EDITORIAL

Electrocardiographic Manifestations of Calcium Abnormalities

Ehud Chorin, M.D., Ph. D.,*† Raphael Rosso, M.D.,*† and Sami Viskin, M.D.*†

From the *Department of Cardiology, Tel Aviv Sourasky Medical Center, Tel Aviv University, Tel Aviv, Israel and †Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

Ann Noninvasive Electrocardiol 2016;21(1):7–9

The cardiac action potential is generated through voltage-gated ion channels allowing flow of ion currents through specific channels embedded in the cell membrane. Not surprisingly, abnormal serum electrolyte levels alter cardiac ion current kinetics. Depending on the alteration, changes in serum electrolyte concentrations affect cardiac conduction, alter the electrocardiogram (ECG), and can be arrhythmogenic or antiarrhythmic. Life-threatening arrhythmias are most commonly associated with potassium disorders, particularly hyperkalemia, and less commonly with disorders of serum calcium (Ca) and magnesium. In some cases, timely diagnosis of electrolyte abnormalities is crucial and emergency therapy for presumed life-threatening electrolyte disorders are often initiated, based on diagnostic ECG changes, even before laboratory results become available.¹

In this issue of *Annals of Noninvasive Electrocardiology*, Sonoda et al.² analyzed the effects of hypercalcemia on the ECG, focusing on its effects on J point elevation and arrhythmias. They compared the ECG of 89 patients with

hypercalcemia (serum Ca level, corrected for serum albumin, >12 mg/dL) with those of 267 age- and sex-matched healthy controls. They found that hypercalcemia was associated with *prolongation* of the PR and QRS intervals (by 12 and 7 milliseconds, respectively) but *shortening* (by 24 milliseconds) of the QT interval. Interestingly, they found an increased incidence of J waves among patients with hypercalcemia (30% vs. 9%, $P < 0.001$). Furthermore, they found J point elevations with various morphologies, including J point with scooped appearance and ST segment elevation, as well as Brugada-type ECG findings and early repolarization. Among 11 patients with J point elevation in the setting of hypercalcemia that underwent a repeated ECG recording after the hypercalcemia resolved, J point elevation disappeared in 8 patients (73%), and the frequency of J point elevation became similar to that seen among controls. In spite of these ECG changes, no arrhythmic events occurred in patients with hypercalcemia. This study confirms and expands previously published data showing an association between hypercalcemia and J point elevation.³

Address for correspondence: Sami Viskin, M.D., Department of Cardiology, Tel Aviv Sourasky Medical Center, Weizman 6, Tel Aviv 64239, Israel. Tel: +972536973311; Fax: +97236972749; E-mail: samiviskin@gmail.com

Conflicts of interest: None.

Financial Disclosures: None.

ELECTROCARDIOGRAPHIC MANIFESTATIONS OF HYPERCALCEMIA

Hypercalcemia is a relatively frequent medical condition. Among its many causes, the most common are cancer and primary hyperparathyroidism.⁴ The QT shortening effects of rising serum calcium levels have been known for years.⁵ This observation is counterintuitive because increased extracellular concentrations of calcium would be expected to increase inward Ca flow during the late stages of repolarization, actually prolonging the QT interval. In fact, elevated extracellular Ca concentration has a stabilizing effect on the membrane, increasing the extent of depolarization needed to initiate an action potential.⁶ A study of the effect of hypercalcemia on the guinea pig ventricular action potential suggested that this decrease in the inward Na/Ca exchange current is largely responsible for the shortening of the action potential.⁷ The correlation between the duration of the QT interval and the serum calcium level, however, is not linear. The QT_{peak} interval (from the beginning of the QRS complex to the apex of the T wave) is particularly shortened during hypercalcemia. In fact, the QT_{peak} interval correlates best with the serum calcium level.⁵ In cases of severe hypercalcemia (serum calcium >16 mg/dL), the duration of the T wave can increase and the QT interval may seem normal even though the ST segment remains shortened.⁸ Successful surgical correction of hyperparathyroidism with reduction in serum calcium concentrations can result in lengthening of the QT and QTc intervals.⁹

Additional ECG abnormalities that may occur in patients with severe hypercalcemia include ST segment elevation, biphasic T waves, and prominent U waves.¹⁰ Changes in T wave morphology, polarity, and amplitude appears with development of hypercalcemia and disappears with normalization of serum calcium level. Flattened or biphasic T waves are prominent in moderate to severe hypercalcemia, mimicking those seen in myocardial ischemia.¹¹ Severe to extreme hypercalcemia can cause development of inverted, biphasic, or notched T wave with a marked decrease in amplitude of T waves.¹²

The association between increased J wave amplitude and hypercalcemia is intriguing. Already in 2003, the Second Consensus Report

on Brugada Syndrome mentioned hypercalcemia and hypokalemia among the causes of "acquired Brugada syndrome"¹³ or "Brugada phenocopy."¹⁴ The ability of increased $[Ca^{2+}]_0$ to accentuate the action potential notch in ventricular epicardium, but not endocardium, and to induce phase 2 reentry was described by Di Diego and Antzelevitch in 1994.¹⁵ This transmural heterogeneity in the early phases of the action potential is the basis for the electrocardiographic inscription of the J wave and its accentuation has been shown to contribute to the augmentation of J waves, giving rise to the J wave syndromes, including Brugada and early repolarization syndromes.^{16,17} The ionic mechanisms underlying the effect of elevated extracellular Ca to accentuate the J waves are thought to include an increase in calcium-activated chloride current ($I_{CL(Ca)}$) secondary to elevation of intracellular levels of Ca,^{18,19} as well as to a reduction of inward sodium and calcium currents secondary to the ability calcium to screen surface charge.²⁰

Interestingly, there are several hereditary conditions associated with deviation of calcium homeostasis, and hereditary arrhythmic disorders. In Brugada syndrome, the archetypal SCN5A mutation leads to loss of sodium channel function but loss-of-function mutations in CACNA1C and CACNB2, responsible for the channels lead to a phenotype of Brugada syndrome with shorter QT intervals.²¹ Conversely, a gain-of-function mutation of the CACNA1C results in Timothy syndrome.²² This gain-of-function mutation results in an impaired open-state voltage-dependent inactivation of the L-type calcium channel, ultimately leading to a markedly prolonged myocardial action potential, clinically characterized by long QT syndrome and syndactyly.²²

ELECTROCARDIOGRAPHIC MANIFESTATIONS OF HYPOCALCEMIA

Hypocalcemia is most commonly caused by hypoalbuminemia, usually related to cirrhosis, nephrosis, malnutrition, burns, chronic illness, and sepsis. Reddy²³ and Khardori²⁴ each separately described a patient with an acute anteroseptal injury pattern on the ECG with no proven subsequent infarction, which they associated with hypocalcemia. In both examples, the patients

involved had complicated coexisting medical problems with associated electrolyte imbalance. Hence, although rarely reported, hypocalcemia can be associated with ST segment elevation, mimicking an acute myocardial infarction or T wave abnormalities.²⁵ It has been speculated that these ECG abnormalities may be attributed to coronary artery spasm.^{26,27} Most commonly, the characteristic ECG manifestation of hypocalcemia is prolongation of the QT interval as a result of lengthening of the ST segment.⁸ Hypocalcemia prolongs the duration of phase 2 of the action potential of cardiac muscle. Furthermore, calcium channel function and calcium influx during phase 2 are modulated by the rate of change of extracellular calcium, all of which impact the QT interval.²⁸ The QT interval prolongation is proportional to the degree of hypocalcemia; nevertheless, the QTc rarely exceeds 140% of normal.²⁵ The T waves are typically normal in duration, amplitude and morphology. Decreased T wave voltage, T wave flattening, terminal T wave inversion, or deeply inverted T waves have rarely been described in cases of severe hypocalcemia.²⁹ Of note, concomitant hypomagnesemia can exacerbate the ECG manifestations of hypocalcemia. Cases of torsade de pointes blamed on hypocalcaemia have been reported³⁰ but these cases usually had additional (QT-prolonging) confounders.

REFERENCES

- Viskin S, Antzelevitch C, Rosso R. Call the cleaners: how to treat drug-induced torsade de pointes. *J Am Coll Cardiol Clin Electrophysiol* 2015 [in press].
- Sonoda K, Watanabe H, Hisamatsu T, et al. High frequency of early repolarization and brugada-type electrocardiograms in hypercalcemia. *Ann Noninvasive Electrocardiol* 2015 [this issue].
- Sridharan MR, Horan LG. Electrocardiographic J wave of hypercalcemia. *Am J Cardiol* 1984;54(6):672-673.
- Stewart AF. Hypercalcemia associated with cancer. *N Engl J Med* 2005;352:373-379.
- Wortzman J, Frank S. The QT interval in clinical hypercalcemia. *Clin Cardiol* 1981;4(2):87-90.
- Weidmann S. Effects of calcium ions and local anesthetics on electrical properties of Purkinje fibers. *J Physiol* 1955;129:568-582.
- Leitch SP, Brown HF. Effect of raised extracellular calcium on characteristics of the guinea pig ventricular action potential. *J Mol Cell Cardiol* 1996;28:541-551.
- Slovic C, Jenkins R. Conditions not primarily affecting the heart. *BMJ* 2002;324:1320-1323.
- Vázquez-Díaz O, Castillo-Martínez L, Orea-Tejada A, et al. Reversible changes of electrocardiographic abnormalities after parathyroidectomy in patients with primary hyperparathyroidism. *Cardiol J* 2009;16:241-245.
- Marriott HJ. Miscellaneous conditions. In: Marriott HJ (ed.): *Practical Electrocardiography*, 8th Edition. Philadelphia, Williams & Wilkins, 1988. pp. 511-543.
- Douglas PS, Carmichael KA, Palevsky PM. Extreme hypercalcemia and electrocardiographic changes. *Am J Cardiol* 1984;54:674-675.
- 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.
- Antzelevitch C, Brugada P, Borggrefe M, et al. Brugada syndrome report of the second consensus conference. *Circulation* 2005;111:659-670.
- Baranchuk A, Nguyen T, Ryu MH, et al. Brugada phenocopy: new terminology and proposed classification. *Ann Noninvasive Electrocardiol* 2012;17:299-314.
- Di Diego JM, Antzelevitch C. High [Ca²⁺]-induced electrical heterogeneity and extrasystolic activity in isolated canine ventricular epicardium. Phase 2 reentry. *Circulation* 1994;89:1839-1850.
- Yan GX, Antzelevitch C. Cellular basis for the Brugada syndrome and other mechanisms of arrhythmogenesis associated with ST segment elevation. *Circulation* 1999;100:1660-1666.
- Yan GX, Antzelevitch C. Cellular basis for the electrocardiographic J wave. *Circulation* 1996;93:372-379.
- Hiraoka M, Kawano S, Hirano Y, et al. Role of cardiac chloride currents in changes in action potential characteristics and arrhythmias. *Cardiovasc Res* 1998;40:23-33.
- Zygmunt AC. The calcium-activated conductance, Ito2, in canine ventricle is a chloride current. *Biophys J* 1993;64:389 Abstract.
- Weidmann S. Effect of calcium and local anaesthetics on electrical properties of Purkinje fibres. *J Physiol (Lond)* 1955;129:568-582.
- Antzelevitch C, Pollevick G, Cordeiro J, 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;115:442-9.
- Splawski I, Timothy KW, Sharpe LM, et al. Ca (V)1.2 calcium channel dysfunction causes a multisystem disorder including arrhythmia and autism. *Cell* 2004;119:19-31.
- Reddy C, Gould L, Gomprecht R. Unusual electrocardiographic manifestations of hypocalcemia. *Angiology* 1974;25:764-768.
- Khadori R, Cohen B, Taylor D, et al. Electrocardiographic findings simulating acute myocardial infarction in a compound metabolic aberration. *Am J Med* 1985;78:529-532.
- Surawicz B. Electrolytes and the electrocardiogram. *Postgrad Med* 1974;55:123-9.
- Lehmann G1, Deisenhofer I, Ndrepepa G, Schmitt C. ECG changes in a 25-year-old woman with hypocalcemia due to hypoparathyroidism. *Hypocalcemia mimicking acute myocardial infarction*. *Chest*. 2000;118(1):260-262.
- Ortega-Carnicer J, de la Nieta DS, Alcazar R. Acute myocardial injury caused presumably by coronary spasm after magnesium fluoro-silicate ingestion. *J Electrocardiol* 2001;34:335-337.
- Davis TME, Singh B, Choo KE, et al. Dynamic assessment of the electrocardiographic QT interval during citrate infusion in healthy volunteers. *Br Heart J* 1995;73:523-526.
- RuDisky BM. ECG abnormalities associated with hypocalcemia. *Chest* 2001;119:668-669.
- Akiyama T, Batchelder J, Worsman J, Moses HW, Jedlinski M. Hypocalcemic Torsades de Pointes. *J Electrocardiol* 1989;22:89-92.