A fundamental relationship between intraventricular conduction and heart rate ☆

Jay W. Mason, MD, [a],* Fabio Badilini, PhD, [b] Martino Vaglio, MS, [b] Robert L. Lux, PhD, [a]
Benhur Aysin, PhD, [c] Thomas E. Moon, PhD, [d] Brock Heinz, BS, [e] Iain Strachan, PhD [f]

[a] University of Utah, Salt Lake City, Utah
[b] AMPS, LLC, New York, New York
[c] Roche Diagnostics, Indianapolis, Indiana
[d] Tarizona eHealth Services, San Carlos, California
[e] Foundry Health, West Bend, Wisconsin
[f] OBS Medical, Abingdon, UK

Abstract

Background: Existence of a relationship between the electrocardiographic QRS interval duration and the diurnally varying heart rate, of consistent sign and magnitude, is controversial and the relationship has not been fully characterized in normal populations.

Methods and results: We analyzed the QRS-RR interval relationship in 884 Holter recordings in 410 normal subjects participating in 5 clinical trials.

The slope of the linear regression of QRS on RR was positive in 93% of subjects with an average slope of 0.0125, which indicates an increase in QRS duration of 1.25 msec for an increase in RR interval of 100 msec. The increase was 15% larger in women than in men. Age had no significant effect on the slope.

Conclusions: In two populations of normal subjects we observed a robust, direct relationship between the spontaneously changing RR interval and intraventricular conduction time represented by the duration of the QRS interval. As heart rate increases, QRS duration decreases. The change is larger in women. These observations have important physiological and clinical implications.

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Keywords: QRS interval; Intraventricular conduction; Heart rate; Rate correction

Introduction

Existence of a predictable relationship between QRS duration and spontaneously changing heart rate within normal populations is controversial. In 2003 Smetana and colleagues [1] made the important and previously unrecognized observation that QRS dependency on heart rate (HR) is observed in Holter recordings. However, five years later the same group [2] observed a positive relationship in men and an equally negative relationship in women, and concluded that "the change in QRS width [with heart rate] was, on average, practically zero." This uncertainty has not been resolved. We tested the hypothesis that a consistent QRS-RR relationship is a generalized property in humans in large, retrospectively collected Holter datasets. The objectives of

this report are to present our observation of the QRS-RR interval relationship, to consider its potential physiological role and underlying mechanism, and to identify the clinical and research implications of the phenomenon.

Materials and methods

Selection of human subjects

All human data was obtained retrospectively from completed, Institutional-Review-Board-approved clinical research studies with subject de-identification. These trials complied with the Declaration of Helsinki and all subjects signed informed consent documents. There were two sources of subjects (Table 1). The 697 pharmaceutical clinical trial Holter monitor recordings were obtained in 223 subjects in four separate studies of a single investigational drug during randomized treatment with placebo or the investigational drug. An additional 187 single Holter recordings obtained in a study of normal subjects were provided by the Telemetric

Table 1
Sources and Characteristics of Human Subjects.

Source	N Subjects	Sex (%M)	Mean Age, Yr ± SD	N Holter Recordings	Analysis Method
Pharmaceutical Clinical Trials	223	78%	42 ± 17	697	BioQT
THEW Archive	187	52%	38 ± 15	187	WinAtrec rate bin

M = male; Yr = years; SD = standard deviation.

Holter ECG Warehouse (THEW, University of Rochester, Rochester, NY). Normal subjects were excluded from enrollment if they had known ventricular and supraventricular ectopy or if it was detected on screening. All available Holter recordings in these two groups were included in the analysis except for one baseline recording in the pharmaceutical clinical trial group in which there were very few analyzable QRS-RR pairs (2631) that were maldistributed across the 24-h recording period.

Electrocardiographic recording and analysis methods

Holter ECG analysis using BioQT

Holter recordings from the pharmaceutical clinical trials were obtained at a 1000 Hz sampling rate with Mortara Instrument (Milwaukee, WI) H-12 Holter recorders in normal volunteers of both sexes and all adult age groups using Mason-Likoff torso lead placement. The data was converted to an XML format and BioQT [3] (OBSMedical, Abingdon, UK) was used to analyze it. The beat-by-beat analysis generated a QRS-RR pair for each normal beat that was recognizable by the software. BioQT uses a hidden Markov model to compare beat morphology to a training set of over 20,000 beats annotated by cardiologists. Beats with non-familiar morphology are not annotated. A linear regression of the QRS duration on the RR interval of the preceding cycle was then performed to determine the QRS-RR slope for each individual Holter recording.

Holter ECG analysis using WinAtrec rate binning

WinAtrec (AMPS LLC, New York, NY) was used to analyze the Holter data provided by THEW. These recordings were obtained at a 200 Hz sampling rate with 3-channel SpaceLab-Burdick (Deerfield, WI) Holter recorders using a pseudo-orthogonal lead system placed on the torso in normal volunteers of both sexes and all adult age groups. Waveform raw data was converted into standard ISHNE (International Society for Holter and Noninvasive Electrocardiology) format for the WinAtrec analysis. WinAtrec prevents digitization error in data with lower sampling frequency (200 Hz) by up-sampling and realigning the signal on the R-wave peak before generating the median template, as previously described [4,5]. Individual beats were assigned to 50 msec RR interval bins and averaged. Automated annotations of each averaged beat were examined and adjusted in the lead with the most easily discerned QRS onset and offset by one of the investigators (JWM). A linear regression of the average QRS duration on the average RR interval of each corresponding rate bin was then performed to determine the QRS-RR slope for each individual Holter recording.

Measurement validation

Interval measurements in the WinAtrec recordings were overread and adjusted when necessary by a cardiologist (JWM). The inter- and intra-reader differences in repeated measurement of QRS intervals in this laboratory are -0.01 ± 4.9 msec and 0.2 ± 3.6 msec (standard deviation, SD). BioQT measurements were not overread. However, BioQT automatically excludes non-sinus beats, noisy beats and unfamiliar beat shapes, and in the original validation of the BioQT method, the difference in measurements by BioQT compared to cardiologist over-readers in this laboratory was -2.1 ± 6.1 msec (SD) for the QRS interval.

Statistical methods

All statistical analyses were performed using JMP version 9.0.3 (SAS Institute, Cary, NC). The mean of the QRS-RR slopes derived from Holter recordings was determined for each Holter by a least squares linear regression of QRS on RR. The influence of age and sex was assessed in a linear regression model. Variance is reported as the standard error unless indicated otherwise.
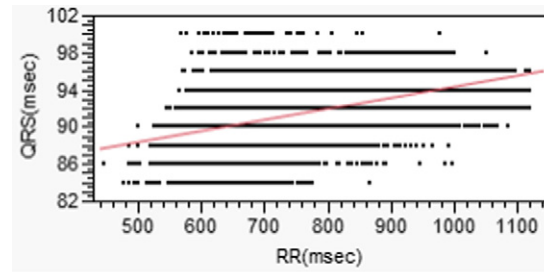
Results

The QRS-RR relationship

Table 2 summarizes the observed relationship between QRS interval duration and the RR interval in the two Holter datasets. The mean slope was positive in both studies and in most individual Holter recordings and individual subjects. The average slope for subjects in the two Holter groups combined was 0.0125 and the average incidence of slope positivity in individuals was 93%.

Fig. 1 shows typical QRS-RR regressions in a subject from the pharmaceutical trial group for all RR intervals and for cycle lengths of 600 and lower, both slopes being positive. The mean R^2 for the group was 0.19 ± 0.141 (SD) and the P-value for the linear fit was statistically significant (<0.05) in 98.5% of the regressions.
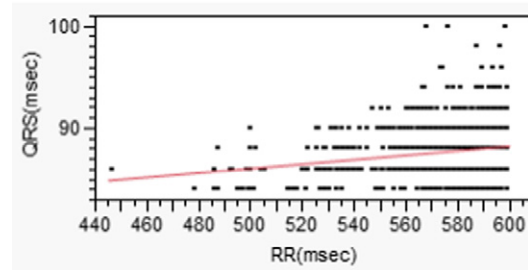
Fig. 2 provides two examples of marked QRS widening with increasing cycle length in the THEW group, while

Table 2
QRS-RR Slope.

Group		Mean Slope	SE	Positive Slope (%)
Pharmaceutical	– by Holter	0.0121	0.00037	94
Trials	– by Subject	0.0124	0.00063	96
THEW archive		0.0127	0.00100	90
Average	– by Holter	0.0122	0.00036	93
	– by Subject	0.0125		93

QRS (msec) =82.4 + 0.0120 x RR(msec)RR; R^2 = 0.348; P <0.001

QRS (msec) =75.17 + 0.0219 x RR(msec); R^2 = 0.036; P <0.001

Fig. 1. A typical example of the linear regression of QRS on RR. The upper panel shows the regression of the entire RR range, and the lower panel shows the RR range restricted to ≤600 msec. The regression formulae, correlation coefficients and P-values for the linear fits are shown below each graph.

Fig. 3 show two examples with lesser widening. In each example the waterfall displays (panels A and C) show the representative beats of each RR bin and panels B and D show a close up view of the QRS complex at short, medium and long cycle lengths, with QRS onset and offset annotations. The three beats are synchronized on the Q-onset.

The RR interval and heart rate distributions over which the QRS duration was examined are displayed Fig. 4. The mean RR interval range was 635 msec and the mean heart rate range was 61 BPM.

The QRS-RR regression fits were minimally improved, if at all, by polynomial modeling, suggesting that the observed positive QRS – RR relationship would be seen at all heart rate ranges. To test this supposition, we examined the fit for all subjects with at least 50 QRS – RR pairs at heart rates above 100 BPM in the pharmaceutical trials group. In those 80 subjects, the average QRS – RR slope for heart rate above 100 BPM was 0.0231 ± 0.00628 and 73% of the slopes were positive. The lower panel of Fig. 1 provides an example of slope calculation at heart rates above 100 BPM.

The influence of drug treatment in the pharmaceutical trial group was examined by comparing the QRS-RR slopes during placebo and active drug treatment in the 68 subjects who crossed over from one to the other. The group means were similar and the difference was not statistically significant (0.0103 and 0.0112, respectively, p = 0.4216), allowing us to combine their Holter analyses during drug and placebo administration.

In the pharmaceutical trials, subjects underwent as many as four Holter recordings. Table 3 shows that the

QRS-RR slope was consistent within subjects with 2, 3 or 4 Holter studies.

The influence of sex and age

Because the QT-RR relationship is influenced by sex [6,7], and both QRS and RR duration are influenced by both age and sex (both longer in men and older individuals [8]) we examined the influences of age and sex on the QRS-RR relationship. Table 4 shows that sex had a statistically significant effect on the QRS-RR slope, while age did not. The parameter estimate for female sex was positive, predicting a larger QRS-RR slope in normal women. The effect size was predicted to be modest: the parameter estimate was 0.0016, indicating that female sex increased the QRS-RR slope intercept (0.0107) in this model by 15%. Age had no significant effect on the QRS-RR slope. The distributions of the QRS-RR slope on the baseline Holter in men and women are compared in Fig. 5.

Discussion

We have observed a consistently positive linear relationship between the duration of the electrocardiographic QRS interval and the RR interval during spontaneously changing heart rate in humans. The relationship is present in adult men and women of all ages and is reproducible within subjects. The phenomenon was observed with two measurement methods in two large, independent datasets, signifying that it is a robust, reliable
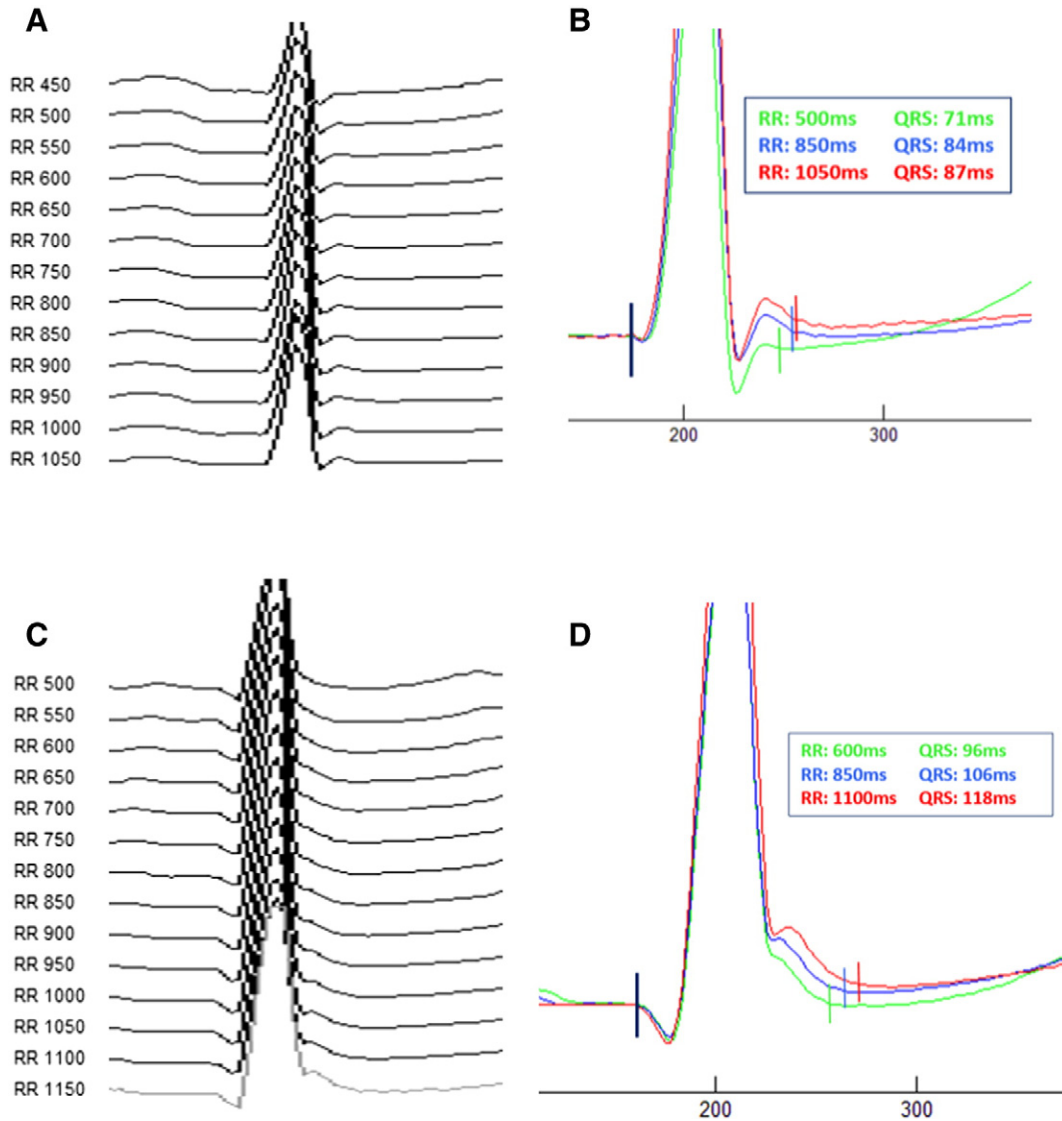
Fig. 2. Two examples of marked change in QRS duration with change in heart rate. These analyses were generated by WinAtrec software from THEW Holter recording in normal volunteers. The upper and lower sets of panels represent two different subjects. The waterfall displays in panels A and C show a cascade of the averaged QRS within each rate bin in lead II. The QRS duration progressively increased through successive rate bins. Panels B and D show superimposed enlarged views of the averaged QRS from short, medium and long RR bins from lead II, with Q-onset and T-offset annotations. An overall increase in the QRS interval of 16 msec occurred with a decrease in rate from 120 bpm to 57 bpm in the upper example, and 22 msec from a rate of 109 bpm to 52 bpm in the lower example.

observation. The observation indicates that intraventricular conduction time, as reflected by QRS duration [9], shortens as the heart rate spontaneously increases.

The average of the QRS-RR regression slopes of all subjects was 0.0125, which predicts an increase in QRS duration of 1.25 msec for each 100 msec increase in RR interval. Thus, a decrease in heart rate from 180 BPM (RR = 333) to 40 BPM (RR = 1500), which occurs in most healthy adults, would be accompanied by an increase in QRS duration of about 15 msec, or roughly 20% of the normal QRS duration. By sex, this change would be approximately 13 msec in men and 17 msec in women. Changes of similar magnitude are illustrated in Fig. 2 and lesser degrees of change are displayed in Fig. 3.

Our description of a consistent increase in QRS duration in response to spontaneous decrease in heart rate within two large groups of normal subjects should resolve the

uncertainty established by conflicting findings of Malik and coworkers [1,2]. In 1976 Ganz and Knappen [10] observed a small positive correlation between RR and QRS in dogs, but discarded its significance concluding that "the PQ and QT intervals clearly decrease as the heart rate increases, whereas the QRS interval is only minimally affected." Schwarzwald and coworkers [11] observed shorter QRS and RR intervals in smaller breeds of horses, but ascribed it to an effect of body weight. Smetana, Malik and colleagues [1,2] attributed the difference between their two studies to more systematic measurements in the more recent study. Goldberger and Bhargava found that QRS duration diminished during treadmill exercise in 25 healthy males [12]. They concluded that this was a result of exercise rather than of an intrinsic, linear relationship between QRS duration and spontaneously changing heart rate. Some investigators have reported no
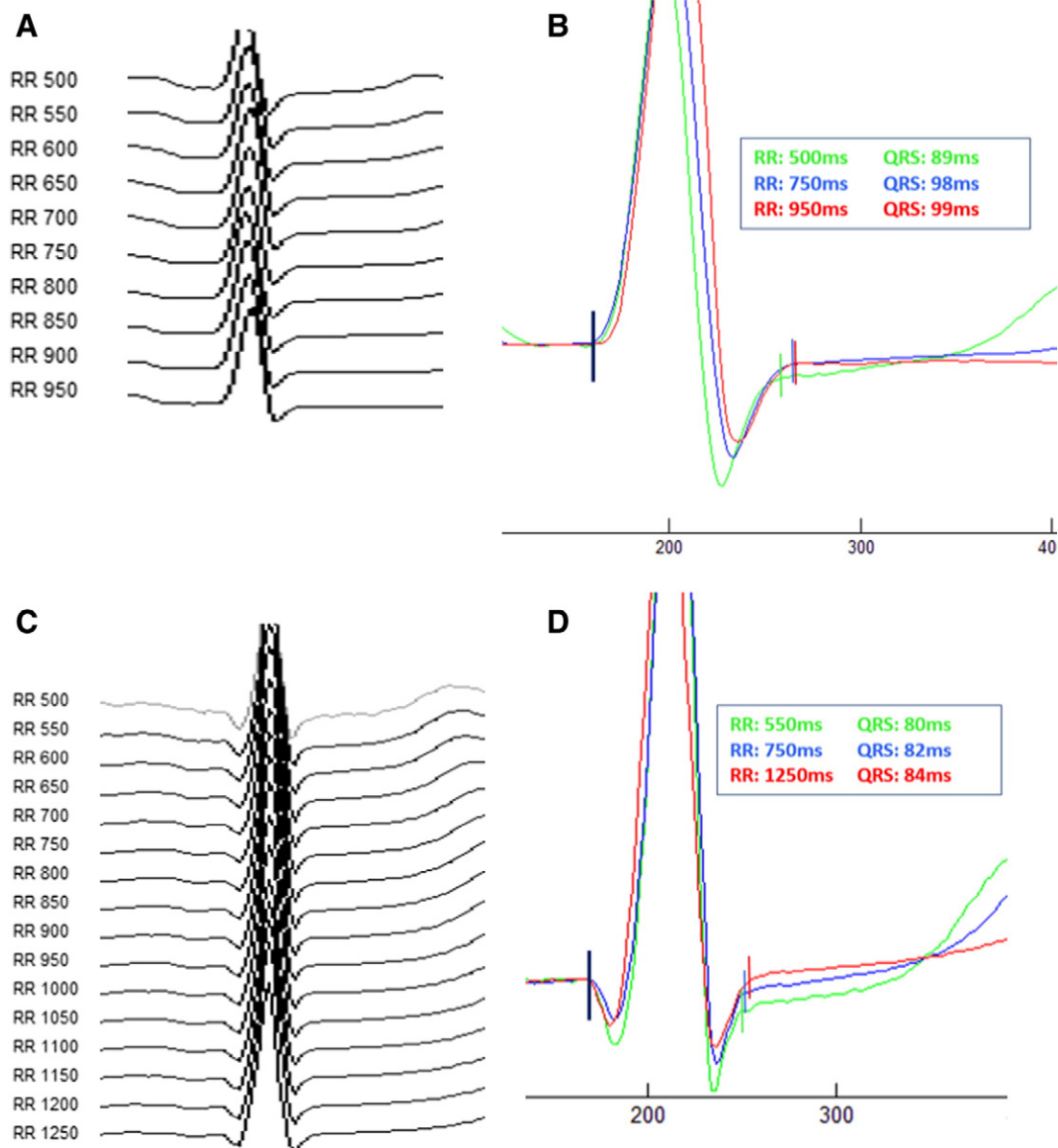
Fig. 3. Two examples of modest change in QRS duration with change in heart rate. The layout of the figure is explained in the legend for Fig. 2. An overall increase in the QRS interval of 10 msec occurred with a decrease in rate from 120 bpm to 63 bpm in the upper example, and 4 msec from a rate of 109 bpm to 48 bpm in the lower example.
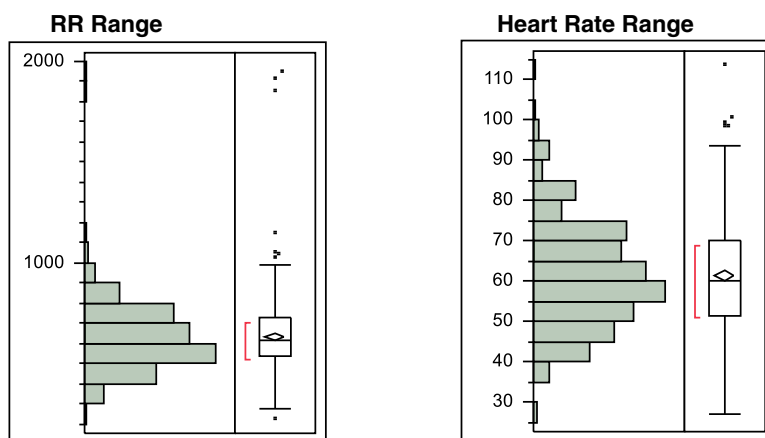
change in QRS duration during exercise [13], while others have reported an increase in subjects with active ischemia [14].

Why has this physiological phenomenon gone unappreciated until now? First, the QRS-RR gradient is too small to be detected by casual observation, unlike the QT-RR gradient, which is steeper and based upon the much larger QT interval, and therefore was recognized before Bazett [15] and Fridericia [16] published their QT- heart rate correction formulae in 1920. Second, methods for automated measurement of QRS duration from long ECG recordings are only recently available. Without the ability to examine tens of thousands of QRS-RR pairs in individual subjects, the robustness of the phenomenon was essentially hidden.

One possible explanation for our observation is that it is a result of reduced QRS amplitude associated with tachycardia, making small initial and terminal voltage levels harder to

detect. Though some have reported no change [13] and others inconsistent change [17], a few studies have found a reduction in QRS waveform amplitude during the tachycardia associated with exercise [18–21] in normal individuals. Madias and Macfarlane [22] artificially reduced QRS amplitude electronically in recordings from normal subjects and found a small reduction of QRS duration measured by a computer algorithm. Using the exercise changes in QRS amplitude observed in normals by Wright, et al. [19] and the effect of QRS amplitude reduction on QRS duration observed by Madias and Macfarlane [22], we calculated a possible QRS-RR gradient reduction related to QRS amplitude of 0.0029. Thus, if reduced waveform amplitude truly is associated with increased heart rate, it could only account for a small proportion (about 25%) of the average QRS-RR gradient that we observed.

Another explanation for our observations could be errors in the measurement algorithms. While this possibility cannot be

Fig. 4. Distribution of the ranges of RR intervals and HR in individual subjects. In those subjects with more than one Holter recording, the first recording was used in this analysis.

excluded, its probability is reduced by the fact that we used separate algorithms for the two datasets, and both gave very similar results. Also, the annotations of one of the two algorithms (WinAtrec) were reviewed by a cardiologist. Finally, it seems more likely that a defective measurement algorithm would result in inconsistent data rather than a systematic observation.

It is important to emphasize the fact that we are examining the change in QRS duration associated with *spontaneous* diurnal change in heart rate, which is best achieved with Holter monitoring under controlled conditions like those achieved in clinical trials. Furthermore, our observations were made in normal subjects. Thus, the potential interfering effect of disease

Table 3
Consistency of QRS-RR Slope, Pharmaceutical Trials.

Holter	N Subjects	Mean Slope	Frequency of Positive QRS-RR Slope			
Two Holters	217		1 of 2	2 of 2		
First		0.0124	210 (97%)	196 (90%)		
Second		0.0122				
Three Holters	212		1 of 3	2 of 3	3 of 3	
First		0.0120	209 (98%)	202 (95%)	188 (88%)	
Second		0.0118				
Third		0.0122				
Four Holters	44		1 of 4	2 of 4	3 of 4	4 of 4
First		0.0090	42 (95%)	41 (93%)	40 (91%)	38 (86%)
Second		0.0102				
Third		0.0100				
Fourth		0.0115				

Table 4
Influence of Sex and Age on QRS-RR Slope.

	Estimate	P Value*
N = 409[†]		
Slope Intercept	0.0107	<0.0001
Sex [F]	0.0016	0.0136
Age	<0.0001	0.1510

* The P value refers to the least squares regression testing of the significance of each estimate's difference from zero.
[†] Only the first Holter recording included in this analysis. F = female.

Female

Male

Quantiles

100.0%	maximum	0.07818		100.0%	maximum	0.04668
99.5%		0.07818		99.5%		0.04635
97.5%		0.05506		97.5%		0.03458
90.0%		0.03326		90.0%		0.02363
75.0%	quartile	0.0213		75.0%	quartile	0.01542
50.0%	median	0.01061		50.0%	median	0.00979
25.0%	quartile	0.00384		25.0%	quartile	0.00488
10.0%		-0.0003		10.0%		0.00171
2.5%		-0.0042		2.5%		-0.0057
0.5%		-0.0056		0.5%		-0.0158
0.0%	minimum	-0.0056		0.0%	minimum	-0.0188

Moments

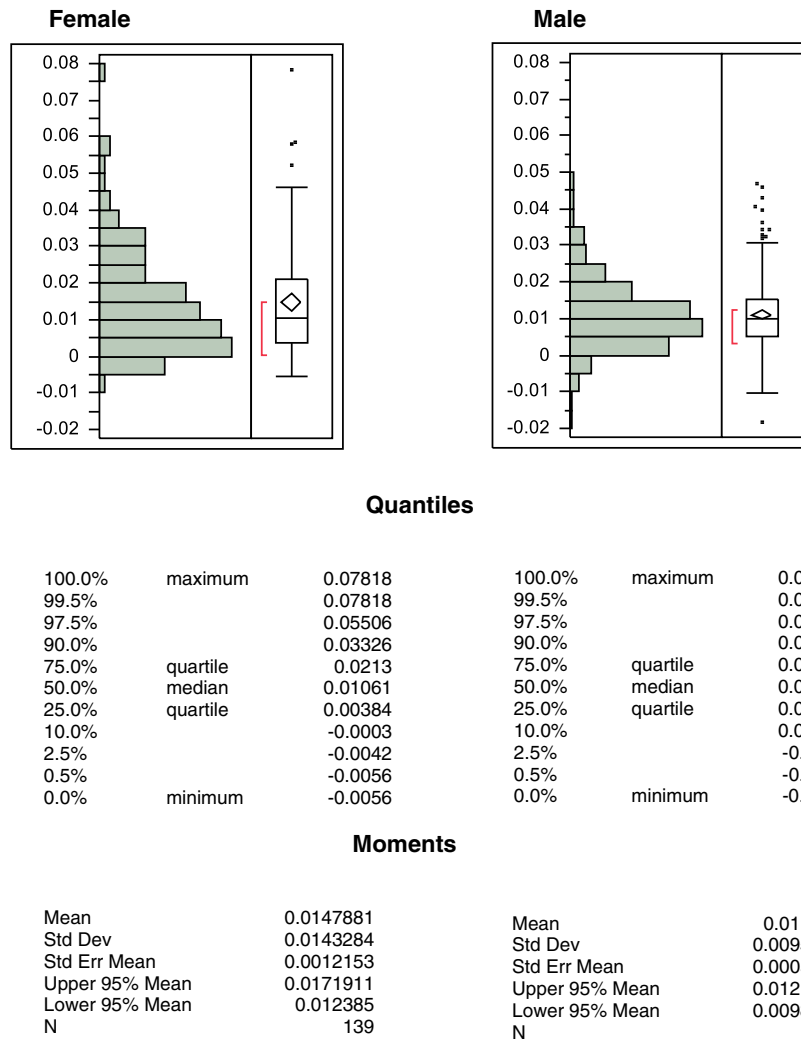|				
Mean	0.0147881		Mean	0.011033
Std Dev	0.0143284		Std Dev	0.0095217
Std Err Mean	0.0012153		Std Err Mean	0.0005795
Upper 95% Mean	0.0171911		Upper 95% Mean	0.0121739
Lower 95% Mean	0.012385		Lower 95% Mean	0.0098922
N	139		N	270

Fig. 5. Distribution of QRS-RR slopes in men and women on the first Holter recording. Though the peak of the frequency of the distribution occurs at a slightly lower slope interval in women than in men, the distribution in women is more positively skewed, resulting in higher median and mean values in women.

states, such as ischemia [14], and drug effects, such as class Ic antiarrhythmic drugs [23], were obviated. The observed positive relationship between QRS and RR duration may be counterintuitive to clinicians aware of the common occurrence of QRS aberrancy with the decrease in RR associated with premature atrial beats, atrial pacing and supraventricular tachycardia, which suggests an inverse relationship. However, aberrancy occurs after a sudden change in cardiac cycle length, while the relationship we observed occurred in the setting of gradual spontaneous change in heart rate. The former may be a result of insufficient recovery in unconditioned Purkinje tissue [24], while the latter appears to be a normal, necessary physiological adjustment, as discussed below.

Is there a physiological need for the QRS duration to increase with cycle length? Ventricular ejection time does have a predictable, direct, linear relationship with the RR interval [25]. A teleological explanation for this relationship is that lengthening the QRS prolongs ventricular ejection time, which provides the additional time needed to eject the increased ventricular volume related to longer filling times at slow heart

rates. Likewise, shortening of the QRS duration and ejection time during tachycardia increases the time available for filling, counterbalancing the rate-related shortening of diastole.

What physiological mechanism could be responsible for the observed QRS-RR relationship? Previous studies in animals employing ECG [26] and invasive HV interval measurement [27] did not show a decrease in QRS duration or intraventricular conduction time during incremental supraventricular pacing. Two studies [28,29] in humans with and without structural heart disease, employing signal averaged electrocardiography for precise determination of QRS duration, also failed to show shortening of the QRS during incremental atrial pacing. Thus, the QRS change we observed during spontaneous change in heart rate must not be a result of the change in heart rate per se. This raises the possibility that the physiological process that causes spontaneous heart rate change may, itself, concomitantly mediate the change in QRS duration.

One candidate for dual control of heart rate and QRS duration is sympathetic activity. At rest heart rate is

controlled in humans by an even balance of vagal and sympathetic influences, but during the increase in heart rate associated with physical activity, sympathetic influences become predominant [30]. Beta receptor activation has been shown both to increase sodium current, resulting in increased intraventricular conduction velocity, and to shorten QRS duration [31].

The heightened effect of heart rate on QRS duration in women is reminiscent of the larger QT-RR slope seen in women compared to men, which has been directly ascribed to sex hormones [6–8], but no data is available to explore that potential explanation for the QRS-RR relationship.

Should the QRS interval, like the QT interval, be rate-corrected in the interpretation of the electrocardiogram? The slope of QRS on RR is an order of magnitude smaller than that of QT, but because the QRS is about one-fifth the duration of the QT interval, the relative influence of RR on QRS is about half that of its effect on QT. There has been a longstanding appreciation of the association of QRS prolongation with a variety of cardiac risks [32–39], much like there is for the QT interval [40–46]. In addition, the exact magnitude of QRS prolongation is a critical factor in the decision for and response to biventricular pacing in patients with heart failure [47]. Thus, correction of the QRS interval for rate could be helpful in clinical decision making. It would provide a more robust assessment of drug effects on the QRS both in the clinical setting and in the development of new drugs. Finally, it would be possible to assess QT interval abnormalities more directly by subtracting the rate-corrected QRS interval from the rate-corrected QT interval to derive a more specific, rate-independent repolarization time.

Conclusions

We have characterized a robust, consistent relationship between cardiac cycle length and QRS complex duration that occurs during spontaneous diurnal change in heart rate in humans. We have proposed, as a potential mechanism for the phenomenon, concomitant sympathetic modulation of intraventricular conduction time and heart rate. Determination of the basic mechanism(s) responsible for our observation would be valuable, as it could provide new basic physiological insight.

Clinical implications

Correction of the QRS interval for heart rate may be useful in clinical care and research, but this speculation requires prospective assessment. The observed phenomenon of decreasing intraventricular conduction time with increasing heart rate might contribute to the heart's ability to adjust to hemodynamic alterations caused by changes in heart rate. Understanding of the mechanism responsible for our observation might open avenues for therapeutic adjustment of QRS duration, which has an important role in heart failure, heart block and arrhythmogenesis. Corroboration of our findings in other populations using other measurement software would be helpful.

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