTcI for each treatment group in Lab 1 (left panel) and Lab 2 (right panel).

Figure 6 shows the p-value plots for evaluating the treatment effects of atenolol on QTcF, QTcP, and QTcI. The results indicate that the effect of atenolol on QTcF is statistically significant only at one time point, 1-hour post-dosing in the high dose group, only in Lab 2. The p-value was 0.031 and the group means change in QTcF between high dose and control was -5.7 ms. The effects of atenolol on QTcF are not statistically significant at any other time points. The use of QTcF to evaluate the treatment effect of atenolol is questionable because Fridericia's correction factor is not appropriate in this study. The magnitude of changes in QTcF is found to be very different from that in QTcP and QTcI as shown in figure 5. In addition, the effect of atenolol is not found to be significant in QTcP, or QTcI from either laboratory.

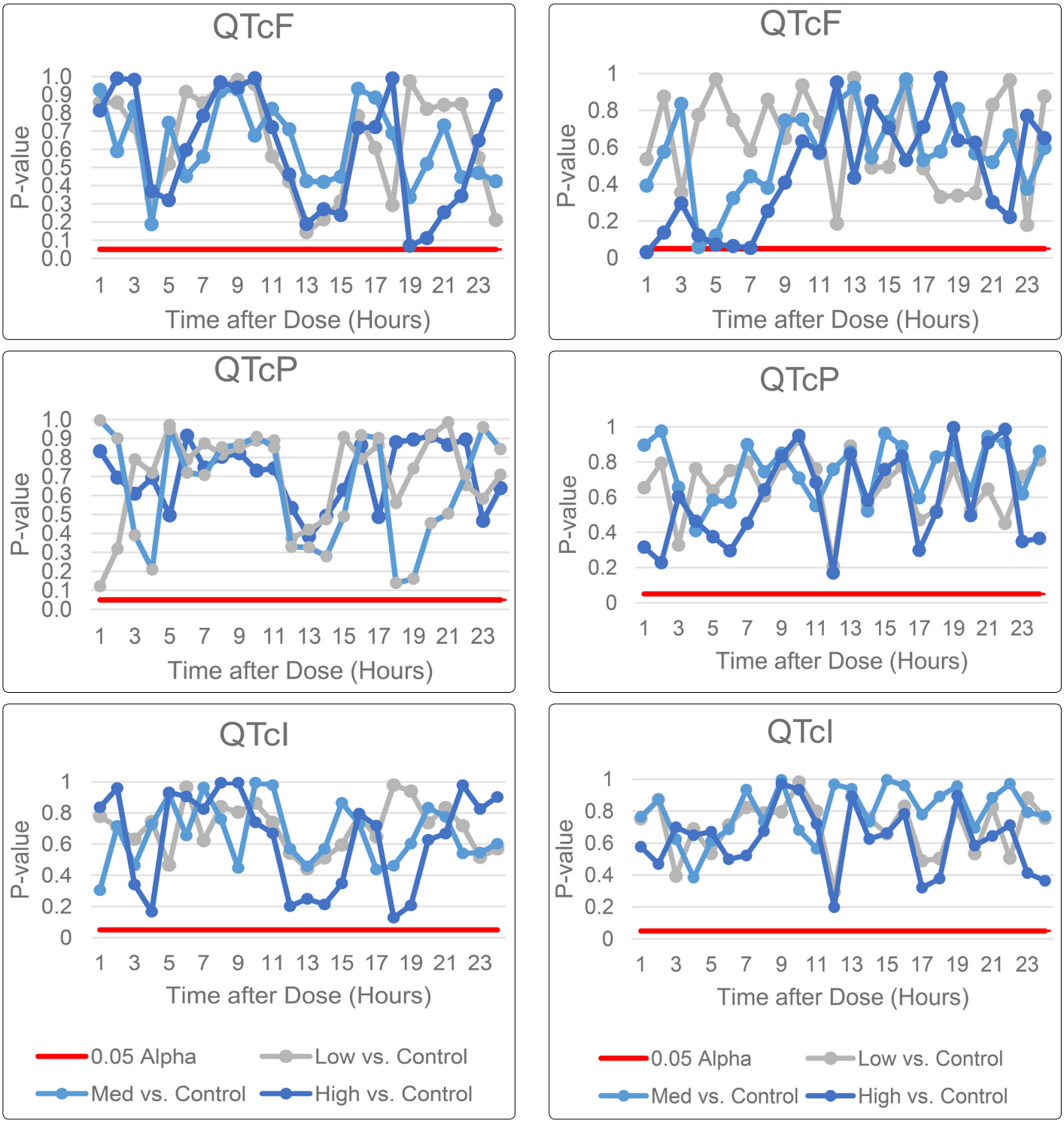

Figure 6. p-values of each dose of atenolol compared with vehicle control at each post-dosing time point for studies conducted by Lab 1 (left panel) and Lab 2 (right panel). The p-value of 0.05 serves as the reference line.

Discussion and Concluding Remarks

The purpose of this study was to investigate the effect of atenolol on the QT interval in beagle dogs. Literature regarding the atenolol effect on QT is limited and the clinical use of atenolol to treat patients with long-QT syndrome has been inconclusive. Using the data from Health and Environmental Sciences Institute, our analysis concludes that

atenolol results in no statistically significant QT changes in beagle dogs. These results have not been reported previously.

As heart rate plays a key role on the assessment of QT interval, we investigated whether the conventional Fridericia's correction factor is adequate for use in beagle dogs. The goal of any QT correction for heart rate procedure is to reduce QT measurement error by effectively dissociating the effects of heart rate or RR, yielding a more stable measure, QTc. While other approaches to model the QT-RR relationship might be employed [8], we found the linear regression model on a log-log scale to be appropriate in our studies. In addition to a study-specific population-based correction factor, we also derived the animal-specific correction factor, analogous to the approach proposed by Malik et al. [7] for human. We concluded that Frederica's formula was not adequate for beagle dogs in our studies as it tended to over-correct for RR.

The statistical evaluation of treatment effect was conducted by comparing the QTc changes from baseline from each atenolol group versus control. While there was a statistically significant QTcF difference at 1-hour post-dosing in Lab 2, it was clinically insignificant due to the very small difference between high dose atenolol and vehicle control (5.7 ms). Considering that there are no statistically significant changes from baseline in QTcP or QTcI, a plausible explanation for this outlier data point could be that Frederica's correction may not be appropriate for beagle dogs, leading to inaccurate measurements and conclusions from the statistical analysis. The other possibility of this potential false positive finding is that there is no multiplicity adjustment made in the statistical analysis. If an underlined type I error is 0.05 and there are 24 independent hypothesis tests (24 hourly time points), the chance of observing a positive finding within the 24-hr period is $1-(1-0.05)^{24}=0.708$, i.e., there is an over 70% chance of having a statistically significant change at any time point even though the treatment effect is null. In practice, the 24 tests are not likely to be independent because of the time course dependent successive QT measurements. The significant finding in QTcF may also be attributed to the variability in heart rate, QT interval, animal handling or dosing procedure in Lab 2, or other sources of inherent error.

It is noted that the implications of this study may not be applicable to a human. Holzgrefe et al. [10] examines cross-species and human translation of QT prolongation induced by moxifloxacin. They show that all preclinical QT/QTc results are consistent when accurately modeled and evaluated, and the outcomes can be transferrable across species including man. Accurate translation of other drug-induced QT results remains limited and problematic. As a receptor blocker, atenolol binds to specific proteins that may be present in humans but not beagle dogs due to a medley of other possibilities that could explain an efficacy in humans but not beagle dogs. Further studies of atenolol's clinical use in treating patients with long-QT syndrome are needed [5]. Finally, the study design with a sample size of eight in a Latin square design may be adequate for exploratory evaluation of atenolol effects on QT. The hope was that by repeating the experiments in two laboratories, inherent variability may be reduced and the conclusions are more conclusive. However, we recognize the data sets are limited and additional exploration is needed.

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