AMPS-QT

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AMPS-QT is a quarterly journal dedicated to all the people and organizations involved in the world of cardiac safety. Published by AMPS LLC, it covers all aspects of methodology and software technology related to clinical trials and Thorough QT studies.

Editorial

Whether ones like to drive very fast cars and watch Formula 1 races on TV or not, there is still one thing that put us all in the same pool: we mostly depend on transportations on wheels powered by engines. You may not be aware that most of the innovative technology we benefit from when we drive around was in fact originally designed and developed for racing cars, which are a sort of laboratory where the most innovative ideas are implemented and tested, and eventually may trickle down to the general automotive market, as a sort of side effect. In a somewhat similar fashion, the research for new compounds and the consequent need to assess the variations induced on the HR and QT have triggered a series of interesting ideas which could possibly be implemented in clinical practice. Does QRS duration vary with changes in HR? If so, should the QRS be corrected for HR, like the QT interval? These are physiologically interesting questions that have clinical relevance, as it is discussed in this quarter's AMPS-QT contribution by Jay W. Mason, arguably one of the most famous and experienced cardiologists active in the cardiac safety industry. Jay is not only a very proficient cardiologist, dedicated professor, and excellent skier, but ultimately what everybody considers a very nice guy, always available to offer advice when needed. If you wish to contact him feel free to visit his web site: www.jaywmason.com.

A Noteworthy Contribution:

The QRS – HEART RATE Relationship

Jay W. Mason, MD, Professor of Medicine, University of Utah, Chief Medical Officer, Spaulding Clinical Research.

Does QRS duration vary with changes in HR (HR)? If so, should the QRS be corrected for HR, like the QT interval? These are physiologically interesting questions that have clinical relevance.

Background

In collaboration with colleagues at AMPS LLC, we have recently described an inverse relationship between QRS duration and spontaneously varying HR [1, 2]. As a background to this and the questions above, we will first briefly review the effect of HR on the QT and PR intervals, as well as waveform amplitudes.

QT correction

The inverse relationship of the duration of the QT interval on HR is well known and requires no elaboration here. It is important to note that none of the correction methods in use are completely reliable, and the preferred method is often dependent upon subject and situational characteristics. As a result, there are probably more than 100 such formulae in current or past use. Despite this, there is uniform agreement that repolarization status and change in that status cannot be properly determined without a correction.

PR correction

An inverse relationship between the duration of the PR interval and HR has been recognized for decades [3-5]. Recommendations for routine correction of the PR interval, especially in older subjects, have been made [6]. However, to date PR adjustment for HR has not been used routinely in any situations that we are aware of. Rate-related changes in PR, as we will see for QRS, are bivalent, depending on the circumstance, as discussed below.

Amplitude and HR

The amplitude of all components of the QRS waveform are inversely related to HR [7-10]. We are not aware of any recommendation for HR-amplitude correction, however.

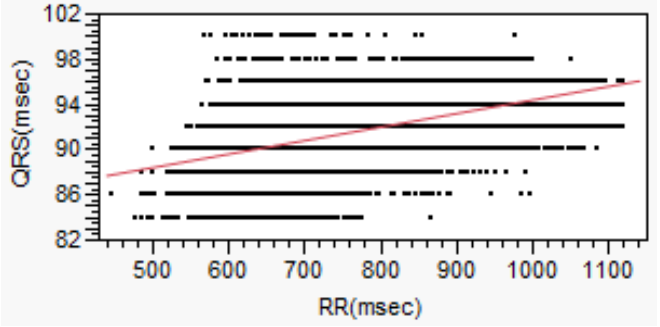
The two types of QRS response to HR

Forced HR change

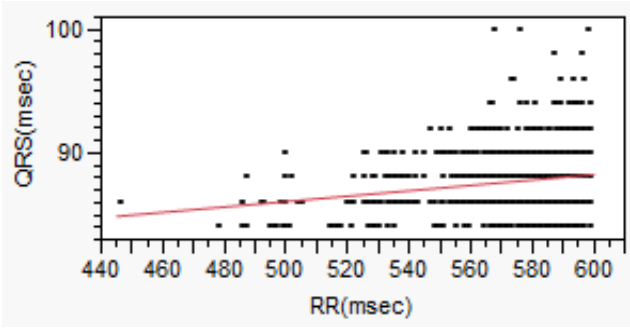
When HR change is not spontaneous, but rather forced, as during atrial pacing or a reentrant supraventricular tachycardia, clinicians have long noted a direct relationship between QRS duration and HR: faster rate produces QRS aberrancy, perhaps a result of Purkinje tissue fatigue [11]. This behavior is opposite to that observed during spontaneous change in HR. Similar behavior of the PR interval under forced change in HR has been observed.

Spontaneous HR change

We recently reported and quantified an inverse relationship of QRS duration to HR observed in Holter monitor recordings under several circumstances [1] (Figure 1). The gradient of this relationship is considerably smaller than that of QT and RR (about 0.0125 compared with about 0.150). Given that normal QRS duration is about one fifth that of normal QT duration, the normalized gradient of QRS:HR is about one half that of QT:RR. We also observed that the gradient was larger in women than in men (Table 1), evocative of the influence of sex on the QT:RR gradient.



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

Figure 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. Reproduced with permission of Elsevier from Fig. 1in Mason, et al [1].*

	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.

Table 1. *Influence of sex and age on the QRS-RR relationship. Sex had a significant influence, increasing the slope in women. Age did not have a significant effect. Reproduced with permission of Elsevier from Table 4 in Mason, et al [1].*

More recently we applied an HR correction of QRS in a research dataset in which both HR (Figure 2) and QRS duration had been altered by quinidine, to determine if the correction could improve the expected positive relationship between quinidine plasma concentration and the increase in QRS duration resulting from the sodium channel blocking properties of quinidine [2]. Indeed, this relationship was considerably improved compared with that of the uncorrected QRS duration (Figure 3).

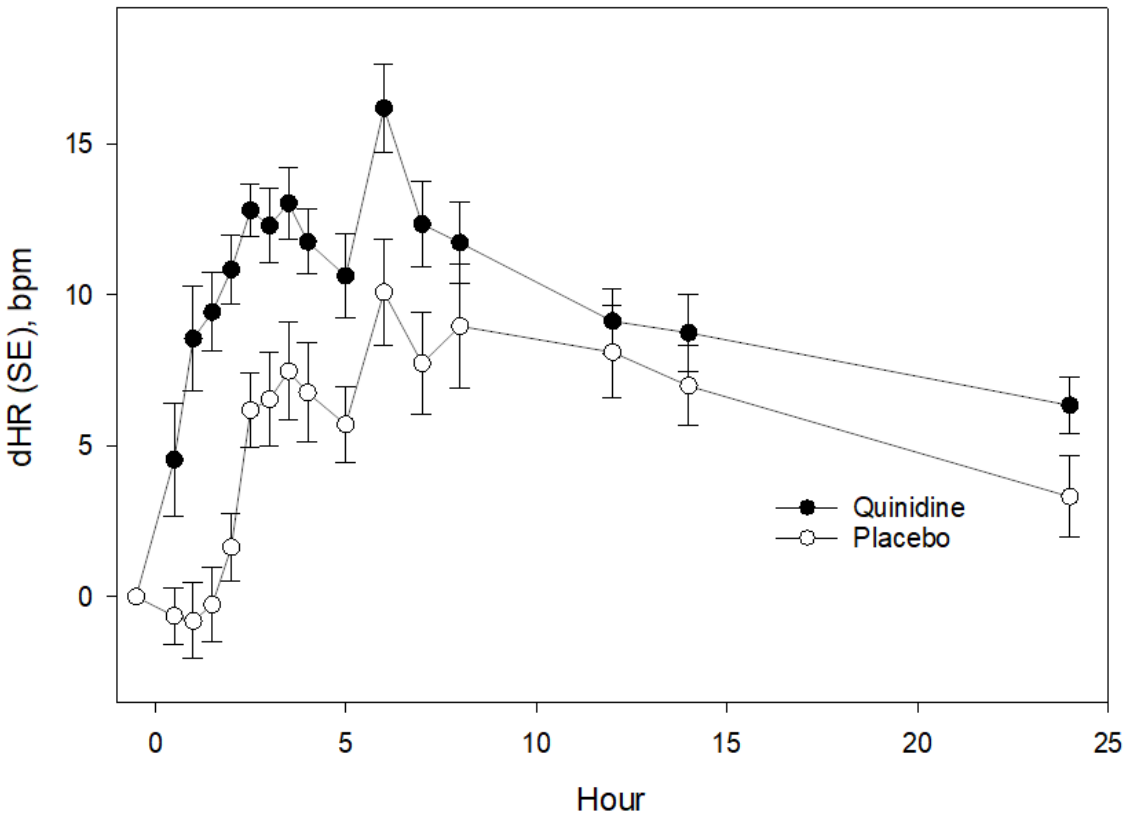


Figure 2. *Comparison of HR changes during placebo and quinidine treatment. dHR in the quinidine group was higher than in the placebo group at all timepoints. Reproduced with permission of Elsevier from Fig. 1 in Mason, et al [2].*

We speculated previously on the mechanism responsible for the QRS-HR relationship [1, 2]. We believe that the best current explanation is the simultaneous effect of sympathetic activity on both HR and QRS. Heightened sympathetic activity is well known to increase HR, but it also causes QRS shortening [12]. Under this hypothesis, during physical activity sympathetic stimulation (with associated parasympathetic withdrawal) brings about the observed increase in HR and decrease in QRS duration concomitantly.

Clinical and research use of the QRS-HR correction

In the research setting, especially in drug development, correction of the QRS could help protect against ascription of small changes in QRS duration to a drug effect, especially when the HR changes from baseline. Since QRS increases are linked to adverse effects, such as infranodal block and ventricular arrhythmias, more precise knowledge of the true drug effect should aide in judging drug safety, both by identifying the non-drug relatedness of and increases in QRS actually due to a decrease in HR as well as missed drug-related increases in QRS obscured by an increase in HR.

In clinical use, QRS-HR correction can be used to normalize the QRS duration for clinical decisions, such as determining the need for and potential benefit of cardiac resynchronization therapy, and judging the true status and change in intraventricular conduction, with its implications for risk and intervention. Accurate quantification of the change in QRS duration associated with a change in HR might provide a more accurate assessment of change in QTc, allowing better decisions regarding management of QT prolongation.

Though generalized QRS correction for HR might be an appropriate strategy, a refinement would be to limit its use to those situations in which alterations in sympathetic activity are associated with HR change, as this may be the exclusive physiological circumstance in which QRS correction would be helpful.

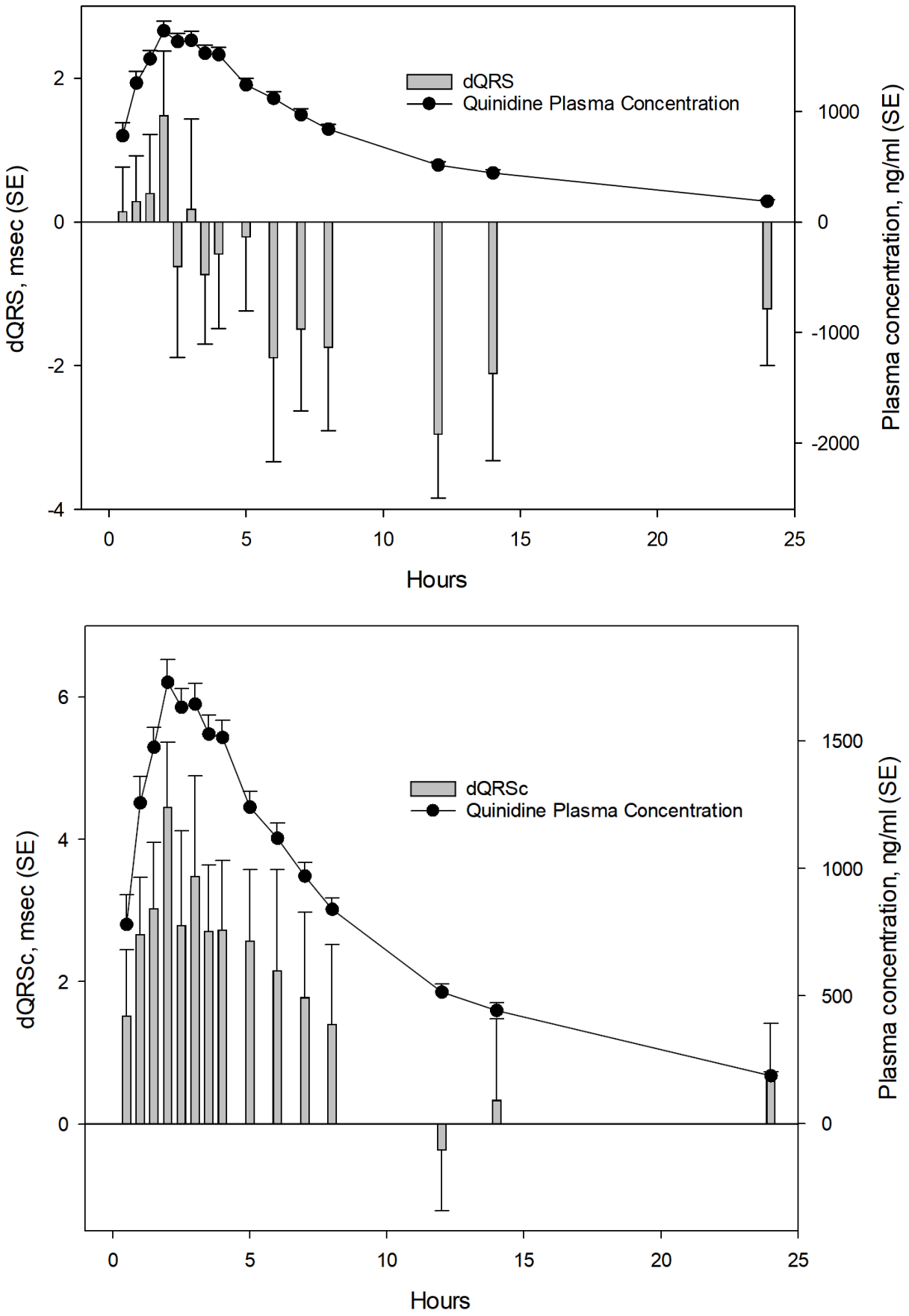


Figure 3. *Comparison of the relationships to quinidine plasma concentration of dQRS (upper panel) and dQRSc (lower panel). dQRS showed only a small, brief rise in QRS duration after quinidine, followed by a decrease despite substantial levels of quinidine. dQRSc showed a larger, sustained rise that correlated well with plasma concentration. Reproduced with permission of Elsevier from Fig. 2 in Mason, et al [2].*

Implementation

How could QRS correction for HR be implemented in research and clinical practice? One helpful first step would be additional corroboration of the observations reviewed here-in. If this led to acceptance of the concept, the correction could certainly be done manually on an as-needed basis. It is relatively easy and straightforward to apply a linear regression concept, using the formula

$$QRSc = QRS + 0.0125 \times (1000 - RR).$$

A more convenient solution would be the inclusion of QRSc as part of the automated output of computerized algorithms in existing commercial electrocardiographs.

References

[1] Mason JW, Badilini F, Vaglio M, Lux RL, Aysin B, Moon TE, Heinz B and Strachan I. A fundamental relationship between intraventricular conduction and heart rate. J Electrocardiol. 2016;49:362-70.

[2] Mason JW, Strauss DG, Vaglio M and Badilini F. Correction of the QRS duration for heart rate. J Electrocardiol. 2019;54:1-4.

[3] Bertrand CA, Godbold EO, Schussler T, Pomper IH and Duffy JC. Heart rate and the PR interval. N Y State J Med. 1972;72:2295-301.

[4] Carruthers SG, McCall B, Cordell BA and Wu R. Relationships between heart rate and PR interval during physiological and pharmacological interventions. Br J Clin Pharmacol. 1987;23:259-65.

[5] Danter WR and Carruthers SG. The heart rate-PR interval relationship: a model for evaluating drug actions on SA and AV nodal function. Br J Clin Pharmacol. 1990;30:490-2.

[6] Soliman EZ and Rautaharju PM. Heart rate adjustment of PR interval in middle-aged and older adults. J Electrocardiol. 2012;45:66-9.

[7] Deckers JW, Vinke RV, Vos JR and Simoons ML. Changes in the electrocardiographic response to exercise in healthy women. Br Heart J. 1990;64:376-80.

[8] Ohlmeier H, Mannebach H and Gleichmann U. Correlation between R-wave amplitude and left ventricular volume at rest and with exercise. Clinical cardiology. 1983;6:29-36.

[9] Surawicz B. Effect of heart rate on QRS voltage: a simple relation that escaped notice. J Cardiovasc Electrophysiol. 2000;11:61-3.

[10] Wright S, Rosenthal A, Bromberg J and Schork A. R-wave amplitude changes during exercise in adolescents with left ventricular pressure and volume overload. Am J Cardiol. 1983;52:841-6.

[11] Moe GK, Mendez C and Han J. Aberrant a-V Impulse Propagation in the Dog Heart: A Study of Functional Bundle Branch Block. Circ Res. 1965;16:261-86.

[12] Wang HW, Yang ZF, Zhang Y, Yang JM, Liu YM and Li CZ. Beta-receptor activation increases sodium current in guinea pig heart. Acta pharmacologica Sinica. 2009;30:1115-22.

AMPS Notebook

Fabio attended the **46th Computing in Cardiology Annual Conference** held in September in Singapore.

Products News

In Q3, we have released version 4.0.0 of CER-S, with all platforms revised and with the addition of the Events Review module. This version is undergoing CE and FDA 510K certification for medical device.