Published in final edited form as:

J Electrocardiol. 2005 October ; 38(4 Suppl): 14–17.

Brugada syndrome and ischemia-induced ST-segment elevation. Similarities and differences[#]

José M. Di Diego, MD^{*}, Jeffrey M. Fish, DVM, and Charles Antzelevitch, PhD

Experimental Cardiology Department, Masonic Medical Research Laboratory, Utica, NY
13501-1787, USA

Abstract

Introduction—ST-Segment elevation is a common electrocardiogram (ECG) manifestation of acute transmural myocardial ischemia in leads facing the injury. Acute myocardial ischemia involving the right-ventricular (RV) outflow tract is known to induce a Brugada-like ECG. In this paper, we examined the electrophysiological bases for the similarities between the ECG characteristics of the Brugada syndrome model induced by terfenadine (5 $\mu\text{mol/L}$) and the ECG manifestations of the acute transmural no-flow ischemia model.

Methods—For both experimental simulations, we used isolated arterially perfused canine RV wedge preparations to record transmembrane action potentials (AP) from endocardium and epicardium together with a transmural pseudo-ECG (ECG); basic cycle length = 400 to 2000 ms.

Results—In the presence of a prominent I_{to} -mediated AP notch, no-flow ischemia causes true ST-segment elevation because of selective depression and loss of the AP dome at some epicardial sites. In the absence of a prominent AP notch, ischemia ultimately produces an apparent ST-segment elevation, which is secondary to a prolongation of the R wave caused by marked transmural conduction delays. Similarly, in the Brugada syndrome model generated in preparations displaying a large epicardial I_{to} , ST-segment elevation was due to loss of the epicardial AP dome at some sites but not at others. Transmural conduction delay giving the appearance of ST-segment elevation is also observed in the Brugada model in preparations exhibiting smaller AP notch. In both models, propagation of the dome from the site at which it is maintained to a site at which it is lost may result in closely coupled phase 2 reentrant extrasystoles.

Conclusion—Our results suggest that I_{to} can modulate the electrocardiographic manifestation of acute ischemia as well as that of the Brugada syndrome, and that both clinical entities are the result of a similar electrophysiological substrate.

Keywords

Electrocardiogram; Electrophysiology; Brugada syndrome; Ischemia; T wave

1. Introduction

Transmembrane action potentials (APs) propagating throughout the heart are the cellular counterparts of the clinical electrocardiogram (ECG). Changes in the ECG induced by disease states including acute myocardial ischemia (AMI) and the Brugada syndrome are therefore necessarily associated with changes in the morphology of the APs and/or in their resting membrane potentials and/or in the conduction properties of the myocardial region in question.

[#]Supported by grants HL37396 and HL47678 from the National Institutes of Health (Dr Antzelevitch); Grants-in-Aid from the American Heart Association, Northeast Affiliate (Dr Di Diego and Dr Fish); and NYS and Florida Grand Lodges F and AM.

* Corresponding author. Tel.: +1 315 735 2217x115; fax: +1 315 735 5648., E-mail address: didiego@mmrl.edu (J.M. Di Diego)..

Previous in vivo studies have shown that, during AMI, endocardial (Endo) conduction remains comparatively preserved at a time when epicardial (Epi) conduction is delayed and fractionated [1–5]. Other studies have demonstrated that, despite similar changes in resting membrane potential, ischemia induces a greater depression of the action potentials of ventricular Epi vs Endo tissues [6,7]. Additional studies have shown a greater Epi sensitivity to a fall of intracellular ATP-induced I_{K-ATP} activation (in response to anoxia) and suggested that this effect may, at least in part, contribute to the greater deterioration of the ventricular Epi action potential to ischemia [8].

Studies performed in our laboratory involving isolated canine ventricular Epi and Endo tissues point to intrinsic cellular electrophysiological differences as the basis for their differential sensitivity to ischemic conditions [9–13]. The presence of a prominent I_{to} -mediated spike and dome morphology (notch) in the epicardium [14] was shown to be, in large part, responsible for the differential response. In isolated Endo and Epi preparations, superfusion with a simulated “ischemic” Tyrode’s solution (6 mmol/L K^+ ; 95% N_2 –5% CO_2 ; pH = 6.8) results in loss of the Epi action potential dome which, in turn, translates into a greater plateau depression relative to that of the endocardium and a marked abbreviation of its action potential [10].

The presence of a large Epi I_{to} is essential for all-or-none repolarization responsible for loss of the action potential dome. It is for this reason that loss of the Epi action potential dome observed under ischemic conditions and conditions mimicking “components” of ischemia (pinacidil-induced $I_{K(ATP)}$ activation [11], elevated extracellular calcium combined with rapid pacing [12]) occurs almost exclusively in right ventricular (RV) Epi tissues, where I_{to} is most prominent [15]. These observations suggest that loss of the Epi AP dome may contribute to the ST-segment elevation observed in patients with RV AMI. Accordingly, in cases in which the proximal portion of the right coronary artery is also compromised, particularly if the RV outflow tract is involved, a Brugada-like ECG is anticipated [16–19].

We have previously proposed a similar cellular mechanism for the Brugada syndrome, in which loss of the dome at some RV Epi sites and accentuation of the notch at others may underlie the ST-segment elevation and negative T wave observed in the right precordial leads of these patients. Phase 2 reentry-induced extrasystoles leading to polymorphic VT or VF was also anticipated [9,20,21]. In addition, the presence of a much greater I_{to} in right- vs left ventricular epicardium has also been proposed to account, at least in part, for the RV nature of this disease [15].

2. Method

2.1. Arterially perfused canine RV wedge preparations

Isolated canine RV wedge preparations with dimensions of approximately $2.5 \times 1.5 \times 1.2$ cm are perfused with Tyrode’s solution through a descending branch of the right coronary artery. The temperature of the perfusate is maintained at 35°C to 37°C and the perfusion pressure at 40 to 50 mm Hg. The wedges are paced with a bipolar electrode contacting the Endo surface (for more details, see Yan et al [22,23] and Shimizu and Antzelevitch [24]).

A transmural ECG is recorded using electrodes consisting of AgCl half cells placed in the Tyrode’s solution bathing the preparation, at 1.0 to 1.5 cm from the Epi and Endo surfaces and along the same axis as the transmembrane recordings (epicardium: “+” pole). Transmembrane APs are simultaneously recorded from 1 or 2 Epi sites and 1 Endo site using floating microelectrodes.

To reproduce the Brugada-like ECG observed in the clinical RV AMI involving the RV outflow tract, global ischemia is induced by stopping the coronary flow for 15 to 20 minutes. To ensure a low P_{O_2} , the tissue chamber is simultaneously superfused with Tyrode's solution equilibrated with N_2 and CO_2 at a rate of 30 to 60 mL/min. In addition, N_2 (95%) and CO_2 (5%) are introduced through a gas line positioned at the bottom of the chamber.

To induce the Brugada syndrome model, we use terfenadine (5 μ mol/L), a combined sodium and calcium channel blocker. To facilitate loss of the Epi action potential dome and the occurrence of phase 2 reentry, the preparations are paced at short cycle lengths (basic cycle length, 400–500 ms) for up to 30 seconds, followed by pacing at a cycle length of 800 ms for 30 seconds, followed by a return to a cycle length of 2000 ms.

3. Results

3.1. Global ischemia model

We observed 2 different types of electrophysiological effects depending on the prominence of spike and dome configuration under control conditions. During the first 5 to 10 minutes, no-flow ischemia can cause loss of the action potential dome (all-or-none repolarization at the end of phase 1) at some RV Epi sites leading to the development of a “true” ST-segment elevation in the ECG (basic cycle length, 800–2000 ms). Propagation of the dome from the region where it is maintained to the region where it is lost may result in phase 2 reentry (a phase 2–dependent reexcitation phenomenon) and the generation of a closely coupled extrasystoles. The phenomenon, however, is observed rarely and only in RV wedge preparations displaying prominent I_{to} -mediated notch. In this regard, we observed important differences in the magnitude of I_{to} -mediated spike and dome morphology in the RV Epi between females and males [25] (more prominent in the latter) as well as among breeds (unpublished observation).

In preparations displaying a less prominent phase 1, a preferential abbreviation of the Epi action potential dome can be observed in association with a major slowing of transmural conduction occurring at approximately 10 to 15 minutes after interruption of the coronary flow. Ischemia-induced conduction delays lead to an “apparent” ST-segment elevation in the ECG. Under these conditions, and despite a greater abbreviation of the Epi action potential, the epicardium repolarizes after the endocardium leading to a reversal of the polarity of the T wave. Although the ECG displays an “apparent” ST-segment elevation, the transmembrane recordings clearly show that the electrocardiographic changes are due principally to a slowing of transmural conduction, and that the “apparent” ST-segment elevation is in fact a prolongation of the R wave (in the wedge, the R wave is the time interval between Endo and Epi phase 0). This wide R wave is, in turn, secondary to a major step delay in impulse transmission in midmyocardial to deep-subepicardial regions as revealed with intramural unipolar electrogram recordings. Eventually, the epicardium may become inexcitable at 15 to 20 minutes of ischemia, leading to a disappearance of the negative T wave, and the ECG may resemble that of the Endo AP morphology.

3.2. Brugada syndrome model

In the Brugada syndrome model induced by terfenadine (5 μ mol/L), the loss of the action potential dome occurs at some Epi sites. Accentuation of the Epi AP notch and loss of the dome result in an ST-segment elevation in the ECG. The wide notch in the Epi action potentials where the dome is maintained delays repolarization beyond that of endocardium and results in inversion of the T-wave polarity. Propagation of the dome from the site where it is maintained to a site where it is lost results in phase 2 reentrant extrasystoles. The I_{to} blocker, 4-aminopyridine (2 mmol/L), restores the action potential dome, normalizes the ECG, and prevents the development of phase 2 reentry and VT.

4. Discussion

Our data suggest that acute transmural global ischemia performed in RV wedges can lead to loss of the dome, “true” ST-segment elevation, and extrasystolic activity induced by phase 2 reentry similar to that encountered in models of the Brugada syndrome. In the wedge preparation exposed to global ischemia, this occurs relatively rarely and usually in RV wedges displaying a prominent Epi spike and dome configuration. In the vast majority of preparations, global ischemia causes a dramatic increase in transmural conduction time leading to development of an “apparent” ST-segment elevation secondary to a widening of the R wave.

Loss of the action potential dome giving rise to “true” ST-segment elevation and closely coupled phase 2 reentrant extrasystoles may more likely develop within the border zone of the ischemic region [26] or during low-flow ischemia, conditions at which K^+ accumulation leading to membrane depolarization and thus to a reduction of the Epi notch (due to inactivation of I_{to}) and slowing of conduction (due to inactivation of I_{Na}) is minimized.

In summary, our results suggest that (1) in the presence of a prominent I_{to} -mediated action potential notch, RV ischemia can lead to “true” ST-segment elevation secondary to selective depression of the Epi action potential dome, transmural dispersion of repolarization, and phase 2 reentry capable of precipitating VT/VF; (2) the same electrophysiological substrate may be operative in the Brugada syndrome; (3) in the absence of a prominent action potential notch, RV ischemia leads to an apparent ST-segment elevation, which is actually a prolongation of the R wave caused by marked transmural conduction delays; (4) a similar prolongation of the R wave can be observed in our Brugada syndrome model performed in preparations displaying a less prominent Epi notch.

Agents or conditions that cause an outward shift in the balance of currents present at the end of phase 1 repolarization, either by inhibiting I_{Na} (flecainide) or I_{Ca} (verapamil) or by activating I_{K-ATP} (pinacidil), are capable of causing loss of the action potential dome in RV Epi tissues displaying a large I_{to} -mediated notch. Although changes in I_{to} may not be responsible for precipitating the loss of the dome phenomenon in most cases of RV AMI or Brugada syndrome, the presence of a prominent I_{to} -mediated action potential notch appears to be a prerequisite. It is safe to state therefore that I_{to} can modulate the electrocardiographic manifestation of these 2 clinical conditions as both entities appear to be the result of a similar electrophysiological substrate.

4.1. Limitation of the study

The isolated ventricular wedge preparation offers the advantage of a direct correlation of transmembrane and electrocardiographic activity. Although this methodology permits assessment of the cellular mechanism responsible for the electrocardiographic manifestations of ischemia as well as of Brugada syndrome models, we must recognize that the clinical ECG is likely to see a much more complex distribution of voltage gradients.

Acknowledgements

We gratefully acknowledge the expert technical assistance of Robert Goodrow, Judy Hefferon, and Andy Pitoniak.

References

1. Boineau JP, Schuessler RB, Eisenberg SB, et al. Potential distribution mapping of ventricular tachycardia. In: Shenasa M, Borggreffe M, Breithardt G, editors. Cardiac mapping. Mount Kisco (NY): Futura Publishing Co; 1993. p. 85.

2. Williams DO, Scherlag BJ, Hope RR, El-Sherif N, Lazzara R. The pathophysiology of malignant ventricular arrhythmias during acute myocardial infarction. *Circulation* 1974;50:1163. [PubMed: 4138987]
3. Elharrar V, Gaum WE, Zipes DP. Effects of drugs on conduction delay and the incidence of ventricular arrhythmias induced by acute coronary occlusion in dogs. *Am J Cardiol* 1977;39:544. [PubMed: 848439]
4. Ruffy R, Lovelace ED, Knoebel SB, Mueller TM, Zipes DP. Relationship between changes in left ventricular bipolar electrograms and regional myocardial blood flow during acute coronary occlusion in the dog. *Circ Res* 1979;45:764. [PubMed: 498440]
5. Scherlag BJ, El-Sherif N, Hope RR, Lazzara R. Characterization and localization of ventricular arrhythmias resulting from myocardial ischemia and infarction. *Circ Res* 1974;35:372. [PubMed: 4417558]
6. Gilmour RF Jr, Zipes DP. Different electrophysiological responses of canine endocardium and epicardium to combined hyperkalemia, hypoxia, and acidosis. *Circ Res* 1980;46:814. [PubMed: 7379247]
7. Kimura S, Bassett AL, Kohya T, Kozlovskis PL, Myerburg RJ. Simultaneous recording of action potentials from endocardium and epicardium during ischemia in the isolated cat ventricle: relation of temporal electrophysiologic heterogeneities to arrhythmias. *Circulation* 1986;74:401. [PubMed: 3731429]
8. Furukawa T, Kimura S, Furukawa N, Bassett AL, Myerburg RJ. Role of cardiac ATP-regulated potassium channels in differential responses of endocardial and epicardial cells to ischemia. *Circ Res* 1991;68(6):1693. [PubMed: 2036719]
9. Lukas A, Antzelevitch C. Phase 2 reentry as a mechanism of initiation of circus movement reentry in canine epicardium exposed to simulated ischemia. *Cardiovasc Res* 1996;32:593. [PubMed: 8881520]
10. Lukas A, Antzelevitch C. Differences in the electrophysiological response of canine ventricular epicardium and endocardium to ischemia: role of the transient outward current. *Circulation* 1993;88:2903. [PubMed: 8252704]
11. Di Diego JM, Antzelevitch C. Pinacidil-induced electrical heterogeneity and extrasystolic activity in canine ventricular tissues. Does activation of ATP-regulated potassium current promote phase 2 reentry? *Circulation* 1993;88:1177. [PubMed: 7689041]
12. Di Diego JM, Antzelevitch C. High $[Ca^{2+}]$ -induced electrical heterogeneity and extrasystolic activity in isolated canine ventricular epicardium. Phase 2 reentry. *Circulation* 1994;89:1839. [PubMed: 7511994]
13. Billman GE. Ro 40–5967, a novel calcium channel antagonist, protects against ventricular fibrillation. *Eur J Pharmacol* 1992;229:179. [PubMed: 1490522]
14. Liu DW, Gintant GA, Antzelevitch C. Ionic bases for electrophysiological distinctions among epicardial, midmyocardial, and endocardial myocytes from the free wall of the canine left ventricle. *Circ Res* 1993;72:671. [PubMed: 8431990]
15. Di Diego JM, Sun ZQ, Antzelevitch C. I_{to} and action potential notch are smaller in left vs. right canine ventricular epicardium. *Am J Physiol* 1996;271:H548. [PubMed: 8770096]
16. Shimizu W. Acquired forms of Brugada syndrome. In: Antzelevitch C, Brugada P, Brugada J, Brugada R, editors. *The Brugada syndrome: from bench to bedside*. Oxford: Blackwell Futura; 2004. p. 166.
17. Kataoka H. Electrocardiographic patterns of the Brugada syndrome in right ventricular infarction/ischemia. *Am J Cardiol* 2000;86(9):1056. [PubMed: 11127953]
18. Kataoka H, Kanzaki K, Mikuriya Y. Massive ST-segment elevation in precordial and inferior leads in right ventricular myocardial infarction. *J Electrocardiol* 1988;21(2):115. [PubMed: 3294329]
19. Indik JH, Ott P, Butman SM. Syncope with ST-segment abnormalities resembling Brugada syndrome due to reversible myocardial ischemia. *PACE* 2002;25(8):1270. [PubMed: 12358180]
20. Yan GX, Antzelevitch C. Cellular basis for the Brugada syndrome and other mechanisms of arrhythmogenesis associated with ST segment elevation. *Circulation* 1999;100:1660. [PubMed: 10517739]
21. Antzelevitch C. The Brugada syndrome: ionic basis and arrhythmia mechanisms. *J Cardiovasc Electrophysiol* 2001;12(2):268. [PubMed: 11232628]

22. Yan GX, Shimizu W, Antzelevitch C. Characteristics and distribution of M cells in arterially-perfused canine left ventricular wedge preparations. *Circulation* 1998;98:1921. [PubMed: 9799214]
23. Yan GX, Antzelevitch C. Cellular basis for the normal T wave and the electrocardiographic manifestations of the long QT syndrome. *Circulation* 1998;98:1928. [PubMed: 9799215]
24. Shimizu W, Antzelevitch C. Cellular basis for the ECG features of the LQT1 form of the long QT syndrome: effects of β -adrenergic agonists and antagonists and sodium channel blockers on transmural dispersion of repolarization and torsade de pointes. *Circulation* 1998;98:2314. [PubMed: 9826320]
25. Di Diego JM, Cordeiro JM, Goodrow RJ, et al. Ionic and cellular basis for the predominance of the Brugada syndrome phenotype in males. *Circulation* 2002;106(15):2004. [PubMed: 12370227]
26. Yan GX, Joshi A, Guo D, et al. Phase 2 reentry as a trigger to initiate ventricular fibrillation during early acute myocardial ischemia. *Circulation* 2004;1036. [PubMed: 15302777]