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Influence of Sympathetic Heart Rate Modulation on RT Interval Rate Adaptation in Conscious Dogs

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PLADYS, P., ET AL.: Influence of Sympathetic Heart Rate Modulation on R Interval Rate Adaptation In Conscious Dogs. *The objective was to test if changes in autonomic tone still influenced the RT-RR relationship when full RT adaptation is completed, when heart rate is controlled, and when beat-to-beat variability is abolished by atrial pacing. Eight dogs (8–11 kg) were chronically instrumented with atrial pacing electrodes. Digital ECG (1,000 Hz, 12 bits) were recorded from healthy conscious dogs during spontaneous sinus rhythm and during atrial pacing. The protocol was repeated before and after atenolol (2 mg/kg), prazosin (0.5 mg/kg), or atenolol + prazosin. A vocal incitation was used as sympathetic stimulation. Beat-to-beat quantitative analysis of the RT interval (from QRS apex to end of T wave) was correlated with the preceding RR by linear regression. In spontaneous rhythm, atenolol increased RR ($P < 0.001$), RT ($P < 0.001$), and short-term heart rate variability ($P < 0.01$) and decreased RT-RR slopes ($P < 0.001$). Prazosin did not significantly modify any parameter. Sympathetic stimulation decreased RR ($P < 0.001$), RT ($P < 0.05$), and short-term heart rate variability ($P < 0.01$) and increased RT-RR slopes ($P < 0.001$). In atrial pacing, the RT-RR slopes were steeper during pacing than during spontaneous rhythm but were not modified by pharmacological manipulation of the autonomic nervous system. During sinus rhythm the RT-RR relationship is increased by sympathetic stimulation and decreased by β-blockade. When heart rate modulation and the effects of the time delay in RT rate adaptation are abolished by atrial pacing, the influence of autonomic tone on RT rate adaptation disappears. (PACE 2000; 23[Pt. I]:1604–1610)*

QT, beta-adrenergic antagonists, autonomic nervous system, heart rate

Introduction

The measurement of the QT interval on electrocardiogram (ECG) represents a marker of global ventricular repolarization in vivo.[1,2] The QT interval duration is known to be sensitive to many and various factors.[3–5] The heart rate and, particularly, the duration of the preceding cardiac cycles are the primary sources of QT changes.[1,2,5–9] The autonomic nervous system (ANS), which can act directly at the cellular level or indirectly through modulation of heart rate, is also an important source of QT changes. This has been well illustrated by the prolongation of the QT interval duration observed during sleep independent of heart rate that has been recognized as a consequence of the circadian changes in sympathovagal balance.[3,4,9–11] Another important factor that can influence the relationships between QT interval and the preceding cardiac cycle is the time delay required for the QT interval to complete a full adaptation after an instantaneous change in heart rate. This "QT delay" phenomenon has been documented in animals and in humans and the time required to achieve the full adaptation to a change in cardiac cycle length has been estimated to be between 2 and 3 minutes in humans.[12] QT delay can influence the relationship between the QT interval and the preceding cardiac cycle length (QT-RR). Indeed, since a part of the QT rate adaptation follows RR changes with a time lag, a lower QT-RR relationship may be expected in the presence of a high beat-to-beat heart rate variability.

Abnormalities of ventricular repolarization present several prognostic clinical implications in myocardial infarction, in long QT syndromes, or in sudden infant death syndrome, particularly as a marker of the propensity for cardiac arrhythmia.[13–16] Thus, investigating the respective contribution of interdependent factors such as heart rate, sympathetic tone, heart rate variability (HRV), and

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QT delay phenomenon on the QT interval duration appears to be important in understanding cardiovascular pathophysiological settings.

The aim of this study was to test in normal conscious dogs if changes in sympathetic tone still influenced the RT-RR relationship when full RT adaptation is completed, when heart rate is controlled, and when beat-to-beat variability is abolished. We have, thus, inspected the effects of blockade and stimulation of sympathetic drive on the QT interval duration with and without atrial pacing. The latter condition was used to evaluate the effects of sympathetic manipulations independently of heart rate change and time delay in QT rate adaptation.[6,17–21]

Methods

Materials

The study was conducted using eight adult healthy dogs (Fauves de Bretagne, weight 8–11 kg). Experimental procedures and postoperative care of animals was approved by the Ethics Committee of SmithKline Beecham Laboratoires Pharmaceutiques and are in compliance with National Institutes of Health (NIH) guide for the care and use of laboratory animals (NIH Publication no. 85–23, revised 1996) for the use of experimental animals. Prior to the surgical procedure, a standard ECG (leads I, II, III) was recorded in all animals at rest to check for normal repolarization and conduction pattern.

Surgical Procedure

Dogs premedicated with amoxicillin (1.0 g, intramuscularly [IM], Clamoxyl, SmithKline Beecham, Nanterre, France) were anesthetized with sodium pentobarbitone (30.0 mg/kg, intravenously [IV], Pentobarbital, Sanofi, Gentilly, France) and ventilated with room air (Harvard 613 ventilator, Harvard Apparatus, South Natick, MA, USA). Under sterile conditions, a left thoracotomy was performed through the fourth intercostal space to expose the heart. Pairs of stainless steel pacing electrodes (MFEP 19, Ethicon, Neuilly/Seine, France) were sutured on the left atrial appendage. The pericardium was closed and the surgical incision was repaired. Two implantable electrodes were subcutaneously positioned at the top of the right foreleg and the top of the left hindleg to record a lead II ECG. All wires were subcutaneously tunneled to the neck and exteriorized between the scapulae. At the end of surgery, antibiotherapy was performed and analgesia (buprenorphine 0.3 mg, IM, Temgesic, Schering Plough, Levallois-Perret, France) was given as required. Dogs were allowed to recover for 3 weeks at least before starting ANS manipulations and data acquisition.

Atrial Pacing

Atrial pacing was performed using a Grass programmable stimulator (S8800, Grass Instruments, Quincy, MA, USA) connected to isolation units (SIU-5, Grass). Rectangular impulses (4-ms duration) were applied with an amplitude 1.5-fold the stimulation threshold (range 6.4–10.2 V). Six consecutive pacing steps of 5-minute duration each were performed. The pacing rate was increased stepwise with a programmed instantaneous switch between each step (pacing cycle length 545, 500, 460, 430, 400, and 353 ms). An initial pilot study demonstrated no difference between stepwise and random increases in pacing rate (data not shown).

Data Acquisition

Electrocardiographic data were recorded with a digital ambulatory Holter ECG recorder (Burdick PC card recorder 6632; Burdick Inc., Milton, WI, USA) while the dog was lying quietly on the bench. Lead II obtained from implantable electrodes was used for ECG analysis.

Study Design

All recordings were performed in the morning (9–12 AM), the animals being awake and quiet in a soundproof room. The experimental protocol (51-minute total duration) has been summarized in Figure 1. A 5-minute period of spontaneous heart

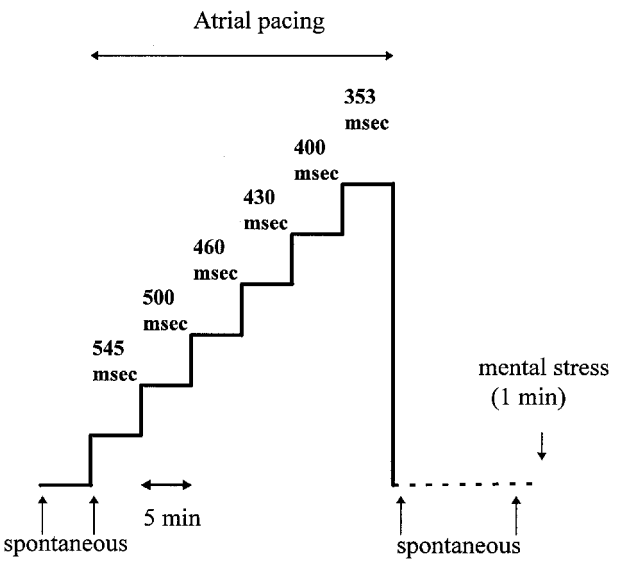

Figure 1. *Schematic representation of the experimental protocol. Continuous electrocardiogram (ECG) was recorded during the entire protocol (51-minute duration). A 5-minute step of spontaneous heart rate was recorded before the atrial pacing. Fifteen minutes after the end of atrial pacing, a 1-minute period of physiological adrenergic stimulation (vocal incitation as a surrogate mental stress) was performed.*

rate was recorded before atrial pacing. Fifteen minutes after the end of atrial pacing, a sequence of physiological sympathetic stimulation was performed. This mental stress consisted in a 1-minute continuous noisy vocal incitation, which maintained a significant tachycardia (increase in heart rate > 20%) in controlled conditions. The duration was limited to avoid the adaptation of heart rate that occurred with prolonged exposure (> 90 s). No adaptation phenomenon was observed when vocal incitation was repeated. The ECG was recorded continuously during the whole protocol.

This experimental protocol was followed in the basal state (control: isotonic saline infusion) and was repeated after pharmacological autonomic manipulations in a randomized manner. A 48-hour washout period was observed between each condition.

To achieve β1-adrenergic blockade, atenolol (Sigma Chemical Co., St. Louis, MO, USA) was administered for 30 seconds at a dose of 2 mg/kg, IV.[22] The drug was administered 15 minutes before the ECG recordings.

To achieve α1-adrenergic blockade, 0.5 mg/kg of prazosin (Sigma) was administered for 30 seconds, 20 minutes before the ECG recordings. Reinjection of a maintenance dose of prazosin (0.25 mg/kg) was performed every 45 minutes.[23]

In a pilot study, atropine was used to achieve parasympathetic blockade. Atropine induced a high increase in heart rate that did not allow the atrial pacing protocol nor data analysis (data not shown) to be performed. Consequently, the effect of atropine could not be evaluated in the present study.

Four experimental conditions were thus studied: control, atenolol, prazosin, and atenolol + prazosin. All conditions were tested during spontaneous heart rate and atrial pacing.

ECG Processing

ECG recordings were acquired with a digital recorder at the sampling frequency of 1,000 Hz and amplitude resolution of 12 bits. The ECG signal (stored on a removable hard disk PCMCIA card) was transferred to a standard personal computer. Beat-to-beat analysis of ECG was performed with an algorithm developed and validated in the Holter Laboratory of Lariboisiere Hospital as previously described.[24,25] The algorithm executes the following series of beat-to-beat steps: detection of QRS complex, estimation of a dynamic isoelectric line which was removed from the measured ECG, low pass ECG data filtration, and detection of the end of the T wave. On the basis of all cursors automatically detected, the algorithms provided beat-to-beat time series of RR intervals (from QRS apex to next QRS apex) and RT interval (from QRS apex to end of T wave) as a surrogate of the QT interval. However, all ECG tracings and relative fiducial points were visually inspected and all misplaced cursors were even rejected (leading to missing data in the beat-to-beat sequences) or manually adjusted.

In each case, a 5-minute period of spontaneous heart rate was analyzed before atrial pacing. During atrial pacing the analysis was performed on the last minute of each 5-minute period to avoid the effects of the delay in adaptation of QT duration.[12] During mental stress, the parameters were analyzed during a 1-minute period that began after 15 seconds of stimulation and lasted for the rest of the vocal incitation period.

The analysis of HRV was performed using time-domain analysis on the 5-minute periods except during sequences of vocal incitation where it was performed on only the 1-minute periods. Mean RR, standard deviation (± SD), and root mean square successive differences (rmssd) (which represents the square root of the mean of the sum of the squares of differences between adjacent normal RR intervals) were recorded. SD reflects global HRV and depends on the influence of sympathetic and parasympathetic drives. The rmssd reflects the respiratory sinus arrhythmia that depends principally on parasympathetic input.[26] The relative short-term RT variability was studied as proposed by Raeder et al.[27] using the calculation of the adjustment of the first RT interval following a cycle change as follows: $\Delta RT/\Delta RR$ (ms/ms) = $(RT—RT_{-1}) / (RR—RR_{-1})$, where RT_{-1} and RR are the immediately preceding intervals and RT_{-1} is the cycle length preceding RR.

Statistical Analysis

Statistica software (Statistica for Windows, StatSoft Inc., Tulsa, OK, USA) was used, and data are expressed as mean value ± SD. Linear regression analysis with the least mean square method was used to study the beat-to-beat relationship between RT duration and the preceding cardiac cycle length during spontaneous heart rate (RT-RR) and during atrial pacing (RT-RRp). In all dogs, to compare the RT-RR slopes during spontaneous heart rate and during atrial pacing we only used data obtained at the same selected mean and range of RR (mean 448 ± 10 ms, range 353–545 ms).

A nonparametric variance analysis (Kruskall-Wallis test) followed by posthoc Wilcoxon test was performed when appropriate. A P value < 0.05 was considered statistically significant.

Results

All the experiments were performed with the eight instrumented dogs. The initial standard ECG of each dog showed normal patterns of repolarization and conduction.

Table I.

Effects of Autonomic Manipulations on ECG Parameters During Spontaneous Heart Rate

	Mean RR ms	SD ms	rmssd ms	Mean RT ms	ΔRT/ΔRR %	RT-RR Slopes 10^{-3}	r
Control	536 ± 90	112 ± 37	131 ± 60	182 ± 15	2.2 ± 0.9	21.9 ± 10.2	0.40 ± 0.20
Atenolol	807 ± 163***	173 ± 64**	242 ± 104**	208 ± 14**	0.4 ± 0.2**	7.5 ± 3.3***	0.21 ± 0.21**
Prazosin	604 ± 91	157 ± 43**	155 ± 57	188 ± 7	1.8 ± 0.6	20.6 ± 9	0.44 ± 0.19
Atenolol + prazosin	820 ± 72***	171 ± 70**	185 ± 80*	213 ± 13**	0.5 ± 0.3**	7.5 ± 5.8***	0.23 ± 0.21*
Mental stress	419 ± 80***	82 ± 36***	87 ± 58**	177 ± 17*	2.9 ± 1.8	32.9 ± 19.4***	0.32 ± 0.24
Mental stress + prazosin	462 ± 43**	83 ± 54**	65 ± 59**	186 ± 9	2.4 ± 1.5	30.4 ± 16.3***	0.42 ± 0.33

* $P < 0.05$ vs control, ** $P < 0.01$ vs control, *** $P < 0.001$ vs control. Values are mean ± SD.
RT = RT interval measured from QRS apex to end of T wave; SD = standard deviation of RR; rmssd = root mean square successive difference between adjacent RR; r = correlation coefficient of the RT-RR relationship; ΔRT/ΔRR = relative short term RT variability.

Spontaneous Heart Rate

The effects of autonomic manipulations are summarized in Table I. In the control state the calculated RT-RR slope value was 21.9 ± 10.2 10^{-3} with a correlation coefficient of 0.40 ± 0.20. Application of a vocal incitation decreased mean RR, SD, rmssd, and RT duration. The RT-RR slope and r coefficient were significantly increased. Atenolol produced opposite results with an increase in mean RR, SD, rmssd, and RT duration and a decrease in RT-RR slope, ΔRT/ΔRR, and r coefficient. Although prazosin caused initial reflex tachycardia during the 20-minute stabilization, prazosin administered alone did not significantly alter any parameter (except SD) during the control state nor during the vocal incitation. As expected, the effects of the vocal incitation were abolished after infusion of atenolol alone or after atenolol + prazosin. The effects of atenolol + prazosin were compared with those of prazosin alone. We observed an increase in mean RR ($P < 0.05$) and a decrease in RT-RR slope and ΔRT/ΔRR ($P < 0.05$) but no significant modification in HRV parameters (rmssd and SD).

Atrial Pacing

The results of changes in autonomic conditions are summarized in Table II. In the control state, the RT-RRp slope value was 95 ± 25 10^{-3} with a correlation coefficient of 0.76 ± 0.10. The RT-RRp relationship was not modified with any of the pharmacological manipulations (atenolol, prazosin, or atenolol + prazosin).

Comparison Between Spontaneous Heart Rate and Atrial Pacing

Comparisons were performed for the same range of cardiac cycle lengths (Table II and Fig. 2). In the control state, the RT-RRp slope was steeper for each dog during atrial pacing and the RT duration was better correlated to the preceding cardiac cycle length during atrial pacing than during spontaneous heart rate. The same results were noted after prazosin administration. No comparison was possible after atenolol administration due to the different range of RR duration.

Discussion

We observed that, in sinus rhythm, sympathetic stimulation determined a significant increase

Table II.

Calculated Slopes of the Relationships Between RT and RR Intervals During Atrial Pacing (RT-RR_p) and During Spontaneous Heart Rate (RT-RR)

	Atrial Pacing		Spontaneous Rate (selected range)	
	RT-RR_p Slopes (10^{-3})	r	RT-RR Slopes (10^{-3})	r
Control	95 ± 25	0.76 ± 0.10	43 ± 23**	0.49 ± 0.12*
Atenolol	97 ± 23	0.84 ± 0.07		
Prazosin	134 ± 54	0.88 ± 0.11	72 ± 21*	0.57 ± 0.13*
Atenolol + prazosin	145 ± 39	0.90 ± 0.09		

Selected data observed from the same range of heart rate (353–545 ms).
* $P < 0.05$ vs pacing; ** $P < 0.01$ vs pacing.
RT = RT interval measured from QRS apex to end of T wave; r = correlation coefficients.

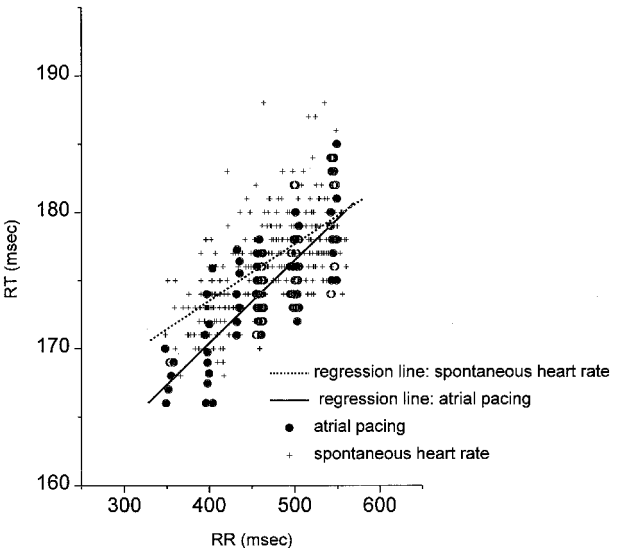

Figure 2. *Comparison of RT-RR relations in spontaneous heart rate and during atrial pacing. Representative scatterplot obtained in a single dog in the control state. The comparison between values obtained in spontaneous heart rate and during atrial pacing was performed in the same range of cardiac cycle lengths. RT = RT interval measured from QRS apex to end of T wave.*

of the slope of the RT-RR relationship whereas atenolol caused a reduction, thus, confirming previous results.[28] Atrial pacing abolishes the RR fluctuations and can be used to change the heart rate independent of autonomic tone. The RT interval was analyzed after 4 minutes of fixed heart rate to abolish the effects of the time delay required for a full adaptation of QT duration. Therefore, our results on the influence of ANS on the RT-RR relationship are independent of the effects of ANS on the heart rate modulation and on the time delay for QT rate adaptation. The main findings of the present study that was performed in quiet conscious dogs are that (1) the RT-RR relationship is steeper during atrial pacing than during sinus rhythm, and (2) the RT-RR relationship is no longer modulated by sympathetic tone when the heart rate is controlled by atrial pacing. These results suggest that the heart rate modulation (effect of ANS at the sinoatrial node level), alone or together with the time delay in QT rate adaptation (effect of ANS at the ventricular level),[29] explains the influences of sympathetic tone in the determination of RT-RR relationship.

β-Adrenergic blockade has been widely used in clinical conditions to diminish sympathetic induced cardiac arrhythmia. For example, it was used to treat the long QT syndrome and experimental reports have demonstrated its beneficial effects, but the mechanisms involved in the antiarrhythmic effect of β-adrenergic blockade are still unclear.[30] Studies performed in humans have shown a decrease of QT rate dependence after administration of nadolol or propranolol.[27,28] We found the same results in conscious dogs after acute administration of atenolol during spontaneous rhythm. The low RT-RR relationship observed after β-adrenergic blockade was associated with a low relative short-term RT variability (calculated by $\Delta RT/\Delta RR$). This is consistent with the observation of Sarma et al.[8] who studied humans after nadolol administration. Indeed, these authors reported that the increase in variations of RR intervals duration were not associated with any increase in variations of QT interval duration. During atrial pacing we found that the rate dependence of RT is not altered after atenolol administration. This result is in agreement with the absence of significant effect of propranolol infusion on QT-RR slope reported during atrial pacing in humans.[6] These apparent discrepancies concerning the effects of β-adrenergic blockade on the RT-RR relationship between sinus rhythm and atrial pacing could be explained by different mechanisms. The first hypothesis could be that the QT interval loses the ability to lengthen when the spontaneous RR interval is sufficiently prolonged by β-adrenergic blockade. This is suggested by the monoexponential relationships described between QT and RR.[25] This mechanism could explain the low RT-RR relationship and the low relative short-term RT variability observed in the present work when the RR interval is prolonged by β-adrenergic blockade. During atrial pacing the same RR interval durations were studied. These RR intervals were shorter than in physiological conditions. In such a situation, the fact that atenolol does not modify the RT-RR relationship could also be simply explained if we consider that RT depends primarily on the absolute value of the preceding RR.

HRV alone cannot explain the variations in the RT-RR relationship. We observed significant differences in RT-RR relationships between prazosin and atenolol + prazosin during sinus rhythm despite a similar HRV. Therefore, it is not possible to conclude that HRV has a direct effect on the RT-RR relationship. However, in the other conditions the observations that when HRV decreased the RT-RR slopes increased (during sympathetic stimulation or atrial pacing) and when HRV increased the RT-RR slope decreased (after atenolol administration) may suggest an involvement of HRV in association with other mechanisms.

It has been demonstrated that the changes in cycle length observed during sinus rhythm affects the duration of ventricular repolarization of several subsequent beats in humans.[27] This observation that a time delay is required for the full adaptation of the repolarization has been quantified after sustained changes in cardiac cycle length.[12,18] Using this method, Zaza et al.[29] have reported a de-

crease in adaptation of endocardial action potential duration after left stellectomy suggesting the possibility of an effect of ANS on the QT delay. If an important part of the RT adaptation is delayed, it becomes plausible that an attenuation of the changes in the RT intervals could result from marked opposite variations of RR duration. This could explain the weak RT-RR relationship and the low RT relative variability observed after β-adrenergic blockade during spontaneous rhythm. In this hypothesis, when heart rate variations are decreased (atrial pacing or stress) the changes in RR intervals could not exert opposite effects on the following RT intervals. This could lead to a more achieved RT adaptation and, consequently, to an increase in the RT rate dependence. We cannot definitely conclude about the relevance of this hypothesis from the present study because we were unable to demonstrate to what extent the adjustment of RT depends on each of the preceding RR_{-n} during spontaneous rhythm. We observed that the relationships between RT and the preceding RR were weaker in conscious dogs than those reported in humans. Therefore, this relationship has not been established between RT and the preceding RR_{-n} (data not shown). Moreover, the magnitude of interbeat variations of RT was small and it has been recently shown that only 66 ± 2% of RT variability was driven by RR variability in young humans and only 26 ± 4% in older subjects.[31]

α-Adrenergic receptors have been proposed to play a prominent role in ventricular repolarization and cardiac arrhythmia.[23] Prazosin is an α1-adrenergic blocking substance known to decrease the cesium induced early after depolarization and ventricular arrhythmia in dogs.[32] In the present study, prazosin administration did not modify the RT-RR relations in normal conscious dogs. This may suggest that the mediation of the antiarrhythmic effect of α1-blockade is not dependent on RT rate adaptation, but we cannot rule out the possibility of an α1-adrenergic influence in cases of abnormal ventricular repolarization.

We used vocal incitation as a surrogate mental stress. As expected, we observed a decrease in RR, RT interval duration, and rmssd. This was associated with an increase in the RT-RR relationship with no significant modification in the relative short-term RT variability. As atenolol blockade only, but not prazosin, was able to inhibit the effect of vocal incitation, it is likely that the beta but not the α1-adrenergic receptors are involved in this type of sympathetic stimulation effect. From the present results, it was not possible to establish if vocal incitation caused a decrease of RT duration dependent on the tachycardia alone or also on a direct effect on the ventricular repolarization. Several other experimental data may suggest such a direct effect.[17,33,34] The apparent increase in the dependence of the RT interval on the preceding RR has to be interpreted cautiously. Indeed, the increase in the RT-RR relationship was not associated with an increase in the relative short-term RT variability suggesting an absence of significant modification in the short-term adaptation of the repolarization. Therefore, it is possible that the increase in the RT-RR relationship involves a long-term adaptation phenomenon that could result from the conjunction of low heart rate variability and QT delay.

There are some methodological implications of our findings. Our results confirm the limitation of the "correction formulae" that have been proposed to adjust QT interval duration for differences in heart rate.[1,5,7,8] These corrections do not consider the possible contribution of HRV and of QT delay and the range of RR interval studied. This could lead to wrong assessments concerning the effect of different interventions on QT interval duration. The potential clinical implications of our findings concern cardiac arrhythmia. Low HRV and a lack of adaptation of QT duration, specially in response to adrenergic stimulation, has been proposed to be involved in the genesis of cardiac arrhythmia and sudden death.[35] From our results we can speculate that most of the effects of sympathetic tone on the RT rate adaptation are mediated by the heart rate modulation and/or the time delay in QT rate adaptation, but further studies are required to delimit the respective role of each of these phenomena. The conjunction of these two phenomena could influence the quality of the QT adaptation in response to an abrupt change in heart rate and could, therefore, be involved in the occurrence of cardiac arrhythmia. An enhanced short-term adaptation could reduce the number of reactivations required for the tissue involved in a functional reentrant pathway to reach its final refractoriness, on the opposite a prolongation could facilitate the R on T phenomenon after an abrupt increase in heart rate.[27]

Limitations of the Study

The resting heart rate in quiet dogs is similar to that of humans although this may be due to a higher parasympathetic tone, because in healthy dogs at rest the sinoatrial node activity is mainly under vagal control. This explains the great HRV observed in dogs as compared to that described in humans. Nevertheless, this model is particularly relevant to study the role of heart rate modulation. HRV parameters were analyzed on 5-minute periods except during vocal incitation where it was performed on only 1-minute periods. In this situation, it was impossible to prolong recordings in stable conditions due to the occurrence of heart rate adaptation to mental stress. We believe that

the fact that HRV was analyzed only during the 1-minute period during vocal incitation did not affect the main results of the present study, which principally considered high frequency variability. Indeed the duration of the period of monitoring is essentially known to affect the standard deviation that is an index of global time-domain variability (the total variance increases with the length of the recording).[36]

The algorithm developed for ECG analysis measures the duration of the interval comprised between the beginning of the R wave and the end of the T wave and not really the QT interval. This does not represent a real limit because we did not observe any variation in the QR interval for the dogs we studied. Our ECG processing allows a precise standardized beat-to-beat RT duration measurement that can be considered a valid index of ventricular repolarization. The use of linear regression analysis is allowed only for a RR interval duration $>$ 350 ms, thus taking into account the range of cardiac frequencies.[26]

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References

1. Bazett HC. Analysis of the time relations of electrocardiograms. Heart 1920; 7:353–370.
2. Seed WA, Noble MIM, Oldershaw P, et al. Relation of human cardiac action potential duration to the interval between beats: implications for the validity of rate corrected QT interval (QTc). Br Heart J 1987; 57:32–37.
3. Molnar J, Zhang F, Weiss J, et al. Diurnal pattern of QTc interval: How long is prolonged. Possible relation to circadian triggers of cardiovascular events J Am Coll Cardiol 1996; 27:76–83.
4. Morganroth J, Brozovich FV, McDonald JY, et al. Variability of the QT measurement in healthy men, with implications for selection of an abnormal QT value to predict drug toxicity and proarrhythmia. Am J Cardiol 1991; 67:774–776.
5. Sagie A, Larson MG, Goldberg RJ, et al. An improved method for adjusting the QT interval for heart rate (the Framingham heart study). Am J Cardiol 1992; 70:797–801.
6. Cappato R, Alboni P, Pedroni P, et al. Sympathetic and vagal influences on rate dependent changes of QT interval in healthy subjects. Am J Cardiol 1991; 68:1188–1193.
7. Karjalainen J, Viitasalo M, Mäntäri M, et al. Relation between QT intervals and heart rates from 40 to 120 beats/min in rest electrocardiograms of men and a simple method to adjust QT interval values. J Am Coll Cardiol 1994; 23:1547–1553.
8. Sarma JSM, Venkataraman K, Samant DR, et al. Effect of propranolol on the QT interval in normal individuals during exercise: a new method for studying interventions. Br Heart J 1988; 60: 434–439.
9. Sarma JSM, Singh N, Schoenbaum MP, et al. Circadian and power spectral changes of RR and QT intervals during treatment of patient with angina pectoris with nadolol providing evidence for differential autonomic modulation of heart rate and ventricular repolarisation. Am J Cardiol 1994; 74:131–136.
10. Browne KF, Zipes DP, Heger JJ, et al. Influence of the autonomic nervous system on QT interval in man. Am J Cardiol 1982; 50: 1099–1103.
11. Murakawa Y, Inoue H, Nozaki A, et al. Role of sympato-vagal interaction in diurnal variations of QT interval. Am J Cardiol 1992; 69:339–343.
12. Franz MR, Swerdlow CD, Liem LB, et al. Cycle length dependence of human action potential duration in vivo. Effects of single extrastimuli, sudden sustained rate acceleration and deceleration and different steady state frequencies. J Clin Invest 1988; 82:972–979.
13. Day CP, Mc Comb JM, Campbell RWF. QT dispersion: An indicator of arrhythmia risk in patients with long QT intervals. Br Heart J 1990; 636:342–344.
14. Schwartz PJ, Malliani A. Electrical alternation of the T wave: Clinical and experimental evidence of its relationship with the sympathic nervous system and with the long QT syndrome. Am Heart J 1975; 89:45–50.
15. Schwartz PJ, Wolf S. QT interval prolongation as predictor of sudden death in patients with myocardial infarction. Circulation 1978; 57:1074–1077.
16. Schwartz PJ, Stramba-Badiale M, Segantini A, et al. Prolongation of the QT interval and the sudden infant death syndrome. N Engl J Med 1998; 338:1709–1714.
17. Akhras F, Rickards AF. The relationship between QT interval and heart rate during physiological exercise and pacing. Jpn Heart J 1981; 22:345–351.
18. Dickhuth HH, Bluemner E, Auschwelk W, et al. The relationship between heart rate and QT interval during atrial stimulation. PACE 1991; 14:793–799.
19. Lau CP, Freedman AR, Fleming S, et al. Hysteresis of the ventricular paced QT interval in response to abrupt changes in pacing rate. Cardiovasc Res 1988; 22:67–72.
20. Lombardi F, Sandrone G, Torzillo D, et al. Spectral analysis of short term RTapex interval variability during sinus rhythm and fixed atrial rate. Eur Heart J 1996; 17:769–778.
21. Ogushi Y, Hamlin RL. Rate of changes of QT interval in response to a sudden change in the heart rate in dogs. Am J Vet Res 1994; 55:1618–1623.
22. Karim F, Al Obeidi M. Modification of carotid chemoreceptor induced change in renal haemodynamics and function by carotid baroreflex in dogs. J Physiol Lond 1993; 466:599–610.
23. Billman G. Effect of alpha1 adrenergic antagonists on susceptibility to malignant arrhythmias: Protection from ventricular fibrillation. J Cardiovasc Pharmacol 1994; 24:394–402.
24. Badilini F, Maison-Blanche P, Childers R, et al. QT interval analysis on ambulatory ECG recordings: A selective beat averaging approach. Med Biol Eng Comput 1998; 36:1–10.
25. Extramania F, Maison-Blanche P, Badilini F, et al. Circadian modulation of QT rate dependence in healthy volunteers: Gender and age differences. J Electrocardiol 1999; 32:33–43.
26. Kleiger RE, Stein PK, Bosner MS, et al. Time domain measurement of heart rate variability. Cardiol Clin 1992; 3:487–498.
27. Raeder EA, Albrecht P, Perrott M, et al. Kinetics of cycle length dependence of ventricular repolarisation: Effect of autonomic blockade. J Cardiovasc Electrophysiol 1995; 6:163–169.
28. Merri M, Moss AJ, Benhorin J. Relation between ventricular repolarisation duration and cardiac cycle length during 24 hours recordings. Circulation 1992; 85:1816–1821.
29. Zaza A, Kline RP, Malfatto G, et al. Sympathetic modulation of the relation between ventricular repolarisation and cycle length. Circ Res 1991; 68:1191–1203.
30. Hanich RF, Levine JH, Spear JF, et al. Autonomic modulation of ventricular arrhythmia in caesium chloride-induced long QT syndrome. Circulation 1988; 77:1149–1161.
31. Lombardi F, Colombo A, Porta A, et al. Assessment of the coupling between Rtapex and RR interval as an index of temporal dispersion of ventricular repolarization. PACE 1998; 21:2396–2400.
32. Bendavid J, Zipes DP. Alpha adrenoceptor stimulation and blockade modulates cesium induced early after-depolarisation and ventricular tachyarrythmia in dogs. Circulation 1990; 82:225–233.
33. Ahmed MW, Kadish AH, Golderberg JJ. Autonomic effect on the QT interval. ANE 1996; 1:44–53.
34. Fananapazir L, Bennet DH, Faragher EB. Contribution of heart rate to QT interval shortening during exercise. Eur Heart J 1983; 4:265–271.
35. Fei L, Gill JS, Katritsis D, et al. Abnormal autonomic modulation of QT interval in patients with idiopathic ventricular associated with clinically normal hearts. Br Heart J 1993; 69:311–314.
36. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability standards of measurement, physiological interpretation and clinical use. Circulation 1996; 93:1043–1065.