Published in final edited form as:

Heart Rhythm. 2010 October ; 7(10): 1472–1474. doi:10.1016/j.hrthm.2010.07.027.

A gain-of-function I_{K-ATP} mutation and its role in sudden cardiac death associated with J-wave syndromes

Charles Antzelevitch, PhD, FHRS and Hector Barajas-Martinez, PhD

Masonic Medical Research Laboratory, Utica, New York

Early repolarization (ER), consisting of a J-point elevation, a notch or slur on the QRS (J wave), and tall/symmetric T waves, is predominantly found in healthy young male patients and has traditionally been regarded as totally benign.^{1,2} The observation in 2000 that an ER pattern in the coronary-perfused wedge preparation can easily convert to one in which phase 2 reentry gives rise to polymorphic ventricular tachycardia/ventricular fibrillation (VT/VF) prompted the suggestion that ER may in some cases predispose to malignant arrhythmias in the clinic.^{3,4} Sporadic case reports and experimental studies have long suggested a critical role for the J wave in the pathogenesis of idiopathic ventricular fibrillation (IVF).^{5–12} A definitive association between ER and IVF has been presented in more recent reports.^{13–16}

The high prevalence of ER in patients with IVF suggests that ER may be a necessary condition for the development of IVF. Although not a sensitive marker for sudden cardiac death (SCD), due to its high prevalence in the general population, ER when observed in patients with syncope or a malignant family history of sudden cardiac death may be prognostic of risk. A transient J-wave augmentation secondary to a shift of the balance of currents active in the early phases of the action potential portends a high risk for VF in patients with ER.

Based on the available data pointing to an association of risk with spatial localization of the early repolarization pattern, a classification scheme was proposed in which type 1 is associated with an ER pattern predominantly in the lateral precordial leads; this form is very prevalent among healthy male athletes and is thought to be largely benign. Type 2, showing an ER pattern predominantly in the inferior or inferolateral leads, is associated with a moderate level of risk, and type 3, showing an ER pattern globally in the inferior, lateral, and right precordial leads, seems to be associated with the highest level of risk and is often associated with electrical storms.⁴ Brugada syndrome (BrS) represents a fourth variant, in which ER is limited to the right precordial leads.

Electrocardiographic (ECG) changes in both BrS and ERS are dynamic,^{12,17,18} with the most prominent ECG changes appearing just before the onset of VT/VF.^{5–12,17–19} The amplitude of J waves, barely noticeable during sinus rhythm, may become progressively augmented with increased vagal tone and bradycardia and still further accentuated after successive extrasystoles and compensatory pauses giving rise to short-long-short sequences.

Because of the similarity in ECG characteristics, clinical outcomes, and risk factors and because they share a common arrhythmic platform related to amplification of I_{to} -mediated J waves, these congenital and acquired syndromes have been grouped under the heading of J-wave syndromes.⁴

Data relative to the genetic and molecular basis for J-wave syndromes are relatively limited. BrS has previously been associated with mutations in 7 different genes, including *SCN5A*, *GPD1L*, *CACNA1C*, *CACNB2b*, *SCN1B*, *KCNE3*, and *SCN3B*, whereas ERS has been associated with mutations in *KCNJ8*, *CACNA1C*, and *CACNB2*.^{4,20,21} Haissaguerre et al²¹ were the first to associate *KCNJ8* with ERS in the case of a young female patient with more than 100 recurrences of VF unresponsive to beta-blockers, lidocaine/mexiletine, verapamil, and amiodarone. Recurrences of VF were associated with marked accentuation of the early repolarization pattern at times mimicking acute myocardial ischemia, although coronary angiography during one of the episodes was normal. However, functional expression data for the S422L missense mutation in *KCNJ8* were not presented to substantiate the association of the genotype with the phenotype.²¹

This important deficiency has been partially addressed by a study reported by Medeiros-Domingo et al²² in this issue of the *Journal*. This talented group of investigators genetically screened 87 probands with BrS and 14 with ERS and found 1 BrS and 1 ERS proband with an S422L-*KCNJ8* (Kir6.1) mutation; the variation was absent in 600 control subjects. The investigators coexpressed the *KCNJ8* mutation with adenosine triphosphate (ATP) regulatory subunit *SUR2A* in COS-1 cells and measured I_{K-ATP} using whole-cell patch-clamp techniques. The investigators report a significantly larger I_{K-ATP} for the mutant versus wild type in response to a high concentration of pinacidil (100 μ M). Although no ATP was added to the pipette solution, presumably to induce I_{K-ATP} , no data are presented in the absence of pinacidil. Under baseline conditions, normal intracellular ATP levels maintain the I_{K-ATP} channels closed. The presumption is that the S422L-*KCNJ8* mutant channels fail to close properly at normal intracellular ATP concentrations, thus resulting in a gain of function. The gold standard for demonstrating a change in sensitivity to ATP involves the study of inside-out patches with the internal membrane exposed to different ATP concentrations. These data unfortunately are not provided, and a full characterization of the functional consequence of this mutation awaits such studies. This notwithstanding, the findings presented further implicate *KCNJ8* as a novel J-wave syndrome-susceptibility gene and a gain-of-function in the cardiac K_{ATP} Kir6.1 channel (in the presence of pinacidil) secondary to *KCNJ8*-S422L mutation as a novel pathogenic mechanism in BrS and ERS.

ATP-sensitive channels (K_{ATP}), originally discovered by Noma et al²³ in heart, have since been found in many tissues, including pancreatic, skeletal muscle, kidney, and brain cells.²⁴ K_{ATP} channels, which remain closed at normal $[ATP]_i$, open as $[ATP]_i$ and the ATP/adenosine diphosphate ratio decline during hypoxia or ischemia, thus regulating calcium entry, contraction, and oxygen utilization.²⁵ K_{ATP} channels are thought to be hetero-octameric in structure, consisting of 4 pore-forming subunits (*KCNJ8*-encoded Kir6.1 or *KCNJ11*-encoded Kir6.2), and 4 regulatory subunit sulfonylurea receptors (SUR): *ABCC8*-encoded SUR1 or *ABCC9*-encoded SUR2A in the heart.^{26,27}

Coassociation of Kir6.2 and SUR2A was long thought to be the principal subunit combination comprising K_{ATP} channels in the heart and conferring cardioprotection under ischemic conditions. As discussed by Medeiros-Domingo et al,²² a number of studies have raised some serious questions regarding the predominant role of Kir6.2. Recent studies suggest that within a single K_{ATP} channel, more than 1 Kir6.x or SURx subunit can coexist.^{28–32}

A number of studies point to relatively high expression of Kir6.1 in cardiomyocytes.^{33–37} In the mouse, Morrissey et al³⁸ used immunolocalization assays to demonstrate that both Kir6.1 and Kir6.2 as well as SUR2 (but not SUR1) are expressed in a sarcomeric striated pattern, suggesting their presence in T-tubules in ventricular cardiomyocytes and that Kir6.1 is more strongly expressed in epicardial ventricular myocytes. This transmural distribution is consistent with the observation that K_{ATP} channels are more prominently activated by ischemia in

epicardium vs. endocardium^{39,40} and may be related to the finding by Furukawa et al⁴¹ that ATP-regulated K⁺ channels are activated by a smaller reduction in intracellular ATP in feline epicardial versus endocardial cells.

This heterogeneous transmural distribution of Kir6.1, if present in humans, likely contributes to the development of ST-segment elevation observed in patients with BrS- and ERS-carrying mutations in *KCNJ8* or *SUR2A*. The presence of an additional repolarization force during the early phases of the epicardial action potential, due to a gain of function of I_{K-ATP}, can generate an early repolarization pattern in the ECG by causing depression of the epicardial action potential dome.⁴ In the presence of a prominent transient outward current (I_{to}), commonly seen in right ventricular epicardium,⁴² the addition of I_{K-ATP} can lead to an accentuation of the action potential notch, thus amplifying the normal J wave, resulting in an ST-segment elevation, characteristic of BrS. A further outward shift in the balance of currents active during the early phases of the epicardial action potential, due to augmented vagal influence (I_{K-Ach} activation), bradycardia (greater availability of I_{to}), or mild ischemia (more I_{K-ATP}), can then lead to heterogeneous loss of the action potential dome, thus creating a dispersion of repolarization within epicardium and between epicardium and endocardium. This marked electrical heterogeneity may then facilitate the development of phase 2 reentry and polymorphic VT.^{4, 43}

The study by Medeiros-Domingo et al²² advances our understanding of this sudden cardiac death susceptibility gene and its role in the pathogenesis of J-wave syndromes. The *KCNJ8*-S422L mutation, now reported in 2 ERS and 1 BrS probands, provides further evidence for a role for I_{K-ATP} in inherited and possibly acquired life-threatening channelopathies. This mutation in *KCNJ8* may prove to be a hotspot, and we look forward to additional studies of its action to alter the biophysical properties of I_{K-ATP}, as well as assessment of its pathogenicity.

Acknowledgments

Supported by grant HL47678 (Dr. Antzelevitch) from the National Heart, Lung, and Blood Institute and the New York State and Florida Masonic Grand Lodges.

References

1. Wasserburger RH, Alt WJ. The normal RS-T segment elevation variant. *Am J Cardiol* 1961;8:184–192. [PubMed: 13783301]
2. Mehta MC, Jain AC. Early repolarization on scalar electrocardiogram. *Am J Med Sci* 1995;309:305–311. [PubMed: 7771499]
3. Gussak I, Antzelevitch C. Early repolarization syndrome: clinical characteristics and possible cellular and ionic mechanisms. *J Electrocardiol* 2000;33:299–309. [PubMed: 11099355]
4. Antzelevitch C, Yan GX. J wave syndromes. *Heart Rhythm* 2010;7:549–558. [PubMed: 20153265]
5. Yan GX, Antzelevitch C. Cellular basis for the electrocardiographic J wave. *Circulation* 1996;93:372–379. [PubMed: 8548912]
6. Geller JC, Reek S, Goette A, Klein HU. Spontaneous episode of polymorphic ventricular tachycardia in a patient with intermittent Brugada syndrome. *J Cardiovasc Electrophysiol* 2001;12:1094. [PubMed: 11573705]
7. Daimon M, Inagaki M, Morooka S, et al. Brugada syndrome characterized by the appearance of J waves. *PACE* 2000;23:405–406. [PubMed: 10750145]
8. Kalla H, Yan GX, Marinchak R. Ventricular fibrillation in a patient with prominent J (Osborn) waves and ST segment elevation in the inferior electrocardiographic leads: a Brugada syndrome variant? *J Cardiovasc Electrophysiol* 2000;11:95–98. [PubMed: 10695469]
9. Komiya N, Imanishi R, Kawano H, et al. Ventricular fibrillation in a patient with prominent J wave in the inferior and lateral electrocardiographic leads after gastrectomy. *PACE* 2006;29:1022–1024. [PubMed: 16981930]

10. Shinohara T, Takahashi N, Saikawa T, Yoshimatsu H. Characterization of J wave in a patient with idiopathic ventricular fibrillation. *Heart Rhythm* 2006;3:1082–1084. [PubMed: 16945806]
11. Riera AR, Ferreira C, Schapachnik E, Sanches PC, Moffa PJ. Brugada syndrome with atypical ECG: downsloping ST-segment elevation in inferior leads. *J Electrocardiol* 2004;37:101–104. [PubMed: 15127375]
12. Shu J, Zhu T, Yang L, Cui C, Yan GX. ST-segment elevation in the early repolarization syndrome, idiopathic ventricular fibrillation, and the Brugada syndrome: cellular and clinical linkage. *J Electrocardiol* 2005;38:26–32. [PubMed: 16226071]
13. Haissaguerre M, Derval N, Sacher F, et al. Sudden cardiac arrest associated with early repolarization. *N Engl J Med* 2008;358:2016–2023. [PubMed: 18463377]
14. Nam GB, Kim YH, Antzelevitch C. Augmentation of J waves and electrical storms in patients with early repolarization. *N Engl J Med* 2008;358:2078–2079. [PubMed: 18463391]
15. Rosso R, Kogan E, Belhassen B, et al. J-point elevation in survivors of primary ventricular fibrillation and matched control subjects: incidence and clinical significance. *J Am Coll Cardiol* 2008;52:1231–1238. [PubMed: 18926326]
16. Tikkanen JT, Anttonen O, Junttila MJ, et al. Long-term outcome associated with early repolarization on electrocardiography. *N Engl J Med* 2009;361:2529–2537. [PubMed: 19917913]
17. Kananuki H, Ohnishi S, Ohtuka M, et al. Idiopathic ventricular fibrillation induced with vagal activity in patients without obvious heart disease. *Circulation* 1997;95:2277–2285. [PubMed: 9142005]
18. Matsuo K, Shimizu W, Kurita T, Inagaki M, Aihara N, Kamakura S. Dynamic changes of 12-lead electrocardiograms in a patient with Brugada syndrome. *J Cardiovasc Electrophysiol* 1998;9:508–512. [PubMed: 9607459]
19. Nam GB, Ko KH, Kim J, et al. Mode of onset of ventricular fibrillation in patients with early repolarization pattern vs. Brugada syndrome. *Eur Heart J* 2010;31:330–339. [PubMed: 19880418]
20. Burashnikov E, Pfeifer R, Borggrefe M, et al. Mutations in the cardiac L-type calcium channel associated with inherited sudden cardiac death syndromes. *Circulation* 2009;120:S573.
21. Haissaguerre M, Chatel S, Sacher F, et al. Ventricular fibrillation with prominent early repolarization associated with a rare variant of KCNJ8/K_{ATP} channel. *J Cardiovasc Electrophysiol* 2009;20:93–98. [PubMed: 19120683]
22. Medeiros-Domingo A, Tan BH, Crotti L, et al. Gain-of-function mutation, S422L, in the KCNJ8-encoded cardiac K ATP channel Kir6.1 as a pathogenic substrate for J wave syndromes. *Heart Rhythm*. 2010 in press.
23. Noma A, Morad M, Irisawa H. Does the “pacemaker current” generate the diastolic depolarization in the rabbit SA node cells? *Pflügers Arch* 1983;397:190–194. [PubMed: 6878006]
24. Inagaki N, Tsuura Y, Namba N, et al. Cloning and functional characterization of a novel ATP-sensitive potassium channel ubiquitously expressed in rat tissues, including pancreatic islets, pituitary, skeletal muscle, and heart. *J Biol Chem* 1995;270:5691–5694. [PubMed: 7890693]
25. Yokoshiki H, Sunagawa M, Seki T, Sperelakis N. ATP-sensitive K⁺ channels in pancreatic, cardiac, and vascular smooth muscle cells. *Am J Physiol* 1998;274:C25–C37. [PubMed: 9458709]
26. Bryan J, Aguilar-Bryan L. Sulfonylurea receptors: ABC transporters that regulate ATP-sensitive K⁺ channels. *Biochim Biophys Acta* 1999;1461:285–303. [PubMed: 10581362]
27. Zhou ML, Huang Y, Liu DP, Liang CC. KATP channel: relation with cell metabolism and role in the cardiovascular system. *Int J Biochem Cell Biol* 2005;4:751–764.
28. Zhang H, Flagg TP, Nichols CG. Cardiac sarcolemmal K(ATP) channels: latest twists in a questing tale! *J Mol Cell Cardiol* 2010;48:71–75. [PubMed: 19607836]
29. Kono Y, Horie M, Takano M, et al. The properties of the Kir6.1-6.2 tandem channel co-expressed with SUR2A. *Pflügers Arch* 2000;440:692–698. [PubMed: 11007308]
30. Chan KW, Zhang H, Logothetis DE. N-terminal transmembrane domain of the SUR controls trafficking and gating of Kir6 channel subunits. *EMBO J* 2003;22:3833–3843. [PubMed: 12881418]
31. Cheng WW, Tong A, Flagg TP, Nichols CG. Random assembly of SUR subunits in K(ATP) channel complexes. *Channels (Austin)* 2008;2:34–38. [PubMed: 18690055]

32. Wheeler A, Wang C, Yang K, et al. Coassembly of different sulfonylurea receptor subtypes extends the phenotypic diversity of ATP-sensitive potassium (KATP) channels. *Mol Pharmacol* 2008;74:1333–1344. [PubMed: 18723823]
33. Morrissey A, Parachuru L, Leung M, et al. Expression of ATP-sensitive K⁺ channel subunits during perinatal maturation in the mouse heart. *Pediatr Res* 2005;58:185–192. [PubMed: 16085792]
34. Erginel-Unaltuna N, Yang WP, Blana MA. Genomic organization and expression of KCNJ8/Kir6.1, a gene encoding a subunit of an ATP-sensitive potassium channel. *Gene* 1998;211:71–78. [PubMed: 9573340]
35. Miki T, Suzuki M, Shibasaki T, et al. Mouse model of Prinzmetal angina by disruption of the inward rectifier Kir6.1. *Nat Med* 2002;8:466–472. [PubMed: 11984590]
36. Kuniyasu A, Kaneko K, Kawahara K, Nakayama H. Molecular assembly and subcellular distribution of ATP-sensitive potassium channel proteins in rat hearts. *FEBS Lett* 2003;552:259–263. [PubMed: 14527696]
37. Wu SN, Wu AZ, Sung RJ. Identification of two types of ATP-sensitive K⁺ channels in rat ventricular myocytes. *Life Sci* 2007;80:378–387. [PubMed: 17097686]
38. Morrissey A, Rosner E, Lanning J, et al. Immunolocalization of KATP channel subunits in mouse and rat cardiac myocytes and the coronary vasculature. *BMC Physiol* 2005;5:1. [PubMed: 15647111]
39. Kubota I, Yamaki M, Shibata T, Ikeno E, Hosoya Y, Tomoike H. Role of ATP-sensitive K⁺ channel on ECG ST segment elevation during a bout of myocardial ischemia. A study on epicardial mapping in dogs. *Circulation* 1993;88:1845–1851. [PubMed: 8403330]
40. Miyoshi S, Miyazaki T, Moritani K, Ogawa S. Different responses of epicardium and endocardium to K_{ATP} modulators during regional ischemia. *Am J Physiol* 1996;271:H140–H147. [PubMed: 8760169]
41. Furukawa T, Kimura S, Cuevas J, Bassett AL, Myerburg RJ. ATP-modulated potassium channels in epicardium and endocardium have different sensitivity to ATP. *Circulation* 1989;80:II–519.
42. 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–H561. [PubMed: 8770096]
43. Antzelevitch C. Brugada syndrome. *PACE* 2006;29:1130–1159. [PubMed: 17038146]