Dynamic assessment of the electrocardiographic QT interval during citrate infusion in healthy volunteers

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Abstract

**Objective**—To investigate changes in the electrocardiographic QT interval during rapidly induced, sustained hypocalcaemia in healthy volunteers.

**Design**—Serial rate corrected QT measurements were made during and after a variable rate trisodium citrate infusion designed to "clamp" the whole blood ionised calcium concentration 0-20 mmoll below baseline for 120 min.

**Subjects**—12 healthy teetotters aged 19-36 years who were not receiving medication known to influence calcium homoeostasis.

**Main outcome measures**—Whole blood ionised calcium concentration and QTc intervals (onset of the Q wave to T wave apex divided by the square root of the RR interval).

**Results**—Mean (SD) ionised calcium concentration decreased from 1-18 (0-03) mmoll preinfusion to values close to target (0-98 mmoll) between 10 and 120 min. The QTc interval lengthened from a baseline of 0-309 (0-021) to a maximum 0-343 (0-024) s after 10 min before returning to a stable level from 15 to 120 min (0-334 (0-023) and 0-330 (0-023) s respectively). The change from baseline of both variables expressed as a ratio (AQaTc/AA(Ca2+)) was greater during rapid induction of hypocalcaemia (at 5 and 10 min) than at other times during and after the infusion (P < 0-02).

**Conclusions**—The disproportionate prolongation of QTc interval during prompt induction of hypocalcaemia suggests rate dependency which can be represented by a hysteresis relation between (ionised calcium, QTc) coordinates. This finding may have clinical implications.

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Keywords: QT interval; hypocalcaemia; hysteresis

The effect of changes in serum calcium on the electrocardiographic QT interval was first described over 70 years ago. Several more recent studies have involved detailed electrocardiographic investigation of groups of patients with underlying diseases (including parathyroid dysfunction and malignancy) or undergoing therapeutic procedures (such as blood transfusion and renal dialysis) which produce measurable disturbances of calcium homoeostasis. Despite the lack of a significant association in a number of studies in neonates a simple inverse relation between steady state serum calcium (usually total rather than ionised) and the QT interval has been observed in most of these reports. As QT prolongation is associated with sudden death in a variety of illnesses as well as in apparently healthy individuals, this relation could be useful in clinical situations in which prompt and reliable measurement of serum calcium is indicated but not possible.

The QT interval can be measured from a common starting point at the beginning of the QRS complex to the onset (QoT), apex (QaT) or end (QeT) of the T wave. Although correction for heart rate using Bazett's formula (in which the raw QT interval is divided by the square root of the RR interval to give QTc) was developed for QeT, QoT and QTc intervals have also been used in a variety of electrocardiographic studies including the majority of those concerned with calcium homoeostasis. Despite the lack of a relationship between the QTc interval and serum ionised calcium concentration and each of the three QTc intervals. Nevertheless, such an assumption does not take into account the possibility that the rate of change of serum ionised calcium may also be an important determinant of changes in QTc, in a way analogous to the dynamic parathyroid hormone response to the same stimulus.

Intensive electrocardiographic monitoring was performed in healthy volunteers during a 2 h period of controlled hypocalcaemia induced using the previously reported citrate 'clamp' technique to assess the effect of a rapid change in serum ionised calcium on the QTc interval.

**Subjects and methods**

**SUBJECTS**

Twelve healthy teetotal Malaysian adults (eight males and four females) of mean (SD) age 33 (5) years were studied. None of the subjects was taking regular medication and none had a history of illnesses known to influence calcium homoeostasis. All had given witnessed informed consent to participation as controls in a study of calcium metabolism in acute malaria. The study protocol was approved by the ethics committee of the Ministry of Health, Malaysia.
METHODS
Each participant attended after fasting for more than 4 h. Intravenous cannulae were inserted into both arms after 15 min of bed rest, one to allow frequent blood sampling and the other for administration of fluids. A twelve lead electrocardiogram was taken to confirm that baseline QTc intervals (measured from standard lead II, see later) and other electrocardiographic indices were within normal limits. A venous blood sample was drawn into calcium saturated heparin for determination of the basal whole blood ionised calcium concentration at the bedside using a calcium selective electrode (ICA-2; Radiometer, Copenhagen). Obtained values were not corrected for venous blood pH. The sampling cannula was flushed with small volumes of sterile normal saline to ensure patency.

An infusion of sterile isotonic trisodium citrate solution was then started at 0.85 mmol citrate/kg body weight/h using a motor driven syringe pump (Perfusor; Braun, Germany). Further blood samples were taken at 5 and 10 min and the infusion rate was changed at these times on the basis of the ionised calcium concentration using a modification of the formulae reported by Schwartz et al which are designed to 'clamp' the ionised calcium at a concentration of 0.2-20 mmol/l below baseline within 30 min of the start of infusion. Further samples for ionised calcium were taken at 5 min intervals for the first 60 min and then at 10 min intervals during the second hour, with further small adjustments of the citrate infusion rate to maintain the target serum ionised calcium concentration.

A long electrocardiograph rhythm strip from standard lead II at 50 mm/s chart speed was taken at each sampling time. At each time point QT, QaT, and QeT intervals were measured for each of three complexes by a single observer using a ruler. All QT measurements were taken from the onset of the QRS complex. When the origin of the T wave could not be clearly identified it was taken as the point on the ST segment furthest from a straight line between the R-ST junction and the T wave apex. The end of the T wave was the point at which it returned to the T/P baseline or, if U waves were present, the lowest point of the curve between T and U wave peaks. QoTc, QaTc, and QeTc were calculated from raw intervals and Bazett's correction, and average values were used in further analysis. Patients were withdrawn from the study if the QaTc was greater than 0.55 s. After the 120 min sample and rhythm strip had been taken the citrate infusion was stopped and a further blood sample and strip were taken 15 min later to confirm restoration of the serum ionised calcium concentration and QTc intervals toward normal.

As QaTc is known to correlate better with the simultaneous ionised calcium concentration than QeTc and as errors in the determination of QoTc can reflect accurate identification of the apex of the T wave, QaTc was the standardised interval used in analysis. Changes in the whole blood ionised calcium concentration and QaTc from baseline (0 min) were calculated for each time point and expressed as a ratio. Differences between variables during rapid induction of hypocalcaemia (at 5, 10 and 15 min) were analysed by paired Student's t test using a 2% level of significance. Data are reported as mean (SD).

Results
All participants remained asymptomatic during citrate administration apart from minor irritation at the infusion site in four individuals. The mean baseline whole blood ionised calcium concentration was 1.18 (0.03) mmol/l and the target reduction was achieved promptly (0.98 (0.04) mmol/l at 10 min). The whole blood ionised calcium concentration remained stable at close to 0.20 mmol/l below baseline between 10 and 120 min (fig 1). The mean citrate infusion rate was reduced to 0.33 mmol/kg/min at 10 min and there were further progressive reductions during the remainder of the infusion period to a mean rate of 0.28 mmol/kg/min at its end. The ionised calcium concentration rose to 1.06 (0.03) mmol/l 15 min after the end of infusion. Prompt determination of the QaTc at the bedside revealed that all values remained less than 0.50 s.

The coefficient of variation for triplicate uncorrected QaT values for all participants and time points was 1.8%. The raw QTc interval lengthened during induction of hypocalcaemia in all participants from a baseline of 0.270 (0.019) s to 0.291 (0.018) s at 5 min and a maximum of 0.294 (0.018) s at 10 min. The mean QaTc remained between 0.290 and 0.294 s between 15 and 120 min. QoT and QeTc intervals showed similar trends (data not shown). The RR interval remained close to baseline (0.77 (0.09) s) at 5 (0.74 (0.11) s) and 10 min (0.74 (0.12) s), and subsequently. Consistent with these data the QaTc interval was prolonged by an overall mean of 11% by 10 min but, thereafter, the QaTc interval decreased to a stable but prolonged mean value of 7.5% greater than baseline (fig 1).

![Figure 1](http://heart.bmj.com) Mean (SD) change in the whole blood ionised calcium concentration (lower panel) and QaTc interval (upper panel) in 12 healthy volunteers during and at 15 min after a 2 h citrate clamp designed to maintain the ionised calcium concentration at 0.2 mmol/l below baseline.
The change in whole blood ionised calcium concentration relative to that of baseline ($\Delta[Ca^{2+}]$) at 5 min was significantly less than at 10 and 15 min ($P < 0.02$ in each case; see fig 1), while the corresponding change in QTc from baseline ($\Delta$QTc) during the first 15 min of infusion was greatest at 10 min ($P < 0.02$ vs 5 and 15 min). The greatest change in QTc relative to the calcium ion concentration ($\Delta$QTc/$[Ca^{2+}]$) was at 5 min ($P < 0.02$ vs 10 and 15 min). The ($\Delta$QTc/$[Ca^{2+}]$) ratio at 10 min was significantly higher than that at 15 min ($P = 0.004$) with stable values at subsequent time points during and after the infusion (fig 2).

Figure 3 shows a composite graph relating mean ionised calcium concentration and QTc prolongation at key times during the study. There is separation of QTc changes during induction of hypocalcaemia and subsequent recovery which indicates a hysteresis relation.

Discussion

The present data support the concept that the rate of change of whole blood ionised calcium concentration is an important influence on cardiac repolarisation. Although the levels of induced hypocalcaemia were well within acceptable limits of safety, $^{15,16}$ disproportionate prolongation of the QTc interval was seen during the first 10 min of each study relative to values during subsequent steady state ionised hypocalcaemia. The majority of previous studies have shown a relation between QT prolongation and steady state hypocalcaemia over a generally wider range than our data, $^{5,14}$ but none has included a within subject dynamic assessment in which rate effects are considered. Hypocalcaemia prolongs the duration of phase two of the action potential of cardiac muscle, with consequent effects on the ST segment of the electrocardiogram and, by implication, the QT interval. In addition to the effect of extracellular calcium concentration itself on calcium influx during phase two, the rate of change of extracellular calcium may also modulate calcium channel function in cardiac cell membranes.

A limitation of the present study is that data from leads other than standard lead II were unavailable at times other than baseline. Variability in QT intervals between leads reflects regional variation in ventricular repolarisation which, together with the length of the QT' interval itself, appears to be a substrate for arrhythmia. $^{21}$ Studies evaluating a possible relation between whole blood ionised calcium concentration and QT dispersion, especially within the first 10 min of a citrate clamp, would be of interest. In addition, more frequent electrocardiographic assessment would better characterise relations such as that found in the present study, the protocol for which was based on previous recommendations. $^{18,19}$

Our findings relate to healthy volunteers studied under controlled conditions using a technique which lowers the whole blood ionised calcium concentration without affecting the concentrations of other electrolytes, including potassium and magnesium, which may influence the QT interval. $^{7}$ In clinical situations in which the ionised calcium concentration is lowered promptly, such as during rapid transfusion of citrated blood products, $^{22}$ increased sympathetic tone, simultaneous changes in serum potassium, and even administration of drugs known to affect ventricular repolarisation may invalidate the use of electrocardiographic monitoring as a guide to a safe transfusion rate and the need for intravenous calcium replacement. Nevertheless, further studies of a possible hysteresis relation would be of interest and importance in such patients.

The relations found in the present study parallel those describing the dynamic parathyroid hormone response to changing serum ionised calcium concentrations. $^{17}$ In the latter situation, the exaggerated production of parathyroid hormone in the face of a rapidly decreasing ionised calcium concentration constitutes a potentially important counter regulatory mechanism for maintaining calcium homeostasis. In the case of potentially deleterious QT prolongation the important response would seem to be its stabilisation and partial reversal within minutes of the whole blood ionised calcium concentration attaining a steady subnormal concentration.
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