Hypercalcemia QoT QaT and QeT intervals - 2010

Dr. Andrés R. Pérez Riera

Hypercalcemia **Causes:** Hypercalcemia is divided into PTH-mediated hypercalcemia (primary hyperparathyroidism) and non–PTH-mediated hypercalcemia.

1)   PTH-mediated hypercalcemia is related to increased calcium absorption from the intestine.

2)   Non–PTH-mediated hypercalcemia includes the following:

(2.1) **Hypercalcemia associated with malignancy:** Unlike PTH-mediated hypercalcemia, the elevation of calcium that results from malignancy generally worsens until therapy is provided. Hypercalcemia caused by malignancy is the result of increased osteoclastic activity within the bone. This results from one or both of the mechanisms that follow:

(2.1-a) Extensive localized bone destruction may result from osteolytic metastasis of solid tumors. Evidence indicates that many malignant cells may release local osteoclastic activating factors.

(2.1-b) Increased calcium levels resulting from malignancy caused by a PTH-related protein is a second mechanism. This protein is a humeral factor that acts on the skeleton to increase bone reabsorption; it acts on the kidney to decrease excretion of calcium. The gene that produces this protein is present in many malignant tissues.

(2.2)   **Granulomatous disorders:** High levels of calcitriol may be found in patients with sarcoidosis and other granulomatous diseases. In these disorders, the increased level of calcitriol results from production within the macrophages, which constitute a large portion of some granulomas.

(2.3)   **Iatrogenic:** In some cases, elevation of calcium is a known adverse effect of appropriate dosage. In other cases, large ingestions must be taken to induce the increase in calcium levels.

Obtain a complete review of current medications for patients presenting with hypercalcemia. Record any vitamin use.

(2.4) Other causes of hypercalcemia

(2.4-1) Neoplasms (nonparathyroid) - Metastasis to the bone from breast, multiple myeloma, and hematologic malignancies (Breast cancer is one of the most common malignancies responsible for hypercalcemia.);

(2.4-2) Nonmetastatic (humoral-induced) - Ovary, kidney, lung, head and neck, esophagus, cervix, lymphoproliferative disease, multiple endocrine neoplasia, pheochromocytoma, and hepatoma.

(2.4-3) Pharmacologic agents - Thiazide, calcium carbonate (antacid), hypervitaminosis D, hypervitaminosis A, lithium, milk-alkali syndrome, and theophylline toxicity.

(2.4-4) Endocrinopathies (nonparathyroid) - Hyperthyroidism, adrenal insufficiency, and pheochromocytoma.

(2.4-5) Familial hypocalciuric hypercalcemia.

(2.4-6) Tertiary hyperparathyroidism - Postrenal transplant and initiation of chronic hemodialysis.

(2.4-7) Miscellaneous - Immobilization, hypophosphatasia, primary infantile hyperparathyroidism, AIDS, and advanced chronic liver disease

ECG FEATURES IN HYPERCALCAEMIA

Hypercalcemia may produce ECG abnormalities related to altered trans-membrane potentials that affect conduction time.

QT interval shortening is common secondary to absence of the ST segment. The QoT, QaT, and QeT intervals which are measured from the beginning of the QRS complex to the origin (O), apex (A), and the end (E) of the T wave, respectively are very short. At very high levels, the QRS interval may lengthen, T waves may flatten or invert and a variable degree of heart block may develop.

Heart rate (HR) Symptomatic sinus node dysfunction: It is very rarely observed. *Shah AP, Lopez A, Wachsner RY, et.al.Sinus node dysfunction secondary to hyperparathyroidism. **J Cardiovasc Pharmacol Ther. 2004; 9:145-147.*** There is description of tachy-brady syndrome. (*Carpenter C, May ME, Case report: cardiotoxic calcemia. Am J Med Sci 1994; 307: 43-44.*);

PR or PQ interval is prolonged in some cases. The PR interval tended to be prolonged in the case of hypercalcemia, but the change was

statistically insignificant. *(Saikawa T, Tsumabuki S, Nakagawa M, QT intervals as an index of high serum calcium in hypercalcemia. Clin Cardiol. 1988;11:75-78.)*

ST segment: Absence of the ST segment or almost absent is the rule. The ST reduces or retrenches in length or duration. When ST is present could be depressed or with ST segment elevation mimicking acute myocardial infarction. *(Nishi SP, Barbagelata NA, Atar S, Birnbaum Y, Tuero E. Hypercalcemia-induced ST-segment elevation mimicking acute myocardial infarction. J Electrocardiol. 2006 Jul;39(3):298-300.) (Littmann L, Taylor L 3rd, Brearley WD Jr.ST-segment elevation: a common finding in severe hypercalcemia. J Electrocardiol. 2007;40:60-62.) (Turhan S, Kilickap M, Kilinc S ST segment elevation mimicking acute myocardial infarction in hypercalcaemia. Heart. 2005;91:999.) (Ashizawa N, Arakawa S, Koide Y, ET AL . Hypercalcemia due to vitamin D intoxication with clinical features mimicking acute myocardial infarction. Intern Med. 2003; 42:340-344.).* J point is the isoelectric union of QRS complex with ST segment. It represents the end of depolarization and the beginning of repolarization. Prominent and positive J point level is named J wave, considered typical but not pathognomonic of severe hypothermia, because it has also been described in hypercalcemia *Carrillo-Esper R, Limon-Camacho L, Vallejo-Mora HL, et al.Non-hypothermic J wave in subarachnoid hemorrhage Cir Cir. 2004;72:125-129.* and others clinical circumstances: Non-hypothermic J wave or the "normothermic" Osborn wave *(Otero J, Lenihan DJ. The "normothermic" Osborn wave induced by severe hypercalcemia. Tex Heart Inst J. 2000;27:316-317)*: . Electrocardiographic J wave could be result of hypercalcemia aggravated by thiazide diuretics *(Topsakal R, Saglam H, Arinc H, Eryol NK, Cetin S. Electrocardiographic J wave as a result of hypercalcemia aggravated by thiazide diuretics in a case of primary hyperparathyroidism. Jpn Heart J. 2003;44(6):1033-1037.;*

T wave becomes flatten or invert in hypercalcemia. Secondly, flattened or biphasic T waves are prominent in moderate to severe hypercalcemia, mimicking those seen in myocardial ischemia **(*Douglas PS, Carmichael KA, Palevsky PM. Extreme hypercalcemia and electrocardiographic changes. Am J Cardiol 54: 674–675, 1984.*).** Changes in T wave morphology, polarity, and amplitude either appeared with development of hypercalcemia or disappeared with normalization of serum calcium level. In addition to shortening the QT interval, severe to extreme hypercalcemia can cause development of inverted, biphasic, or notched T wave with a marked decrease in amplitude of T waves. **(*Ahmed R, Yano K, Mitsuoka T, Ikeda S, Ichimaru M, Hashiba K. Changes in T wave*

morphology during hypercalcemia and its relation to the severity of hypercalcemia. J Electrocardiol 1989; 22: 125–132,).

QT or QTe interval: the QT interval sometimes is shortened. The corrected QT intervals (QTc), particularly the QaTc interval, are reliable indicators of clinical hypercalcemia **(*Ahmed R, Hashiba K. Reliability of QT intervals as indicators of clinical hypercalcemia. Clin Cardiol1988; 11: 395–400,*)(*Nierenberg DW, Ransil BJ. Q-aTc interval as a clinical indicator of hypercalcemia. Am J Cardiol 1979; 44: 243–248,*).** From 74 patients (hypocalcemia: 41 patients, hypercalcemia 13 patients, 20 patients as control) without heart disease examined, a prolongation of the relative QT-interval was found in 90% and a flat or inverted T-wave in 25% of the patients with hypocalcemia. In 77% of the patients with hypercalcemia the QT-interval was shortened. A good, clinically useful correlation between the QT-interval and the serum calcium-concentration could be established in patients with hypocalcemia and hypercalcemia. *(So CS, Batrice L, Volger E.Electrocardiographic changes in electrolyte inbalance. Part 2: Alterations in serum calcium Med Klin. 1975; 70: 1966-1968.).*

Sensitivity of QoTc, QaTc, and QeTc in predicting high serum calcium concentration is 83%, 57%, and 39%, respectively, and specificity is 100%, 100%, and 89%.These observations suggest that QT intervals can serve as an indicator of high serum calcium concentration and that the QoTc seems to be a good indicator of the three QTc's. *(Saikawa T, Tsumabuki S, Nakagawa M, QT intervals as an index of high serum calcium in hypercalcemia. Clin Cardiol. 1988; 11:75-78.)*

Q-aTc: Very short **Q-aTc** interval. This interval is measured from the beginning of QRS complex to apex of T wave corrected for heart rate. Q-aTc interval is the more easily and precisely measured at elevated calcium levels and exhibited the strongest correlation over the range of calcium levels measured. The relation is linear and could be used to estimate serum calcium levels from measured Q-aTc intervals. When all other factors known to affect the Q-T interval are ruled out, the shortening of the Q-aTc interval (≤270ms) appears to be a useful clinical indicator of hypercalcemia. Hypermagnesemia normalizes the QaTc interval, which is usually shortened by isolated hypercalcemia. Combined hypercalcemia and hypermagnesemia can be caused by swallowing excessively salty water.

Q-oTc: Very short **Q-oTc** interval. This interval is measured from the beginning of QRS complex to onset of T wave corrected for heart rate.

Moderate hipercalcemia, in spite of causing a shortening of the repolarization phase (QT-interval), has no clinically significant effect on

cardiac conduction.(*Rosenqvist M, Nordenstrom J, Andersson M, et al.Cardiac conduction in patients with hypercalcaemia due to primary hyperparathyroidism. Clin Endocrinol (Oxf). 1992; 37:29-33*.) ;

The correlation between serum ionized calcium (Ca++) levels and three ECG QT intervals (Q-oTc, Q-aTc and Q-eTc) was assessed in 20 adult patients. The relationship between each QT interval and Ca++ level, based on 209 Ca++ determinations through a range of 1.0 to 4.0 mEq/ liter, is best described by a hyperbolic function. Although Q-oTc, and Q-aTc predict Ca++ levels more accurately than Q-eTc, all QT intervals are clinically unreliable as guides to the presence of hypercalcemia. Similarly, the usefulness of the QT intervals in the diagnosis of hypocalcemia is limited by the wide distribution of normal values. (*Rumancik WM, Denlinger JK, Nahrwold ML, et al. The QT interval and serum ionized calcium. JAMA. 1978;240:366-368.*).

Corrected QT intervals were determined in 13 patients with severe chronic hypercalcemia. The Qo-Tc interval was short in only 2 of 14 instances; Qa-Tc in 5 of 15 instances, and Qe-Tc in 5 of 16 instances. The correlations between serum calcium and the QTc measurement were not significant when evaluating either linear or curvilinear (quadratic) relationships. Small and inconsistent changes were found when comparing the QT intervals before the development of the hypercalcemic episode, during hypercalcemia, or after successful treatment. The authors conclude that shortening of the QT interval is an unreliable index of clinical (chronic) hypercalcemia. (*Wortsman J, Frank S. The QT interval in clinical hypercalcemia. Clin Cardiol. 1981; 4: 87-90.*).

The Q-Tc interval is not a useful clue to the presence of hypercalcemia. Hypercalcemia of greater than 13 mg/dl (3.25 mM/L) was unaccompanied by ECG changes. (*Ellman H, Dembin H, Seriff N.The rarity of shortening of the Q-T interval in patients with hypercalcemia. Crit Care Med. 1982;10:320-322*).

Exceptionally Long QT interval was described in severe hypercalcemia. *Ortega-Carnicer J, Ceres F, Sanabria C. Long QT interval in severe hypercalcaemia. Resuscitation. 2004;61:242-243.*

Acute hyperparathyroidism developed in a previously normocalcemic 64-year-old woman during the first week after a coronary operation. Prolonged QT interval in the ECG and hypercalcemia were documented on the fourth postoperative day. Neck exploration on the fifth postoperative day revealed a lower right parathyroid adenoma. Parathyroidectomy resulted in rapid and dramatic improvement of the clinical picture and normalization of laboratory values. (*Siclari F, Herrmann G, Dralle H. Acute hypercalcemic crisis after an open heart operation. Ann Thorac Surg. 1990; 50:831-832.*).

Hypercalcemia QoT QaT and QeT intervals and Antzelevitch syndrome relationships

The QT interval can be divided into **QoT, QaT,** and **QeT** intervals, which are measured from the beginning of the QRS complex to the origin (O), apex (A), and the end (E) of the T wave, respectively. (See Figure 1)

QT intervals are corrected for heart rate by Bazett's formula

QTc = QT/square root of R-R.

$$QTc = \frac{QT\ measured}{\sqrt{RR}}$$

Figure 1

Antzelevitch Case 1A

Q-aT: 240ms
Extremely short.
ST-segment is absent
Conclusion: This mutation has hyperkalcemic like pattern.
Values <270ms are typical of severe Hyperkalemia.

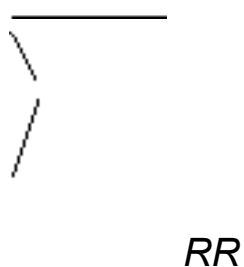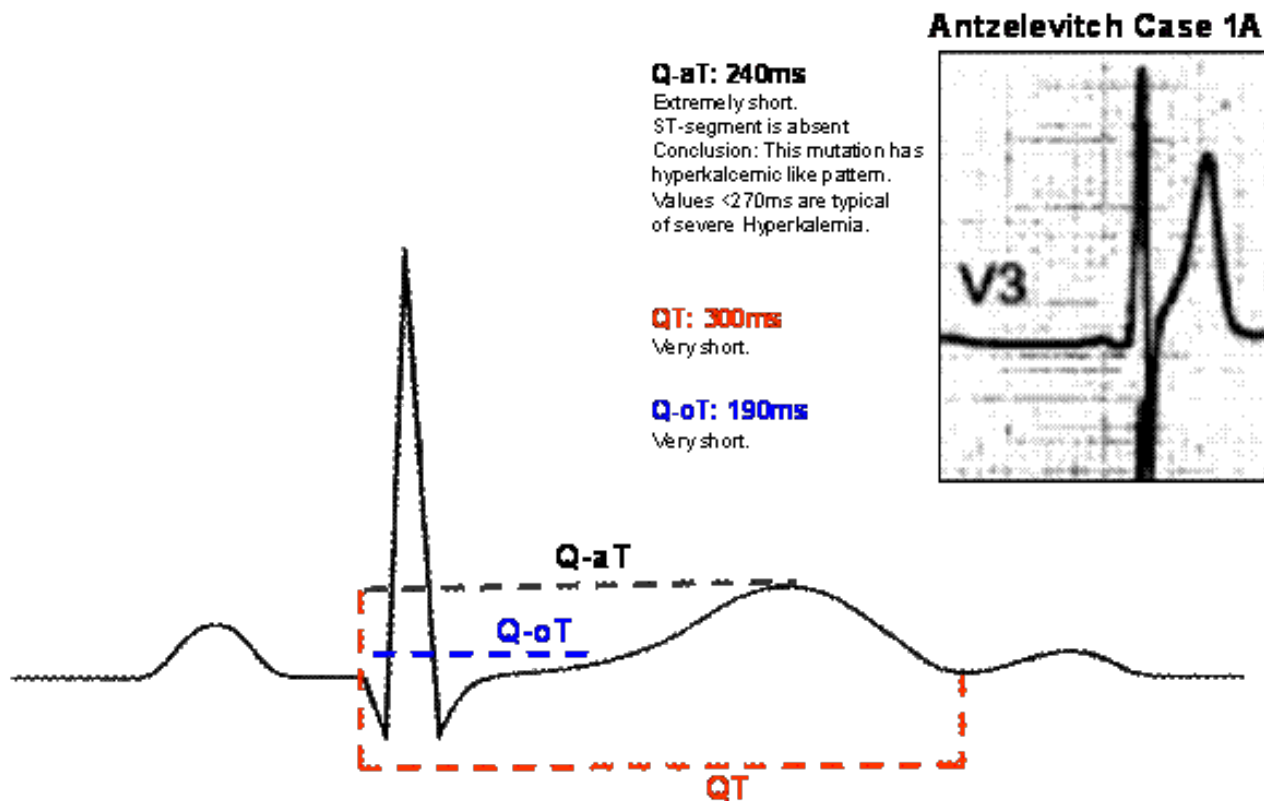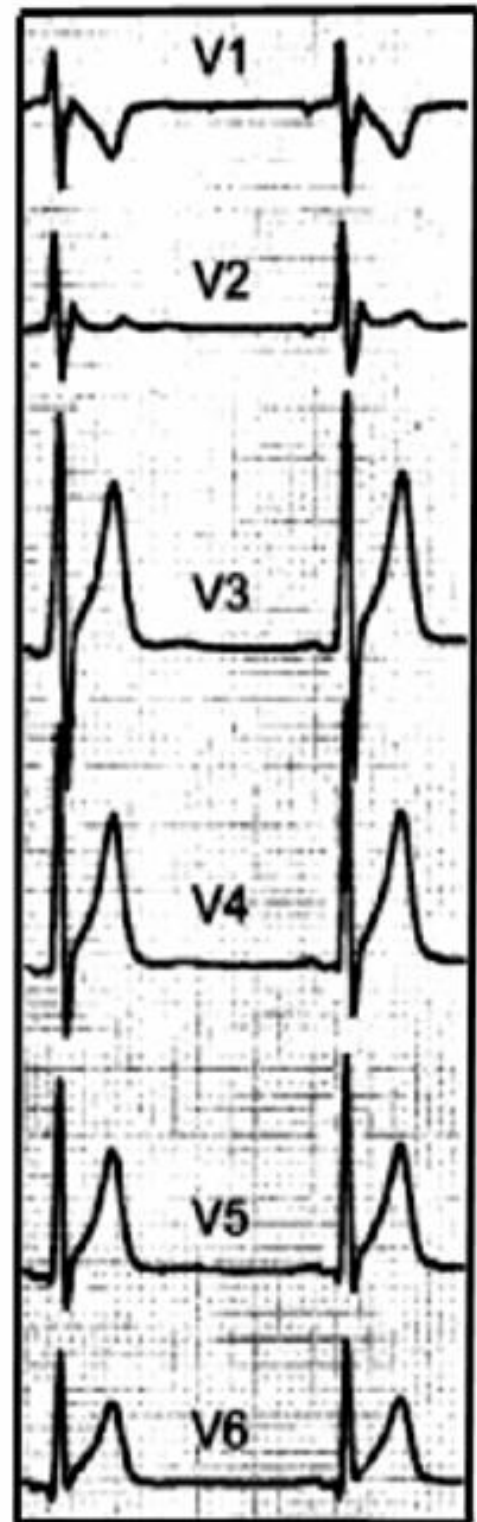QT: 300ms
Very short.

Q-oT: 190ms
Very short.

Q-aT

Q-oT

QT

A Patient 1

Baseline

A 25-year-old white male of European descent, presented with aborted SCD. QTc was 330 ms, and a coved-type ST-segment elevation was observed in V1 and V2 after an ajmaline challenge.

Antzelevitch C , Pollevick GD, Cordeiro JM,et al. Loss-of-Function Mutations in the Cardiac Calcium Channel Underlie a New Clinical Entity Characterized by ST-Segment Elevation, Short QT Intervals, and Sudden Cardiac Death. Circulation. 2007 Jan 30;115(4):442-9.

Q-aTc: From the beginning of QRS complex to apex of T wave corrected for heart rate. Q-aTc interval is the more easily and precisely measured at elevated calcium levels and exhibited the strongest correlation over the range of calcium levels measured. The relation is linear and could be used to estimate serum calcium levels from measured Q-aTc intervals.

When all other factors known to affect the Q-T interval are ruled out, the **shortening of the Q-aTc interval (≤270ms) appears to be a useful clinical indicator of hypercalcemia.**

ECG changes of severe hypercalcemia (>14 mg/dl) can mimic acute myocardial infarction or Brugada sign. Calcium shortens phase 2 of the cardiac muscle action potential, leading to shortening of the ST segment. As the ST segment is difficult to measure however, QT intervals have been used to evaluate the ECG effects of hypercalcemia. The shortening of QaTc seen in hypercalcemia produces a high takeoff of the ST segment simulating acute myocardial ischemia or Brugada syndrome. ST-segment elevation is a common finding in severe hypercalcemia. These are causes of non-hypothermic J wave: hypercalcemia, Brugada syndrome, acute brain injury, cardiac arrest, dysfunction of cervical sympathetic system and others.

In this case of Antzelevitch et al, the Q-aTc interval is very short and after Ajmaline test the authors observed the Brugada type 1 patter.

Conclusion: this mutation has a phenotype "hypercalcemic like".

Heart Rate Variability: Primary hyperparathyroidism (pHPT) patients lacked the circadian rhythm of the low frequency to high frequency ratio, suggesting an increased sympathetic drive to the heart at nighttime. A modulation of the adrenergic control of circulation seems to be associated with hypercalcemia and/or chronic PTH excess, but its biological relevance needs further investigations. (*Barletta G, De Feo ML, Del Bene R, et al. Cardiovascular effects of parathyroid hormone: a study in healthy subjects and normotensive patients with mild primary hyperparathyroidism. **J Clin Endocrinol Metab. 2000 May; 85:1815-1821**.*). Sympathetic vascular tone, is modulated in part by calcium in normal man. Calcium contributes to the regulation of rhythmic oscillations in blood pressure. (*Munakata M, Imai Y, Mizunashi K, et al.The effect of graded calcium infusions on rhythmic blood pressure oscillations in normal man. : **Clin Auton Res. 1995; 5:5-11**.*)

QT dispersion: hypercalcemia affect ventricular repolarization, is not associated with increased   QT dispersion. (*Yelamanchi VP, Molnar J, Ranade V, et al. Influence of electrolyte abnormalities on interlead variability of ventricular repolarization times in 12-lead electrocardiography. **Am J Ther. 2001 ; 8:117-122.** *).

Arrhythmias and Hipercalcemia:

Holter monitoring was performed in eight patients with advanced breast cancer and paraneoplastic hypercalcemia. In spite of several reports of cardiac arrhythmias, none were found in these patients. *(Lazzari R, Pellizzari F, Brusaferri A, et al.Hypercalcemia and changes in cardiac rythm Minerva Med. 1991;82:255-257.)*. Hypercalcemia seemed to decrease atrial activity and increase ventricular activity, as evidenced by the appearance of bradycardia, sinus arrest, and Premature Ectopic Beats. Vagal activity seemed altered by the changes in plasma calcium concentrations and involved in the production of the arrhythmia, because atropine could abolish the arrhythmia created by the infusion of the calcium solutions. *(Littledike ET, Glazier D, Cook HM. Electrocardiographic changes after induced hypercalcemia and hypocalcemia in cattle: reversal of the induced arrhythmia with atropine. Am J Vet Res. 1976; 37:383-388.)*. Rarely in Hipercalcemia was observed: **s**pontaneous attacks of ventricular tachycardia: *Chang CJ, Chen SA, Tai CT, et al. Ventricular tachycardia in a patient with primary hyperparathyroidism. Pacing Clin Electrophysiol. 2000; 23: 534-537* **and exceptionally ventricular fibrillation.** Only one case described in the literature *Kiewiet RM, Ponssen HH, Janssens EN, et al. Ventricular fibrillation in hypercalcaemic crisis due to primary hyperparathyroidism. Neth J Med. 2004;62:94-96*.

The electrocardiographic abnormalities in combined hypercalcaemia and hypokalaemia are: absence of the ST segment, prolonged T wave, a shortened **Q-aTc** interval and prominent U waves. (*Chia BL, Thai AC. Electrocardiographic abnormalities in combined hypercalcaemia and hypokalaemia--case report. Ann Acad Med Singapore. 1998; 27:567-569*.).

The electrocardiographic abnormalities in combined hypercalcaemia and hypermagnesemia:
Combined hypercalcemia and hypermagnesemia can be caused by swallowing excessively salty water. Common findings included P wave changes, tendency for prolongation of P-R interval, prolongation of QRS complex, infra-His conduction disturbances, tendency for broadening and inversion of T wave, and the appearance of a prominent U wave. Hypermagnesemia normalizes the QaTc interval, which is usually shortened by isolated hypercalcemia. *(Mosseri M, Porath A, Ovsyshcher I, et al. Electrocardiographic manifestations of combined hypercalcemia and hypermagnesemia. J Electrocardiol. 1990; 23:235-241.)*

Digoxin effects are amplified in Hipercalcemia.
The combined effects of digoxin and hypercalcaemia were studied in the canine heart in situ on the sinoatrial (SA) and atrioventricular (AV) nodes. Measurements were made of heart rate, of conduction time in the AV node by the endocavitary recording of the His bundle potentials, and of the effective refractory period of this node by the extrastimulus method. In the presence of acetylcholine released by vagal endings or infused into the coronary blood, an increase in plasma calcium concentration from 2.50 to 4.60 mmol/l after a 80 micrograms/kg dose of digoxin considerably depressed conduction in the AV node and automatism in the SA node. In the absence of acetylcholine, no bradycardia occurred under the influence of digoxin alone or digoxin and hypercalcaemia, and hypercalcemia enhanced to a lesser extent digoxin-induced depression of conduction in the AV node. These results evidence a potentiation by acetylcholine of the combined effects of digoxin and hypercalcaemia on the SA and AV nodes. *(Lang J, Lakhal M, Timour Chah Q, et al.Vagal role in potentiation by Ca2+ ions of the action of cardiac glycosides on the atrial specialised tissue. J Pharmacol. 1985;16:125-137.)*

See table 1

Table 1
Classification proposal for ECG waves located in the J point
A) J wave
I)   J wave in hypothermia;
II)   J wave in normothermia
        IIa) Hypercalcemia;
         IIb) Nervous system injuries: acute brain injury i.e. subarachnoid hemorrhage, cardiac arrest, and dysfunction of the cervical sympathetic system
        IIc) Early repolarization syndrome (rare).
        IId) Brugada entities:
            (IId1) Familial cases: » 17% Brugada **disease**;
                (IId2) The sporadic cases » 63% Brugada **syndrome**. A genetic basis and the value of mutation screening has to be further determined.
                (IId3) Acquired: A number of drugs and conditions have been reported to   induce transient Brugada-like ST segment elevation. (Brugada sign). hese are named "acquired" forms of Brugada entity similar to the "acquired" forms of long QT syndrome
                (IId4) Antzelevitch syndrome: Short QaT, Q-oT, Q-eT or QT intervals + Brugada signal after ajmaline secondary to mutation in

CACNA1C calcium channel, voltage-dependent, L type, alpha 1C subunit (See characteristics at end)

B) Epsilon wave:
1) Present in a 30% of patients ARVC/D;
2) Ulh's anomaly (Exceptionally observed);
3) Association with coronary heart disease and aortic valve replacement and revascularization surgery.
4) Right ventricular infarction.

The corrected QT intervals (QTc), particularly the QaTc interval, are reliable indicators of clinical hypercalcemia *(Ahmed R, Hashiba K. Reliability of QT intervals as indicators of clinical hypercalcemia. Clin Cardiol 11: 395–400, 1988., Nierenberg DW, Ransil BJ. Q-aTc interval as a clinical indicator of hypercalcemia. Am J Cardiol 44: 243–248, 1979.)*, with abnormal QaTc (<300ms) being observed in moderate to severe hypercalcemia. Secondly, flattened or biphasic T waves are prominent in moderate to severe hypercalcemia, mimicking those seen in myocardial ischemia *(Douglas PS, Carmichael KA, Palevsky PM. Extreme hypercalcemia and electrocardiographic changes. Am J Cardiol 54: 674–675, 1984.)* *(Ahmed R, Yano K, Mitsuoka T, Ikeda S, Ichimaru M, Hashiba K. Changes in T wave morphology during hypercalcemia and its relation to the severity of hypercalcemia. J Electrocardiol 22: 125–132, 1989.)*.

Q-oTc From the beginning of QRS complex to onset of T wave.

CACNA1C calcium channel, voltage-dependent, L type, alpha 1C subunit [Homo sapiens]
This gene encodes an alpha-1 subunit of a voltage-dependent calcium channel. Calcium channels mediate the influx of calcium ions into the cell upon membrane polarization. The alpha-1 subunit consists of 24 transmembrane segments and forms the pore through which ions pass into the cell. The calcium channel consists of a complex of alpha-1, alpha-2/delta, beta, and gamma subunits in a 1:1:1:1 ratio. There are multiple isoforms of each of these proteins, either encoded by different genes or the result of alternative splicing of transcripts. The protein encoded by this gene binds to and is inhibited by dihydropyridine. Many alternate transcriptional splice variants of this gene have been observed but have not been thoroughly characterized

Official Symbol: CACNA1C

Official Full Name: calcium channel, voltage-dependent, L type, alpha 1C subunit

Primary source: HGNC: 1390

See related HPRD: 00246; MIM:114205.

Gene type: protein coding

Ref Seq status: Reviewed.

Organism: Homo sapiens.
Lineage: Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; ; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo

Also known as: TS; CACH2; CACN2; CaV1.2; CCHL1A1; CACNL1A1; MGC120730

CACNB2