Hypercalcemia
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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 transmembrane 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.


**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.*

**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

**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 Cardiol 1988; 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 imbalance. 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 ($\leq 270$ms) 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.


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.\(^\text{(Rumancik WM, Denlinger JK, Nahrwold ML, et al. The QT interval and serum ionized calcium. JAMA. 1978;240:366-368.)}\)

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

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.
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.


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...


Arrhythmias and Hypercalcemia:


The electrocardiographic abnormalities in combined hypercalcaemia and hypokalaemia are: absence of the ST segment, prolonged T wave, a

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 Hypercalcemia.
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 hypercalcemia 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);

IIId) 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. These 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.

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**