The Relationship Between Duration of Q-T Interval and Plasma Ionized Calcium Concentration:

Experiments with Acute, Steady-state [Ca++] Changes in the Dog

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The duration of the Q-T intervals (QTI) of the electrocardiogram and some indices of hemodynamic performance were evaluated during steady-state abnormalities of ionized calcium ([Ca++]') homeostasis in 16 anesthetized closed-chest dogs. [Ca++]' was maintained approximately 60 per cent above or below normal. Progressive changes in QTI occurred for as long as 15 min after onset of steady-state alterations in [Ca++]'. With institution of a hyper- or hypocalcemic plateau, the duration of the corrected intervals between the Q-wave deflection and the origin of the T-wave deflection (Q-oT) and the Q wave and the end of the T-wave deflection (Q-T) were altered pari passu. In view of the progressive changes in QTI observed during the first 15 min of steady-state alterations in [Ca++]', the magnitude of a disturbance in calcium ion balance must be evaluated by direct [Ca++]' measurement. The data also indicate that alterations in [Ca++]' are associated with changes in both ventricular and peripheral vascular function. Hypocalcemia was associated with a step increase in left ventricular filling pressure (LVFP) from 6.8 ± 0.6 to 9.7 ± 0.7 torr, mean ± SEM, a step decrease in mean arterial blood pressure (MAP) from 109 ± 12 to 78 ± 15 torr, and a transient increase in cardiac output (CO) from 4.8 ± 0.2 to 5.7 ± 0.2 l/min, which was limited to the first 5 min of observation. With hypercalcemia, changes in CO and LVFP were insignificant, while MAP increased from 112 ± 6 to 123 ± 8 torr. (Key words: Heart: electrophysiology; cardiac output; vascular pressures. Ions: calcium.)

The most commonly known electrocardiographic manifestation of a change in plasma calcium concentration is a change in duration of the Q-T interval (QTI). In patients who had chronic abnormalities of calcium homeostasis, Bronsky and associates1 and Yu2 found an inverse relationship between QTI and plasma total calcium concentration ([Ca]). Since only the ionized moity of plasma calcium ([Ca++]') is physiologically active,3 it has been postulated that changes in [Ca++]' closely correlate with those in QTI in patients with derangement of calcium balance.4 It has been generally assumed that changes in [Ca] are associated with proportional changes in [Ca++]'. However, investigations in the experimental animal5 and in man6 have demonstrated that concentrations of total and ionized calcium may vary independently. Hence, direct measurement of [Ca++]' is of physiologic and clinical interest. Although a technique is available for rapid laboratory analysis of [Ca++]' in a specimen of whole blood,7,8 an attractive prospect would be that [Ca++]' could be estimated with reasonable accuracy at the patient's bedside by measurement of QTI. These considerations are of clinical interest in view of previous data9 showing that acute and profound changes in [Ca++]' may be encountered in critically ill patients in the absence of factors commonly known to produce such alterations in calcium ion balance.

Recent data10 obtained in patients under unsteady-state conditions have shown that QTI correlates poorly with [Ca++]'. However, some of these data were obtained during transient alterations in [Ca++]' equilibrium. To clarify the possible influence of such unsteady-state deviations of [Ca++]' from the normal range on the QTI-[Ca++]' relationship, we studied this relationship during acute, steady-state deviations of [Ca++]' from normal in the clinical range in the intact, anesthetized dog. Attending alterations in hemodynamic function were also recorded.

Methods

Unpremedicated, unfasted mongrel dogs (18–21 kg) were anesthetized with thiopenatal, 25 mg/kg, intravenously, and spontaneous inhalation of halothane, 1 per cent, in oxygen via auffed endotracheal tube. Inspired halothane concentration was confirmed using a calibrated Dräger Narkotest® analyzer. The femoral veins and arteries were cannulated. A pulmonary-artery balloon-flotation cannula (Edwards Laboratories) was placed; its position was later confirmed at post-mortem examination.

Femoral and pulmonary arterial pressures were recorded continuously on an eight-channel direct-writing oscillograph (Hewlett Packard) via appropriate transducers (Sanborn 267 BC) calibrated with a mercury manometer at frequent intervals. Pulmonary arterial balloon-occluded pressure was recorded intermittently.

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and utilized to estimate left ventricular filling pressure (LVFP)\textsuperscript{18} Mean pressures were determined by electronic integration. Cardiac output was determined by thermodilution.\textsuperscript{13} Body temperature, monitored with an esophageal temperature probe (Yellow Springs Instruments) did not vary more than 0.5 degree C in any dog. Blood-gas tensions and pH were measured by use of standard electrodes (Radiometer), which were maintained at 37 C. For every study of an individual animal, a period of at least an hour elapsed between the time of thiopental administration and the onset of the experiment.

The electrocardiogram was recorded at each measurement interval at a paper speed of 25 mm/sec and heart rate was calculated from the tracing. The duration of QT interval, determined by averaging three complexes in lead II, was identified and measured according to the method of Lepeschkin and Surawicz.\textsuperscript{19} Q-oT\textsubscript{T} and Q-T\textsubscript{T} refer to the origin and end of T-wave deflection, respectively, measured from the time of the

**Fig. 2.** Changes in QT interval and indices of hemodynamic performance during sustained hypocalcemia and hypercalcemia.

*Left,* During sustained hypocalcemia, the first 15 min of observation showed a progressive increase in duration of QT intervals. A step increase in mean pulmonary artery-occluded pressure (which was utilized to estimate left ventricular filling pressure) and a step decrease in mean arterial pressure occurred. Except for a transient increase in cardiac output, recorded for as long as 5 min, this variable was not different from control.

*Right,* During sustained hypercalcemia, the first 15 min of observation showed a progressive decrease in duration of QT intervals. Left ventricular filling pressure and cardiac output were not significantly different from control, and mean arterial pressure was increased 5 min following onset of the hypercalcemic plateau and for the remainder of the observation period.
beginning of the Q-wave deflection (Fig. 1). Correction for heart rate was made by dividing the duration of QT1 by the square root of the duration of the R-R interval.15

Ionized calcium concentration was determined in heparinized samples of whole blood by a thermostatted (37°C) automated flow-through calcium electrode system (Orion SS-20).7,8 The system was calibrated before and after each blood sample with a 1 mM solution of calcium chloride, in which pH was approximately 7.40 and sodium concentration, 150 mM. To avoid electrode drift, a two-point calibration (1 and 2 mM) was performed after measurement of approximately five blood specimens. Of particular value in our experiments was the fact that results of [Ca++] determinations were known within 3 min following withdrawal of the arterial blood specimen, permitting adjustment of the intravenous infusion rates of either citrate or calcium chloride (vide infra) such that steady-state hypo- or hypercalcemia was present.

Plasma total calcium concentration ([Ca]) was determined by EDTA titration using calcine as the indicator,16 total protein concentration (TP) by refractometry,17 sodium and potassium concentrations and osmolality by standard methods. Hypercalcemia was produced by the intravenous infusion of a 0.127 M citrate solution in dextrose (ACD) in which trisodium citrate and citric acid were present in proportions to achieve a final [Na+] of 150 mM. The dextrose concentration was 2.44 per cent. In order to study the possible effects of citrate per se (i.e., without hypercalcemia), a citrate solution was prepared as described above but calcium ion concentration was titrated to approximately 1.10 mM by addition of CaCl₂. Hypercalcemia was produced by the intravenous infusion of a 3.6 M CaCl₂ solution. NaCl was added in a proportion to make the final [Na+] equal to 150 mM. In all solutions, KCl was added to a final [K+] of 4 mM and pH was adjusted to 7.40 by addition of Tris buffer. These adjustments were necessary in order to identify effects of a change in the one variable under study ([Ca++]). Three groups of experiments were carried out.

In Group I (n = 6), hypocalcemia ([Ca++] = 0.43 ± 0.02 mM) was attained by rapid (30 sec) infusion of ACD solution, 1.5 ml/kg, and maintained by further infusion of ACD using a variable-speed infusion pump (Harvard apparatus). Electrocardiographic and hemodynamic measurements were made and arterial blood specimens were withdrawn at 15 sec, at five-minute intervals to 25 min, and then 40 and 60 min following onset of infusion.

In Group II (n = 6), a possible effect of citrate per se was studied by the intravenous infusion of ACD solution in which [Ca++] had been titrated to the normal range (1.10 mM). The infusion rate of this solution and time of measurements were identical to those employed in Group I.

In Group III (n = 4), hypercalcemia ([Ca++] = 1.66 ± 0.02 mM) was attained by rapid intravenous infusion of CaCl₂ solution (12 mg/kg, over a 30-sec period), followed by further CaCl₂ infusion at a rate sufficient to maintain steady-state hypercalcemia as documented by repeated [Ca++] analyses. Measurements were made as described for Group I. Values are given as means ± SEM. Analysis of variance was used to deter-
mine significance. Differences were considered insignificant when $P < 0.05$.

**Results**

Following infusion of the citrate solution, in which calcium ion concentration had been titrated to the normal range, the duration of QT1 and all measured hemodynamic and biochemical variables remained unchanged. Thus, an effect of citrate per se or of the infused volume could be excluded.

Acute, sustained hypocalcemia was associated with a progressive prolongation of the duration of the QT1, with no further significant increase after 15 min of observation (fig. 2). Increments in Q-oTc and Q-Tc intervals were of similar magnitudes at each observation period. Between the 15-sec and the 15-min observation periods, the difference between increases of QT1 observed at two successive observation periods was significant. The duration of the T wave remained unchanged, but the amplitude of T-wave deflection progressively decreased, and 35 min following onset of hypocalcemia, T-wave inversion was apparent (fig. 3) in each animal.

Mean arterial blood pressure (MAP) decreased and LVFP increased 15 sec after the onset of hypocalcemia (fig. 2). These variables remained significantly different from corresponding control values for the remainder of the observation period. Following an initial and transient increase, CO was not different from control 10 min following onset of the hypocalcemic plateau and for the remainder of the observation period. Heart rate remained essentially unchanged.

Acute, sustained hypocalcemia was associated with a progressive decrease in QT1 with no further decrease after 15 min (fig. 2). Incremental changes in Q-oTc and Q-Tc were of similar magnitudes at each time of observation. Between the 15-sec and 15-min observation periods, the difference between decreases in QT1 observed at two successive observation periods was significant. The duration of T wave remained unchanged. MAP was significantly increased throughout the observation period except 15 sec after onset of hypercalcemia, while LVFP and CO were not significantly different from control at any time. Heart rate gradually decreased, reaching significance at 60 min only.

In every animal, $P_{aO_2}$ was more than 150 torr, $P_{aco_2}$ ranged from 37 to 47 torr, and $\rhoH$ was between 7.31 and 7.36. Na$^+$ and K$^+$ values ranged from 146 to 150 and 3.5 and 3.8 mm, respectively. Total protein values ranged from 5.6 to 5.9 g/dl. Osmolalities ranged from 283 to 294 mOsm. During CaCl$_2$ infusion (Group III), [Ca] increased to above control, whereas during citrate infusion (Group I), a change in this variable was insignificant (table I).

**Discussion**

In this study, acute, steady-state abnormalities in [Ca$^{++}$] equilibrium were associated with progressive changes in QT1 that were apparent as long as 15 min after onset of the [Ca$^{++}$] changes. After that period, no further significant change in QT1 appeared. With institution of a hypo- or hypercalcemic plateau, the durations of Q-Tc and Q-oTc were altered pari passu and [Ca$^{++}$] was inversely related to QT1. Our observations also demonstrate that alterations in [Ca$^{++}$] produce changes in both ventricular and peripheral vascular function.

A close relationship between the duration of the QT1 and plasma calcium concentration has been known for more than 50 years. Although subsequent observations$^{18-21}$ have shown that the alterations in QT1 in effect involve the isoelectric segment between QRS and T-wave deflections (i.e., S-T segment), measurement of the duration of QT1 is more reliable, largely because of difficulties inherent to the precise identification of the R-S junction. The QT1 represents the time needed for ventricular activation and repolarization, i.e., it corresponds to mechanical systole.$^{21}$ Changes in [Ca$^{++}$] principally affect the duration of the S-T segment without a significant change in the
durations of other components of the electrocardiogram because the S-T segment is closely related to the plateau phase of the cardiac action potential. The different phases of the action potential, produced by a sequence of movements of different ions across the membrane, are the result of changes in membrane permeability that depend on membrane voltage and time. These ionic translocations may be described in terms of in- and outward currents. Inward currents tend to depolarize the membrane, while outward currents tend to repolarize it. The calcium ion is involved in a slow inward current. Although the precise mechanism of linkage of electrical events at the cell surface to activation of the contractile apparatus is still poorly understood, it seems clear that the trigger for activity of the contractile apparatus is increased myoplasmic [Ca++]]. Factors known to influence the magnitude of calcium influx during the cardiac action potential include the extracellular [Ca++]23 (which is of the order of 10^-3 M whereas the intracellular [Ca++] of the order of 10^-7 M24) and available metabolic energy within the cell.25 The amount of calcium necessary for maximum activation of contraction is 60 μM.22 However, it appears that the actual amount of calcium influx at each depolarization is sufficient for about 10 per cent activation of contractile force.26 Hence, intracellular sites are considered to be important sources of activator calcium, release of which is thought to be dependent upon the calcium inward current.22

In our experiments, steady-state alterations in [Ca++] were produced to encompass the [Ca++] range encountered clinically. Both experimental [Ca++] plateaus were initially associated with progressive changes in QT1, with no further alteration approximately 15 min after onset of each plateau. The inverse relationship between [Ca++] and QT1 (fig. 2) is a reflection of corresponding changes in the duration of cardiac action potential. Indeed, Beeler and Reuter27 and Ochi and Trautwein28 have shown that slow inward current is influenced by extracellular calcium, this current increasing with an increase and decreasing with a decrease in extracellular calcium.

In view of the progressive changes in QT1 during the initial period of steady-state alterations in [Ca++] (fig. 2), quantitative assessment of a disturbance in [Ca++] equilibrium requires direct laboratory analysis. Interpretation of the progression of changes in QT1 during each [Ca++] plateau remains speculative, as is the interpretation of hypocalcemia-induced progressive changes in the amplitude of the T wave, eventually leading to a change in T-wave polarity (fig. 3). This T-wave inversion has also been documented during severe hypocalcemia in the rabbit heart.29 These findings are noteworthy in the clinical setting since T-wave inversion secondary to severe hypocalcemia cannot be readily distinguished from that observed during severe myocardial ischemia.

In our experiments, T-wave duration remained unchanged. Therefore, changes in Q-oTc paralleled those in Q-Tc. These findings are in agreement with data obtained by Bronsky et al.1 in patients who had disturbances in calcium metabolism secondary to abnormalities in parathyroid function. Our findings are contrary to those obtained in neonates by Coletti and co-workers.10 These investigators found a substantially better correlation between Q-oTc and [Ca++] than between Q-Tc and [Ca++] . It must be pointed out, however, that in our experiments, QT1 was examined during steady-state abnormalities in [Ca++] balance without alterations of other biochemical variables.

Our data demonstrate that alterations in [Ca++] influenced both peripheral vascular and ventricular functions (fig. 2). With decreased [Ca++]1, MAP decreased, while CO was not different from control; thus, decreased systemic vascular resistance undoubtedly occurred. With increased [Ca++], MAP was increased, without a change in CO or LVFP, suggesting increased resistance to flow in the peripheral vascular bed. A responsiveness of the peripheral vasculature to [Ca++] changes was not entirely unexpected, since the calcium ion is essential for contraction of all muscles, including cardiac and vascular smooth muscle. Hinke and associates29 demonstrated a rectilinear relationship between flow resistance in an isolated segment of artery and perfusate calcium concentration in the range of approximately 0.4–1.8 mm. Increased resistance to blood flow in the dog forelimb secondary to calcium infusion was shown by Haddy et al.,31 while decreased peripheral vascular resistance is likely to have accounted for decreased arterial blood pressure observed in dogs following EDTA infusion by Medic et al.32

The presence of hypocalcemia-induced left ventricular dysfunction in our study is suggested by increased LVFP without a change in CO recorded from 10 min following onset of the hypocalcemia plateau, despite decreased MAP. A possible influence of citrate per se or its volume would be unlikely in view of our control experiments. Hypercalcemia-induced alterations in stroke volume, heart rate, and LVFP were minimal and insignificant, i.e., CO was maintained against a higher impedance to left ventricular ejection. If myocardial contractile force had remained unchanged, then a decreased CO or increased LVFP might have been expected to occur with increased MAP. On the basis of these considerations, increases of [Ca++] to
approximately 60 per cent above normal might be considered to enhance ventricular performance. However, two points deserve mention. First, this increased myocardial contractile force may not be specifically related to increased \([Ca^{2+}]_i\), and is known to occur with other interventions that increase impedance to left ventricular ejection.\(^3\) Second, ventricular pump performance is best defined by ventricular function curves obtained under experimental conditions allowing major hemodynamic determinants of ventricular function (MAP, HR) to be controlled and held constant. Recent preliminary data from this laboratory\(^4\) on describing the influence of steady-state increases in \([Ca^{2+}]_i\) to approximately 60 per cent above normal on the normal dog heart, obtained under controlled hemodynamic conditions, failed to demonstrate a significant leftward displacement of left ventricular function curves.

Finally, our data demonstrate that an abnormality in calcium homeostasis may not be apparent from \([Ca]\) measurement. Although during citrate infusion, \([Ca^{2+}]_i\) was significantly less than normal, \([Ca]\) was not. This observation, in accord with data obtained both in the experimental animal\(^5\) and in man,\(^6\) underscores the need for evaluation of disturbances in calcium homeostasis in terms of calcium ion concentration.

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