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Regadenoson, a Novel Pharmacologic Stress Agent for Use in Myocardial Perfusion Imaging, Does Not Have a Direct Effect on the QT Interval in Conscious Dogs

Gong Zhao, MD, PhD^{*}, Sabrina Serpillon, PhD[†], John Shryock, PhD^{*}, Eric Messina, BS[†], Xiaobin Xu, MD[†], Manuel Ochoa, BS[†], Luiz Belardinelli, MD^{*}, and Thomas H Hintze, PhD[†]

^{*}Department of Pharmacology, CV Therapeutics, Inc., Palo Alto, CA 94304

[†]Department of Physiology, New York Medical College, Valhalla, NY 10595

Abstract

Our goal was to determine the effect of regadenoson (a novel A_{2A} adenosine receptor agonist) on the QT interval in conscious dogs. Eleven mongrel dogs were chronically instrumented for measurements of blood pressure and ECG. Regadenoson (2.5, 5 and 10 µg/kg, IV) caused a dose-dependent QT interval shortening (QT: 14±3, 24±5 and 27±5 ms, mean±SEM, n=7-11, all p<0.05) associated with significant increases in HR (Peak HR: 114±9, 125±6 and 144±7 bpm). Atrial pacing (135, 150 and 165 bpm) also caused a frequency-dependent shortening of the QT interval (QT: 15±3, 22±3, and 39±5 ms, n=6-7, all p<0.05). Regadenoson- and pacing-induced shortenings in the QT interval were significantly correlated with the R-R interval (r= 0.67 and 0.8, both p<0.05). Regadenoson at 5 and 10 µg/kg did not cause a significant change in HR or QT interval either during atrial pacing at 165 bpm or after administration of propranolol and atropine to prevent HR from changing, or after treatment of dogs with hexamethonium to block autonomic ganglia. Regadenoson (5-10 µg/kg) caused no significant changes of QT interval in the heart in which HR was kept constant via physiological or pharmacological procedures, indicating that regadenoson has no a direct effect on the QT interval.

Keywords

regadenoson; A_{2A} adenosine receptor agonist; the QT interval; pharmacologic stress testing; heart rate; conscious dogs

INTRODUCTION

Regadenoson is a novel A_{2A} adenosine receptor agonist and is, approved by the US FDA in 2008, used as a coronary vasodilator in pharmacologic stress testing conjunction with myocardial perfusion imaging.¹⁻⁴ It has been reported that regadenoson is a selective and potent coronary vasodilator in conscious dogs.⁵⁻⁷ In addition to coronary vasodilation,

Correspondence to: Gong Zhao, MD, PhD 3172 Porter Drive Palo Alto, CA 94304 USA Phone: (650)384-8673 Fax: (650)475-0392
E-mail: gong.zhao@cvt.com.

Regadenoson and the QT interval

regadenoson also causes an increase in heart rate (HR) following iv administration in humans 1-4 and in conscious dogs.⁵⁻⁷

In humans, regadenoson has been reported to increase the Fridericia-corrected QT interval by 4 to 23 ms at 2 min postdose.⁸ We speculated that the increase in the QTc was an indication of hysteresis in the reduction of the QT interval following a rapid increase in HR after regadenoson bolus iv administration, rather than a direct effect of the drug to prolong the QT interval. The QT interval of the ECG represents the time elapsed between ventricular depolarization and repolarization. Prolongation of the QT interval, an electrocardiographic manifestation of prolonged ventricular repolarization, is a known clinical risk factor for the development of severe, life-threatening arrhythmias, including torsades de pointes.⁹ Therefore, it is necessary to determine if regadenoson can cause a significant prolongation of the QT interval.

Sotalol is a non-selective β -adrenergic receptor antagonist and a Class III antiarrhythmic drug known to inhibit K^+ channel on myocytes.¹⁰ It has been reported that sotalol can decrease HR and prolong the QT interval in humans¹⁰ and in dogs.^{11, 12} Therefore, sotalol was used as a positive control, the QT-prolonging drug, in this study.

The objectives of this study were to determine in conscious dogs whether regadenoson (iv) causes changes in the QT interval of the ECG, and whether these changes are independent of changes in HR.

METHODS

Sixteen chronically instrumented male mongrel dogs weighing from 20 to 28 kg were used in this study. The experimental protocols were approved by the Institutional Animal Care and Use Committee of New York Medical College and conform to the Guide for the Care and Use of Laboratory Animals by the US National Institutes of Health.

Surgical Procedures

Dogs were sedated with acepromazine (0.3 mg/kg, im) and anesthetized with pentobarbital sodium (25 mg/kg, iv). After intubation, dogs were artificially ventilated with room air. The chest of each dog was scrubbed with a sterilizing soap and sterilized with iodine solution. A thoracotomy was performed in the fifth intercostal space. A Tygon catheter (Cardiovascular Instruments, Wakefield, MA) was inserted into the descending thoracic aorta for the measurement of blood pressure. A pair of electrodes was sutured onto the surface of the right atrium for atrial pacing to control HR. The chest was closed in layers. The catheter and wires were tunneled subcutaneously and externalized through the skin at the back of the dog's neck. After surgery, the dogs were allowed to recover for 10-14 days. Dogs were trained to lie quietly on the laboratory table before experiments were performed.

Blood Pressure, Heart Rate, and ECG Measurements

Phasic arterial pressure was measured by connecting the previously implanted aortic catheter to a strain gauge transducer (P23 ID, LDS Test and Measurement, Valley View, OH). ECG signals were recorded using Standard limb Lead II or III. Blood pressure and ECG signals

were acquired using a Ponemah Physiology Platform System—Model P3 Plus (a computer-based software package, Version 4.20 or 4.40, Data Sciences International, Valley View, OH). Mean arterial pressure (MAP) was calculated from phasic BP. R-R and QT intervals were measured by the Ponemah Physiology Platform, and HR was calculated from the R-R interval ($\text{HR} [\text{beats/min}] = 60000 / \text{R-R interval} [\text{ms}]$). In some cases (when the heart was atrially paced or the correct QT or R-R intervals could not be measured by the Ponemah system), R-R and QT intervals (10 wave forms) were measured using a ruler after ECG signals were replayed on paper at a speed of 100 mm/sec. A corrected QT interval or QTc was calculated according to Fridericia's formula ($\text{QTcF} = \text{QT}/(\text{R-R})^{1/3}$).¹³

Experimental Protocols

On the day of an experiment, a dog was placed on a table on its right side, where it lay quietly during the experiment. A catheter was inserted into a peripheral vein in the leg and attached to an infusion line to administer drugs without disturbing the dog. ECG electrodes were placed on each leg. The experiment was begun after MAP and HR were stable (usually 20 to 30 min after connecting all recording equipment). During each experiment, BP, HR, and ECG were continuously recorded throughout the entire experiment.

Effects of Atrial Pacing on the QT Interval and MAP (n = 6–7)—When MAP and HR were stable, pacing of the right atrium of the heart was started using a pacemaker (Pace Medical, Inc., Waltham, MA) connected to pacing electrodes previously implanted on the right atrium. The heart was atrially paced for ~5 min at each of three rates (135, 150, and 165 bpm). MAP, HR and ECG signals were recorded.

Effects of Regadenoson on the QT Interval, MAP, and HR

Effects of Regadenoson Alone (n = 6–11) and When the Heart Was Paced at 165 bpm (n = 4) on the QT Interval, MAP and HR: Dogs received bolus injections of regadenoson at 1, 2.5, 5, and 10 $\mu\text{g/kg}$ (iv). After each dose, BP and HR were allowed to return to baseline before the next dose was administered. Dosing intervals were 15, 20, 30, and 45 min after administration of 1, 2.5, 5, and 10 $\mu\text{g/kg}$ regadenoson, respectively. Then, the heart was atrially paced at 165 bpm for 10 min, and the injections of 5 and 10 $\mu\text{g/kg}$ regadenoson were repeated while the heart was atrially paced at 165 bpm.

Effects of Regadenoson on the QT Interval, MAP and HR after Combination of β -Adrenergic and Muscarinic-Cholinergic Blockade (n = 5–8): Dogs were given propranolol (1.0 mg/kg) and atropine nitrate (0.1 mg/kg, 10 min after giving propranolol) intravenously first. Afterwards, 5 and then (30 min later) 10 $\mu\text{g/kg}$ regadenoson were administered intravenously. A second dose of propranolol (0.5 mg/kg) was administered prior to the administration of 10 $\mu\text{g/kg}$ regadenoson to maintain β -adrenergic blockade.

Effects of Regadenoson on the QT Interval, MAP and HR After the Blockade of Autonomic Ganglia (n = 6): On another day, some dogs received hexamethonium (20 to 25 mg/kg, iv, over 30 to 35 min) to block autonomic ganglia. This was followed by an iv injection of 5 $\mu\text{g/kg}$ regadenoson.

Effects of Sotalol on the QT Interval, MAP, and HR (n = 7)—Sotalol (4 mg/kg) was infused intravenously over 10 min in 7 dogs. BP, HR, and ECG were continuously recorded for 60 min after the completion of infusion of sotalol.

Drugs

Regadenoson was supplied by CV Therapeutics, Inc. as a sterile stock solution (Lot No.: 803604, 0.08 mg/mL) in 100 nM sodium phosphate buffer containing 15% propylene glycol and 0.1% disodium edentate (pH 7). Atropine nitrate, hexamethonium, propranolol and (±)-sotalol hydrochloride were purchased from Sigma-Aldrich (St. Louis, MO). Atropine nitrate (1 mg/mL) and hexamethonium (20 mg/mL) were dissolved in normal saline. Propranolol (10 mg/mL) and sotalol (20 mg/mL) were dissolved in distilled water. All drug stock solutions were diluted in normal saline before injection or infusion, as appropriate.

Statistical Analysis

The values of QT and R-R intervals are presented as the average values for ten individual heart cycles at selected time points. Both the absolute change and the percentage change in each parameter relative to baseline (before drug administration) were calculated in each experiment and used for statistical analysis. The statistical significance of a difference between the value of a parameter at baseline and at the indicated time point after drug administration was determined using a One-Way Repeated Measures ANOVA followed by Tukey's Test. Statistical significance of differences between responses to regadenoson in the absence and presence of atrial pacing, propranolol and atropine, or hexamethonium was determined using a Two-Way Repeated Measures ANOVA followed by Tukey's Test. Differences associated with a probability (p) < 0.05 were considered to be significant. A computer-based software package (SigmaStat 2.03, SPSS Science, Chicago, IL) was used for statistical analysis. The relationships between the QT and R-R intervals, during pacing at 135, 150, 165 bpm and response to regadenoson at 1, 2.5, 5 and 10 µg/kg, were fitted using a least squares non-linear regression method. The data for R-R and QT intervals in the presence of regadenoson were fit to the equation: $y = -197.02 + 66.82 \ln(x)$, where x and y are R-R and QT intervals, respectively. The data for R-R and QT intervals during pacing were fit to the equation: $y = -223.04 + 70.23 \ln(x)$. Correlation coefficients were calculated using Prism 3.0 (GraphPad Software, Inc., San Diego, CA). All data are presented as Mean $\pm$ SEM.

RESULTS

Effects of Atrial Pacing on the QT Interval and MAP

When the heart was atrially paced at 135, 150, and 165 bpm, the QT interval was shortened in a frequency-dependent manner by 15 ± 3 , 22 ± 3 and 39 ± 5 ms, respectively, from a baseline value of 224 ± 5 ms ($n = 6-7$, all $p < 0.05$, compared with baseline). The relationship of the QT and R-R intervals when the heart was paced at different rates is shown in Figure 1 (dashed line). The QT intervals were significantly correlated with the R-R intervals ($r = 0.80$, $p < 0.05$). There was no significant change in the QTcF interval during the 3 rates of pacing, as shown in Table 1. Pacing did not cause a significant change in MAP.

Effects of Regadenoson on the QT Interval, MAP, and HR

Effects of Regadenoson Alone on the QT Interval, MAP and HR—Regadenoson at 1, 2.5, 5, and 10 $\mu\text{g/kg}$ caused a dose-dependent shortening in the QT interval associated with an increase in HR (i.e. a shortening in the R-R interval) (Figure 2). The maximum shortening in the R-R interval occurred at ~ 0.5 min, however, the maximum shortening in the QT interval occurred at ~ 2 min following administration of regadenoson as shown in Figure 2. Thus, the shortening of the QT interval lagged shortening of the R-R interval by approximately ~ 1.5 min. Figure 3 Panel A shows the time course of changes in R-R and QT intervals following an iv injection of 5 $\mu\text{g/kg}$ regadenoson. Because the regadenoson-induced changes in both QT and R-R intervals reached a steady state at ~ 3 min following administration, the data at that timepoint (3 min) were used to compare with baseline values. The QT interval was shortened by 14 ± 3 , 24 ± 5 and 27 ± 5 ms, and the R-R interval was shortened by 150 ± 18 , 212 ± 27 and 251 ± 39 ms after injections of 2.5, 5, and 10 $\mu\text{g/kg}$ regadenoson ($n = 7-11$, all $p < 0.05$, compared with baseline values). The relationship between QT and R-R intervals is shown in Figure 1 (solid line). The QT interval was significantly correlated with the R-R interval ($r = 0.67$, $p < 0.05$). There was no statistically significant difference between QT and R-R relationships following administration of regadenoson and atrial pacing ($p > 0.05$) (Figure 1). Regadenoson 1 to 10 μg did not cause a statistically significant change in the QTcF interval (Table 1). Regadenoson at 2.5, 5, and 10 $\mu\text{g/kg}$ caused a slight decrease in MAP (7-13 mmHg) (Table 2).

Effects of Regadenoson (5 and 10 $\mu\text{g/kg}$) on the QT Interval When the Heart Was Atrially Paced at 165 bpm—When the heart was atrially paced at 165 bpm, the value of baseline QT interval at a steady-state was 189 ± 2 ms ($n = 4$), and 5 and 10 $\mu\text{g/kg}$ regadenoson did not cause a significant change in either the QT interval (Figure 3, Panel B), or the QTcF interval (Table 1). Regadenoson did not change the R-R interval in these dogs because their hearts were paced at a constant rate (Table 1). Five and 10 $\mu\text{g/kg}$ regadenoson nonetheless caused a decrease in MAP when the heart was atrially paced at 165 bpm, but only the decrease in MAP by 10 $\mu\text{g/kg}$ regadenoson was statistically significant (Table 2).

Effects of Regadenoson on the QT Interval, MAP and HR after the Combination of β -Adrenergic and Muscarinic-Cholinergic Blockade—After administration of propranolol and atropine to block β -adrenergic and muscarinic-cholinergic receptors, respectively, HR increased from a baseline value of 88 ± 5 to 146 ± 8 bpm, and the QT interval was shortened from 240 ± 7 to 211 ± 6 ms ($n = 9$). Regadenoson (5 and 10 $\mu\text{g/kg}$) did not cause a significant change in the QT interval (Figure 3, Panel C) and the QTcF interval (Table 1) after administration of propranolol and atropine. Regadenoson at 10, but not at 5 $\mu\text{g/kg}$ (at 3 min following administration), caused a slight, but significant increase in HR or decrease in R-R interval after administration of propranolol and atropine. The regadenoson-induced (peak) changes in HR or RR interval were relatively small ($< 5\%$ for 5 $\mu\text{g/kg}$ and $< 8\%$ for 10 $\mu\text{g/kg}$ regadenoson). Regadenoson (5 and 10 $\mu\text{g/kg}$) still caused a decrease in MAP (11 and 19 mmHg, respectively) after treatment of dogs with propranolol and atropine (Table 2).

Effects of Regadenoson on the QT Interval, MAP and HR after the Blockade of Autonomic Ganglia—After administration of hexamethonium to block autonomic ganglia, the baseline HR and the baseline QT interval were 152 ± 6 bpm and 212 ± 3 ms, respectively ($n = 6$). Regadenoson ($5 \mu\text{g/kg}$) did not cause significant changes in QT (Figure 3, Panel D) and the QTcF interval, and R-R intervals (Table 1) or HR (Table 2) after treatment of dogs with hexamethonium. However, regadenoson ($5 \mu\text{g/kg}$) caused a greater decrease in MAP in dogs after treatment with hexamethonium, compared with control (Table 2).

Effects of Sotalol on the QT Interval, MAP, and HR

A ten-minute iv infusion of sotalol (4 mg/kg) caused a sustained and significant prolongation of the QT interval. This prolongation was significant by the end of the 10-minute infusion, and it reached a maximum about 30 min after the completion of infusion, and lasted for longer than 1 hour (Figure 4). Sotalol also caused an increase in the R-R interval (or a decrease in HR). These changes reached statistical significance at 15 min after the completion of sotalol infusion and lasted for longer than 1 hour as shown in Figure 4 and Table 3. Sotalol did not cause a statistically significant change in MAP (Table 3).

DISCUSSION

The most important finding of the study was that regadenoson had no direct effects on the QT interval and HR in conscious dogs, as demonstrated by the finding that regadenoson no longer caused a significant shortening of the QT interval and an acceleration of HR after treatment of dogs with hexamethonium. The second important finding of the study was that the regadenoson-induced shortening of the QT interval was associated with an increase in HR, as indicated by the lack of changes in the QTcF interval following administration of regadenoson. Furthermore, atrial pacing and regadenoson administration caused a similar shortening of the QT interval at the same HR, and the QT intervals were significantly correlated with the R-R intervals following regadenoson administration and during atrial pacing. Regadenoson did not cause changes in the QT interval after treatment of dogs with either propranolol and atropine or hexamethonium, in which regadenoson caused no significant changes in HR. The third finding of the study was that the sotalol-induced prolongation of the QT interval was not directly related to the decrease in HR, but rather occurred before any significant change in HR was observed.

Bolus iv injections of regadenoson (1 to $10 \mu\text{g/kg}$) caused a dose-dependent and slight decrease in MAP (up to $\sim 13 \text{ mmHg}$) and a dose-dependent increase in HR (up to $\sim 60 \text{ bpm}$) in conscious dogs, consistent with our previous results.^{5–7} Regadenoson injections also caused dose-dependent shortening of the R-R and QT intervals. The maximum shortening of the R-R interval occurred earlier than the QT interval did (Figure 3, Panel A), confirming an earlier observation.¹⁴ To determine whether the regadenoson-induced shortening of the QT interval is related to an increase in HR, atrial pacing was used to mimic the increase in HR. Our results showed that atrial pacing at a steady state (3 to 4 min) caused a frequency-dependent shortening of the QT interval. The QT intervals were significantly correlated with the R-R intervals following regadenoson administration and during atrial pacing ($r = 0.67$

and 0.80, respectively, both $p < 0.05$). The relationships between the QT and R-R intervals observed after regadenoson injections and during atrial pacing were not significantly different (Figure 1). The difference between the two curves at the higher HR (or smaller R-R interval) is likely due to the absence of regadenoson data at the lower R-R intervals or higher HR (e.g. at 165 bpm). The highest dose of regadenoson (10 $\mu\text{g/kg}$) increased HR only up to 144 ± 7 bpm at a steady state (at 3 min following administration) (Table 2). This suggests that the regadenoson-induced change in the QT interval is entirely dependent on the change in HR. This conclusion is supported by our QTcF interval data as well. There were no significant changes in the QTcF interval, although a dose-dependent shortening in the QT interval was observed following administration of 1 to 10 $\mu\text{g/kg}$ regadenoson. Our results further indicated that when the dog heart was atrially paced at 165 bpm, a rate higher than that observed in response to the highest dose of regadenoson (10 $\mu\text{g/kg}$), 5 and 10 $\mu\text{g/kg}$ regadenoson did not cause any significant changes in the QT interval (Figure 3, Panel B). Furthermore, regadenoson did not cause a significant change in the QT interval after treatment of dogs with either propranolol and atropine (Figure 3, Panel C) or hexamethonium (Figure 3, Panel D). Regadenoson did not cause a significant change in HR after treatment with hexamethonium and caused only a 7 to 11 bpm increase in HR (peak response) after treatment with propranolol and atropine (Table 2). Taken together, the results of this study demonstrated that the regadenoson-induced shortening of the QT interval is directly related to the increase in HR in conscious dogs.

The present and previous studies^{5–7} have shown that regadenoson causes a dose-dependent increase in HR in conscious dogs. It has been reported that adenosine increases sympathetic nerve activity in humans, thereby causing an increase in HR.¹⁵ The regadenoson-induced increase in HR appears to be mediated by direct sympathoexcitation in awake rats.¹⁶ In the present study, after treatment of dogs with propranolol and atropine to block β -adrenergic and M-cholinergic receptors, 5 and 10 $\mu\text{g/kg}$ regadenoson caused only a slight (7 to 11 bpm) increase in HR (that might be due to the incompleteness of β -adrenergic and M-cholinergic blockade), and caused no significant changes in the QT interval, demonstrating that the regadenoson-induced increase in HR is mediated by either the increased sympathetic tone or the withdrawal of vagal tone to the heart. To rule out the possibility of direct action of regadenoson on the heart to cause an increase in HR (e.g., via β - and/or M-receptors), hexamethonium was used to block autonomic ganglia without blocking any receptors in the heart. After treatment of dogs with hexamethonium, 5 $\mu\text{g/kg}$ regadenoson caused no significant changes either in HR or in the QT interval, although it caused a greater decrease in MAP, compared with control. This strongly indicates that regadenoson does not have direct effects on HR and the QT interval in conscious dogs.

Sotalol is a non-selective β -adrenergic receptor antagonist and a Class III antiarrhythmic drug. It has been reported that sotalol can cause a decrease in HR and a prolongation of QT interval in humans¹⁰ and dogs.^{11,12} The present results confirm that sotalol prolongs the QT interval and decreases HR in conscious dogs. However, the sotalol-induced prolongation of the QT interval was not directly related to the decrease in HR, as evidenced by the finding that the sotalol-induced prolongation of the QT interval occurred already by the end of the 10-minute infusion of sotalol and HR was not significantly different from baseline at that time (Figure 4), and that the sotalol-induced prolongation of the QT interval reached the

maximum at 30 min after the end of infusion, while the sotalol-induced decrease in HR did not reach the maximum at 30 min.

CONCLUSION

In conclusion, regadenoson (1) causes a dose-dependent shortening in the QT interval associated with an increase in HR, and (2) does not shorten the QT interval when physiological (atrial pacing) or pharmacological (treatment of dogs with either propranolol and atropine or hexamethonium) procedures were used to prevent changes in HR. In contrast, sotalol causes a sustained prolongation of the QT interval that was not directly correlated with a decrease in HR. The findings indicate that regadenoson does not have a direct effect on the QT interval in the conscious dog. Rather, the effect of regadenoson to shorten the QT interval is a response to an increase of HR that may be mediated by activation of the sympathetic nervous system or/and the withdrawal of vagal tone.

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Figure 1.

Intavenous injections of regadenoson caused dose-dependent shortenings in the R-R (increase in HR) and QT intervals in conscious dogs. Filled circles indicate individual values of the R-R and QT intervals at 3 min following administration of regadenoson. Values of the QT and R-R intervals were significantly correlated ($r = 0.67$, $p < 0.05$). Atrial pacing resulted in frequency-dependent shortenings in the R-R and QT intervals. The open triangles indicate individual values of the R-R and QT intervals at 3 or 4 min after the onset of pacing. Values of the QT and R-R intervals were significantly correlated ($r = 0.80$, $p < 0.05$). There was no statistically significant difference between the two curves ($p > 0.05$). Data were from 7 dogs that received both regadenoson and atrial-pacing ($n=6$, for pacing at 135 and 150 bpm).

Figure 2.

Intravenous injections of regadenoson caused dose-dependent shortenings in R-R (Panel A) and QT (Panel B) intervals in conscious dogs. Note that the shortening in the R-R interval occurred sooner than the shortening in the QT interval. Values are means $\pm$ SEM.

Figure 3.

Regadenoson (5 µg/kg, iv) caused shortening of R-R and QT intervals in conscious dogs. There was a lag in the shortening of the QT interval relative to the shortening in R-R interval (Panel A). There were no significant effects on the QT interval in dogs after iv administration of regadenoson when the heart was atrially paced at 165 bpm (Panel B), or after treatment with either propranolol (1.0 and 1.5 mg/kg for 5 and 10 µg/kg regadenoson, respectively) and atropine (0.1 mg/kg) (Panel C), or hexamethonium (20-25mg/kg) (Panel D). Values are means $\pm$ SEM.

A: R-R Interval

B: Q-T Interval

Figure 4.

Intravenous infusion of sotalol (4 mg/kg, over 10 min) caused significant prolongations of R-R (Panel A) and QT (Panel B) intervals in conscious dogs. However, the prolongation of the QT interval occurred earlier than did the prolongation of the R-R interval. This suggests that sotalol-induced QT prolongation is not directly related to the decrease in HR. Values are means $\pm$ SEM, * $p < 0.05$, compared with baseline.

Table 1

Effects of Regadenoson (iv) and Atrial-Pacing on R-R, QT and QTcF in Conscious Dogs in Different Conditions

	n	R-R Interval (ms)		QT Interval (ms)		QTcF Interval (ms)	
		Baseline	3 min	Baseline	3 min	Baseline	3 min
Regadenoson							
1 µg/kg	6	663 ± 36	661 ± 46	233 ± 7	229 ± 8	267 ± 5	270 ± 4
2.5 µg/kg	7	699 ± 42	549 ± 50 *	237 ± 6	223 ± 8 *	268 ± 5	273 ± 5
5 µg/kg	11	701 ± 46	489 ± 23 *	241 ± 5	217 ± 6 *	272 ± 3	277 ± 6
+Pacing at 165 bpm	4	364 ± 1	362 ± 1	190 ± 3	189 ± 3	266 ± 3	264 ± 3
+Propranolol & Atropine	8	421 ± 30	413 ± 21	211 ± 7	211 ± 7	282 ± 5	284 ± 5
+Hexamethonium	6	398 ± 16	402 ± 16	212 ± 3	212 ± 3	288 ± 2	288 ± 4
10 µg/kg	9	675 ± 46	424 ± 17 *	239 ± 9	212 ± 7 *	273 ± 7	282 ± 7
+Pacing at 165 bpm	4	364 ± 1	363 ± 2	187 ± 2	190 ± 4	262 ± 3	266 ± 6
+ Propranolol & Atropine	5	459 ± 38	435 ± 33 *	212 ± 8	212 ± 7	276 ± 6	280 ± 7
Pacing (bpm)							
135	7	589 ± 13	442 ± 2 *	224 ± 5	209 ± 5 *	267 ± 5	274 ± 7
150			399 ± 2 *		199 ± 5 *		271 ± 6
165			362 ± 3 *		189 ± 6 *		265 ± 9

Mean ± SEM.

* p < 0.05, compared with baseline, n = 6 for pacing at 135 and 150 bpm at 3 min. $QTcF = [QT/(R-R)]^{1/3}$. Propranolol: 1.0 and 1.5 mg/kg for 5 and 10 µg/kg regadenoson, respectively; Atropine: 0.1 mg/kg; Hexamethonium: 20-25mg/kg.

Table 2

Effects of Regadenoson (iv) on MAP and HR in Conscious Dogs in Different Conditions

MAP (mmHg)	n	Baseline	0.5 min	1 min	2 min	3 min	4 min	5 min	10 min
1 µg/kg	6	102 ± 2	103 ± 3	101 ± 2	101 ± 2	100 ± 3	101 ± 3	101 ± 2	104 ± 2
2.5 µg/kg	7	101 ± 4	97 ± 4	97 ± 4	94 ± 3*	96 ± 4	98 ± 4	98 ± 5	99 ± 4
5 µg/kg	11	101 ± 3	94 ± 4	91 ± 3*	91 ± 3*	93 ± 3*	94 ± 3	97 ± 4	97 ± 3
+Pacing at 165 bpm	4	102 ± 4	97 ± 6	91 ± 7	99 ± 8	103 ± 9	105 ± 8	105 ± 6	103 ± 7
+Propranolol & Atropine	8	99 ± 4	91 ± 2*	88 ± 3*	89 ± 3*	92 ± 3*	91 ± 4*	90 ± 3*	97 ± 2
+Hexamethonium	6	82 ± 4	46 ± 3*	51 ± 4*	64 ± 6*	79 ± 8	76 ± 7	77 ± 6	76 ± 4
10 µg/kg	9	98 ± 4	88 ± 5*	85 ± 3*	86 ± 3*	88 ± 3*	90 ± 4*	92 ± 3	92 ± 3
+Pacing at 165 bpm	4	110 ± 6	88 ± 10*	90 ± 6*	92 ± 6*	96 ± 5*	98 ± 4	97 ± 4	100 ± 12\$
+ Propranolol & Atropine	5	101 ± 7	82 ± 8*	83 ± 8*	85 ± 5*	89 ± 6*	92 ± 6	94 ± 6	92 ± 3
HR (bpm)									
1 µg/kg	6	92 ± 5	112 ± 8*	107 ± 8*	104 ± 8*	101 ± 7	101 ± 7	97 ± 5	91 ± 5
2.5 µg/kg	7	88 ± 5	121 ± 9*	127 ± 9*	127 ± 11*	114 ± 9*	110 ± 8*	107 ± 11*	96 ± 6
5 µg/kg	11	89 ± 5	129 ± 8*	137 ± 7*	139 ± 7*	125 ± 6*	128 ± 6*	118 ± 5*	99 ± 5
+Pacing at 165 bpm	4	—	—	—	—	—	—	—	—
+ Propranolol & Atropine	8	147 ± 9	153 ± 9*	153 ± 9*	151 ± 9*	149 ± 9	148 ± 9	147 ± 9	146 ± 9
+Hexamethonium	6	152 ± 6	154 ± 4	158 ± 6	159 ± 5	151 ± 6	149 ± 6	149 ± 6	146 ± 7
10 µg/kg	9	92 ± 5	148 ± 8*	152 ± 7*	149 ± 6*	144 ± 7*	135 ± 6*	133 ± 8*	117 ± 7*
+Pacing at 165 bpm	4	—	—	—	—	—	—	—	—\$
+ Propranolol & Atropine	5	134 ± 10	142 ± 10*	145 ± 9*	145 ± 10*	141 ± 10*	141 ± 10*	139 ± 10	135 ± 10

MAP = Mean arterial pressure, HR = Heart rate (calculated from the R-R interval: HR [beats/min] = 60000 / R-R interval [ms]).

Mean ± SEM.

* p < 0.05, compared with baseline

\$ n = 3. Propranolol: 1.0 and 1.5 mg/kg for 5 and 10 µg/kg regadenoson, respectively; Atropine: 0.1 mg/kg; Hexamethonium: 20-25mg/kg.

Table 3

Effects of Sotalol (4 mg/kg, iv over 10 min) on MAP and HR in Conscious Dogs

	Baseline	Stop Sotalol	5 min	10 min	15 min	30 min	45 min	60 min
MAP (mm Hg)	108±3	117±3	112±4	104±4	107±4	114±6	113±6	117±5
HR (beats/min)	89±7	89±7	83±6	81±5	77±6 [*]	75±7 [*]	74±7 [*]	67±7 [*]

MAP: Mean arterial pressure, HR: Heart rate (calculated from the R-R interval: HR [beats/min] = 60000 / R-R interval [ms]); Mean ± SEM, n = 7.

^{*} p < 0.05, compared with the baseline.