THE QT INTERVAL AND CYCLE LENGTH: THE INFLUENCE OF ATROPINE, HYOSCINE AND EXERCISE

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1 Twenty-seven healthy male subjects of mean age 24.3 ± 4.0 years and mean weight 74.9 ± 9.1 kg took part in an investigation to assess the most suitable correction for the QT interval as a function of cardiac cycle length. 547 sets of data points were generated.

2 Atropine 0.6, 1.2 and 1.8 mg, and hyoscine 0.4 and 0.8 mg, and exercise on a bicycle ergometer at power levels of 50–250 watts together with post-exercise values were employed to obtain a range of heart rates. Simultaneous measurement of cardiac output and total peripheral resistance were made.

3 It was found that the traditional square root formula gave an unsatisfactory correction for the QT for supine subjects following atropine and hyoscine. The formula $K = QT/RR^N$ was linearized and fitted to the data by the least squares method and gave a best fit correction with $N = 0.35$, which is close to the cube root correction of Fridericia (1920). Neither stroke volume nor total peripheral resistance were found to provide a further enhancement of the correction. The relationship between QT and cycle length following the exercise protocol was found to be best represented by Bazett's correction but the complex changes in the QT produced by exercise were noted.

4 These findings support the suggestion that either the cube root correction or the best fit correction with $N = 0.35$ provides a better correction factor than the traditional square root correction for the QT interval in clinical pharmacology experiments for data generated in resting patients.

Keywords QT interval atropine hyoscine exercise

Introduction

The QT interval is well known to be affected by disease, by electrolyte abnormalities, notably calcium and potassium, and by drugs such as digitalis and quinidine (Alimurung *et al.*, 1950). It has long been known to shorten with increasing heart rate and must be corrected for this before pharmacological effects can be studied. Usually, the correction of Bazett (1920) is employed, which relates QT to the square root of the cycle length: $K = QT/\text{Sq. root of } RR$; where K is a constant. The relationship of cycle length to QT duration has, however, received no little attention over the last half century, Simonson *et al.* (1962) listing eight formulae originated in attempts to improve on Bazett's correction.

The principal systolic time intervals—the total time of electromechanical systole (QS₂), left ventricular ejection time (LVET) and pre-ejection period (PEP), which depend markedly on heart rate—are also known to be affected by other physiological factors such as left ventricular end diastolic pressure (LVEDP) and left ventricular end diastolic volume (LVEDV), blood pressure and stroke volume (Gibson, 1978). After heart rate, stroke volume is the most important factor, lengthening LVET and

shortening PEP. The addition of stroke volume to the commonly used regression equations has recently been shown to improve the coefficient of determination by about ten percent for LVET and PEP (Staniforth, 1983). If QT measurements are to be of value in clinical pharmacology, then a reliable correction factor is necessary. This work was undertaken to ascertain the most useful relationship between QT and RR, and whether stroke volume or other physiological factors affect the relationship. Atropine or hyoscine or exercise were employed to obtain a range of heart rates and stroke volumes.

Methods

Definition of QT

Standard ECG limb leads were employed and the Q-wave was taken from lead II, even though it has been shown that a slightly earlier onset of Q can be demonstrated in chest lead V₂ (Danzig *et al.*, 1976) because lead II is the classical lead in systolic time interval measurements. The QT interval was measured

to within 5 ms; complexes with baseline irregularity of U-wave interference were discarded.

Ethical review

Approval was obtained for the studies described from the West Middlesex University Hospital Ethical Committee. Subjects gave written informed consent.

Conduct of the study

Healthy male subjects were selected from the West Middlesex University Hospital C.P.U. volunteer panel and attended the Clinical Pharmacology Unit in the morning to obviate circadian rhythm. Mean age and weight were 24.3 ± 4.0 years and 74.9 ± 9.1 kg respectively. They were fitted with four circumferential strip electrodes for impedance cardiography and four ECG limb leads. A phonocardiograph microphone was fixed in the second left interspace and held in place with a rubber stay. All recordings were made on an Ormed M-19 multichannel recorder at a paper speed of 80 mm/s.

Exercise measurements

Subjects sat on the exercise bicycle and a baseline reading was made, after which the subject exercised at 50 watts, when recordings were made, and at 100, 150, 200 and 250 watts, with recordings being made whilst the subjects were still exercising, and also immediately after they had ceased to exercise at each power level. A further series of recordings was made after the 250 watt exercise period while the subjects were returning to their baselines. Blood pressure was measured manually. Noise during exercise made the resting recordings of greater value. A total of 129 useful recordings were obtained in the exercise study, 17 of these during exercise itself.

Atropine and hyoscine

Subjects attended in the morning and received either atropine or hyoscine. Those receiving atropine were given 0.6, 1.2 and 1.8 mg on successive occasions. Those receiving hyoscine attended twice and received 0.4 mg on the first occasion and 0.8 mg on the second occasion. The injections were given through an arm vein in increments of 0.6 mg of atropine or 0.4 mg of hyoscine. A gap of 4 min was allowed between each administration of an injection. Subjects were supine and recordings were made at 2, 4, 6, 10, 15, 30, 45, 60, 90 min and 2 h.

Measurement of stroke volume

An assessment of stroke volume was made using impedance cardiography (Baker *et al.*, 1971); the

formula of Kubicek being employed to calculate the stroke volume, using the relationship between haematocrit and resistivity described by Hill & Thompson (1975), a sample for haematocrit determination being taken on the morning of the study.

Processing of the data

A total of 6–10 complexes were measured to obtain each recorded value, the complexes being selected to span the respiratory cycle. The QT, RR and stroke volume measurements so obtained were stored on floppy discs, and a DEC Minc 11 laboratory computer was employed to do multiple regression analysis using the least squares method.

Results

Selection of cycle length

Controversy has existed as to whether the current RR interval or the preceding RR interval is of most value in deciding the current QT interval. Therefore, a linear regression analysis was first carried out to find the goodness of fit for both current and previous cycle length using the data for the three experimental situations—atropine, hyoscine and exercise. The goodness of fit was assessed by means of the coefficient of determination; the results are given in Table 1. It can be seen that a very slight advantage is found for use of the previous cycle. Therefore, in all subsequent investigations the previous cycle length was employed.

Table 1 Coefficients of determination expressed as percentages for a linear relationship between QT and cycle length for the current and previous cycle

	Previous RR	Current RR
Exercise	68.8	68.7
Atropine	73.6	73.3
Hyoscine	66.4	64.7

The effect of stroke volume and other physiological variables

A linear regression equation was first calculated for the relationship between QT and cycle length for the three experimental situations—with atropine, with hyoscine and during exercise—and the coefficient of determination computed. Stroke volume, systolic blood pressure or total peripheral resistance was then added in as a second physiological variable, giving a regression plane of the form:

$$QT = a + b \times RR + c \\ \times \text{second physiological variable}$$

and the coefficient of determination again calculated. The results are tabulated in Table 2.

Table 2 Coefficients of determination expressed as percentages for cycle length alone and with other physiological variables added

	<i>Exercise</i>	<i>Atropine</i>	<i>Hyoscine</i>
RR alone	68.8	73.6	66.4
RR and SV	69.7	73.9	67.7
RR and TPR	69.5	73.6	66.9
RR and SBP	69.8	73.6	67.6

RR Heart rate
SV Stroke volume
TPR Total peripheral resistance
SBP Systolic blood pressure

Equations derived

A linear relation between QT and cycle length was derived for the three experimental conditions and the equations are given in Table 3, together with published straight line equations.

The relationship between QT and RR following the atropine and hyoscine was formally explored by comparing the slopes of the lines given in Table 3 by means of the *t* test: no significant difference could be shown. However, comparing the slopes following exercise with the slopes for atropine and hyoscine by means of the *t* test gave significant differences ($P < 0.01$ and < 0.01 respectively).

Whilst examination of the graphs for individual subjects did not provide any evidence of departure from a single straight line relationship, a slight curvature can be discerned when the data for all subjects together is examined (see Figures 1, 2 and 3). The curvi-linear relationships of Bazett (1920) and Fridericia (1920) have the advantage of not requiring the knowledge of any parameters in order to calculate the corrected QT. The formula of Bazett and Fridericia suggests that a more general formula of type $K = QT \sqrt{N/RR}$ might provide a suitable model to inves-

tigate the most useful method of correction. This formula can be linearized:

$$\text{Log } K = N \log RR + \log QT$$

and the values of *K* and *N* obtained by regression using the least squares method. The results of these calculations and the data for the atropine/hyoscine and exercise experiments are presented in Figures 1, 2 and 3 and Table 4. Examination of the Figures reveals an interesting finding: clearly the best relationship with $N = 0.353$ (atropine), and $N = 0.356$ (hyoscine) is very close to $N = 0.33$ which corresponds to the cube root formula of Fridericia, whereas for the exercise data the best fit gives a value of $N = 0.468$ which is close to the 0.5 required by Bazett's formula.

Since the subjects were semi-vertical on the exercise bicycle and supine when receiving the parasympatholytics, it was possible that the effect of posture was partially accountable for the differences in the regression line slopes; this was investigated in the experiment described below.

Effect of positional change

The QT and heart rate were measured on 20 subjects, each in five positions: 30° head up, 20° head up, horizontal, 20° head down and 30° head down. The QT was here corrected using Bazett's formula. It was required to determine the extent of the influence of position on QT, both when QT had been corrected and when it had not. The results are presented in Table 5. Analyses of variance were employed to compare the effect of position on corrected and uncorrected QT and on heart rate. The differences brought about by positional change were found to be highly significant statistically. In order to determine where the differences lay, Duncan's multiple range test was employed. Means underscored by the same line are not significantly different at the level of probability indicated. The uncorrected QT displays a maximum between 20 head up and 30 head down, which is significantly higher than either of these at the 5% level. Over the range of positions concerned, QT decreases as the head is lowered, as does heart rate.

Table 3 Parameters for linear relationships between cycle length and QT found following exercise, atropine or hyoscine, together with some published equations

	<i>Intercept</i>		<i>Slope</i>	
Exercise	184.2453	± 38.7922	0.1953	± 0.0534
Hyoscine	254.5585	± 70.244	0.1306780	± 0.5773
Atropine	254.3363	± 33.1576	0.129	± 0.03522
*Simonson <i>et al.</i> (1962)	242.3		0.140	
Adams (1936)	246.2		0.1536	
†Schlamowitz (1946)	167		0.205	

* This equation includes a rather small correction for age here omitted ($\text{age} \times 3 \times 10^{-4}$)

† Used an exercise protocol

Figure 1 The QT interval as a function of cycle length following administration of atropine 0.6–1.8 mg. Least squares regression lines have been fitted to the formula $K = QT/RR^N$, $N = 0.5$ for the traditional square root correction (---) and 0.33 for the cube root correction (.....) and the best fit value of N (—) determined as a parameter.

In order to determine whether positional change had an effect on QT separate from the concomitant heart rate changes, a multiple regression analysis was performed on the logs of the uncorrected QT data with the effect of subjects, positions and heart rates fitted to the data sequentially. This showed that although heart rate had by far the most effect on QT, the effect of position was still significant after the effect of heart rate had been accounted for. None the

less, it is clear that the changes in QT brought about by these changes are relatively small when compared with the exercise induced changes.

Discussion

The existence of so many formulae relating QT to RR points to dissatisfaction with Bazett's formula and the

Figure 2 The QT interval as a function of cycle length following administration of hyoscine 0.8 mg. Least squares regression lines have been fitted to the formula $K = QT/RR^N$, $N = 0.5$ for the traditional square root correction (---) and 0.33 for the cube root correction (.....) and the best fit value of N (—) determined as a parameter.

Figure 3 The QT interval as a function of cycle length generated by a mixed exercise and post-exercise protocol. Least squares regression lines have been fitted to the formula $K = QT/RR^N$, $N = 0.5$ for the traditional square root correction (---) and 0.33 for the cube root correction (.....) and the best fit value of N (—) determined as a parameter.

difficulties involved in applying a single correction formula to data of diverse origin. Simonson (1962) points out that while many formulae are satisfactory over heart rates in the mid range, at high and low rates discrepancies become apparent. Ahnve & Vallin (1982) found Bazett's formula to result in inversion of the relationship between QT and RR, giving proportionately longer corrected QT values at high heart rates obtained during atrial pacing. Their results are entirely consistent with the findings here reported.

Galeazzi *et al.* (1976) found the square root correction unsatisfactory and advocated a linear correction. Bryson *et al.* (1978), following this approach, used $QTI = QT + 1.7 \times HR$. A similar linear correction based on the atropine and hyoscine data here re-

ported would give a correction factor of 1.77. More recently Boudoulas *et al.* (1981) gave a factor of 2.0 for hospitalised male patients of mean age 40 years.

Examination of Table 3 shows that the relationship found between QT and RR following atropine and hyoscine is similar to published equations. The exercise data gave parameters close to those reported by Schlamowitz (1946), who also employed a mixed exercise and post-exercise protocol. However, as a correction for QT a simple straight line relationship was rejected because of the slight curvature which can be seen in the data presented in Figures 1, 2 and 3. Furthermore, no evidence of bisegmentality was found on examination of individual graphs (Schoenwald & Isaacs, 1974).

Table 4 Parameters obtained by a least squares regression analysis using the following formulae: $K = QT/RR^N$; where $N = 0.5$ for Bazett's correction, 0.33 for Fridericia's correction, and is determined as a regression parameter for the best fit. Data was generated using atropine, hyoscine or exercise.

		Atropine	Hyoscine	Exercise
Bazett (1920)	K	0.3994	0.3812	0.3859
	N	0.5	0.5	0.5
Fridericia (1920)	K	0.3843	0.3832	0.3584
	N	0.33	0.33	0.33
Best fit	K	0.3860	0.3829	0.3805
	N	0.353	0.356	0.468

Note: Bazett gave values of K for men of 0.368 and Fridericia gave $K = 0.0822$ which would correspond to 0.38154 when RR rather than 100 RR is used

Table 5 The effect of positional change on the corrected and uncorrected QT interval. Duncan's range test has been carried out to show where statistically significant differences lie; means underscored by the same line are not significantly different at the level of probability indicated.

<i>Untransformed QT</i>						
	<i>Position</i>	<i>30° Head up</i>	<i>20° Head up</i>	<i>30° Head down</i>	<i>20° Head down</i>	<i>Horizontal</i>
	Geometric mean (m/s)	357.7	365.3	371.8	376.2	377.6
Significance levels:	5%					
	1%					
<i>Corrected QT</i>						
	<i>Position</i>	<i>30° Head up</i>	<i>20° Head up</i>	<i>Horizontal</i>	<i>20° Head down</i>	<i>30° Head down</i>
	Geometric mean (m/s)	382	381	377	373	369
Significance levels:	5%					
	1%					
<i>Cycle length (ms)</i>						
	<i>Position</i>	<i>30° Head up</i>	<i>20° Head up</i>	<i>Horizontal</i>	<i>30° Head down</i>	<i>20° Head down</i>
	Geometric mean (m/s)	878	922	1002	1013	1016
Significance levels:	5%					
	1%					

The Nth root best fit formula for atropine and hyoscine data, details of which are given in Table 4, can be seen to be very close to the cube root of Fridericia. Both the best fit, with $N = 0.35$, and Fridericia's cube root correction were analysed to test for their completeness as correction formulae by plotting the corrected QT against heart rate and testing the slope of the regression line for significance. Both the best fit and Fridericia's were good corrections but Bazett's gave a highly significant slope ($P < 0.001$). Boudoulas *et al.*, using a similar data treatment, calculated a value of $N = 0.398$ though they advocate a linear correction.

The relationship between QT and RR found when exercise was used is clearly different with Bazett's formula giving a close approximation to the best possible fit. However, as the data on which these observations was made consisted of values obtained both during exercise and at rest following exercise, this

finding has no predictive value. That exercise produces changes in the QT has been observed by both Knoebel *et al.* (1979) and Yu *et al.* (1950). The relationship between exercise and QT is not a simple one. Yu *et al.* (1950) has shown that K is prolonged during exercise but shortened during the first three minutes of recovery, after which it returns to its resting value. Neither stroke volume, total peripheral resistance, systolic blood pressure nor the Heather index was found to make a useful addition to the regression equations in the atropine, hyoscine or exercise experiments, though changes in the corrected exercise QT are reflected in changes in both peripheral resistance and cardiac output. That haemodynamic factors other than heart rate are relevant is indicated by the rate independent effect of postural change which may be mediated via changed venous return and diastolic volume. Autonomic factors also influence the QT interval; the role of the sympathetic

system has been documented by Schwartz & Malliani (1975) and Abildskov (1976), and the differing roles of the left and right stellate ganglia discussed by Crampton (1979). More recently a direct influence of cholinergic activity on the repolarisation of ventricular myocardium has been suggested by Ahnve & Vallin (1982).

The results of the investigations reported here support the conclusion that a better correction factor, other than the traditional square root, for the QT

interval in clinical pharmacology experiments for data generated in resting patients is provided either by a cube root correction or a correction using $QT/RR^{0.35}$. Such corrections have the advantage of not requiring a slope parameter derived from global regression equations with their dubious applicability to the population under study.

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References

- ABILDSKOV, J.A. (1976). Adrenergic effects on the QT interval of the electrocardiogram. *Am. Heart J.*, **92**, 210-216.
- ADAMS, W. (1936). The normal duration of the electrocardiographic ventricular complex. *J. clin. Invest.*, **15**, 335-342.
- AHNVE, S. & VALLIN, H. (1982). Influence of heart rate and inhibition of autonomic tone on the QT interval. *Circulation*, **65**, 435-439.
- ALIMURUNG, M.M., JOSEPH, L.G., CRAIGE, E. & MASSELL, B.F. (1950). The QT interval in normal infants and children. *Circulation*, **1**, 1329-1337.
- BAKER, L.E., JUDY, W.V., GEDDES, L.E., LANGLEY, F.M. & HILL, D.W. (1971). The measurement of cardiac output by means of electrical impedance. *Cardiovascular Res. Cen. Bull.*, **9**, 135-145.
- BAZETT, H.C. (1920). An analysis of the time-relations of electrocardiograms. *Heart*, **7**, 353-370.
- BOUDOULAS, H., GELERIS, P., LEWIS, R.P. & RITTGERS, S.E. (1981). Linear relationship between electrical systole, mechanical systole and heart rate. *Chest*, **80**, 613-617.
- BRYSON, S.M., WHITING, B. & LAWRENCE, J.R. (1978). Disopyramide serum and pharmacological effect kinetics applied to the assessment of bioavailability. *Br. J. clin. Pharmacol.*, **6**, 409-419.
- CRAMPTON, R. (1979). Preeminence of the left stellate ganglion in the long Q-T syndrome. *Circulation*, **59**, 769-778.
- DANZIG, M.D., ROBERTSON, T.L., WEBBER, L.S., DAY, G. & DOCK, D.S. (1976). Earlier onset of QRS in anterior precordial ECG leads. *Circulation*, **54**, 447-451.
- FRIDERICIA, L.S. (1920). Die Systolendauer im Elektrokardiogramm bei normalen Menschen und bei Herzkranken. *Acta med. Scand.*, **53**, 489.
- GALEAZZI, R.L., BENET, L.Z. & SHEINER, L.B. (1976). Relationship between the pharmacokinetics and pharmacodynamics of procainamide. *Clin. Pharmacol. Ther.*, **20**, 278-289.
- GIBSON, D.G. (1978). Use of the systolic time intervals in clinical pharmacology. *Br. J. clin. Pharmacol.*, **6**, 97-102.
- HILL, D.W. & THOMPSON, F.D. (1975). The effect of haematocrit on the resistivity of human blood at 37°C and 100 kHz. *Med. Biol. Eng.* (March), 182-186.
- KNOEBEL, S.B., LOVELACE, D.E. & FARIS, J.V. (1979). QT interval during exercise. *Circulation* (Abstracts), **59**, 60 (Suppl. II), 745.
- SCHLAMOWITZ, I. (1946). An analysis of the time relationships within the cardiac cycle in electrocardiograms of normal men. I The duration of the QT interval and its relationship to the cycle length (RR interval). *Am. Heart J.*, **31**, 329-342.
- SCHOENWALD, R.D. & ISAACS, V.E. (1974). QT corrected for heart rate: A new approach and its application. *Arch. int. Pharmacodyn.*, **211**, 34-48.
- SCHWARTZ, P.J. & MALLIANI, A. (1975). Electrical alternation of the T-wave: Clinical and experimental evidence of its relationship with the sympathetic nervous system and with the long Q-T syndrome. *Am. Heart J.*, **89**, 45-50.
- SIMONSON, E., CADY, L.D. & WOODBURY, M. (1962). The normal QT interval. *Am. Heart J.*, **63**, 747-753.
- STANFORTH, D.H. (1983). Systolic time intervals: the effect of stroke volume in healthy young men. *Eur. J. clin. Pharmacol.*, **24**, 179-183.
- YU, P.N.G., BRUCE, R.A., LOVEJOY, F.W. & PEARSON, R. (1950). Observations on the change of ventricular systole (QT interval) during exercise. *J. clin. Invest.*, **29**, 279-289.

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