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J Wave Syndromes: Molecular and Cellular Mechanisms

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Abstract

An early repolarization (ER) pattern in the ECG, consisting of J point elevation, distinct J wave with or without ST segment elevation or slurring of the terminal part of the QRS, was long considered a benign electrocardiographic manifestation. Experimental studies a dozen years ago suggested that an ER is not always benign, but may be associated with malignant arrhythmias. Validation of this hypothesis derives from recent case-control and population-based studies showing that an ER pattern in inferior or infero-lateral leads is associated with increased risk for life-threatening arrhythmias, termed early repolarization syndrome (ERS). Because accentuated J waves characterize both Brugada syndrome (BrS) and ERS, these syndromes have been grouped under the heading of J wave syndromes. BrS and ERS appear to share common ECG characteristics, clinical outcomes, risk factors as well as a common arrhythmic platform related to amplification of I_{to}-mediated J waves. However, they differ with respect to the magnitude and lead location of abnormal J waves and can be considered to represent a continuous spectrum of phenotypic expression. Recent studies support the hypothesis that BrS and ERS are caused by a preferential accentuation of the AP notch in right or left ventricular epicardium, respectively, and that this repolarization defect is accentuated by cholinergic agonists. Quinidine, cilostazol and isoproterenol exert ameliorative effects by reversing these repolarization abnormalities. Identifying subjects truly at risk is the challenge ahead. Our goal here is to review the clinical and genetic aspects as well as the cellular and molecular mechanisms underlying the J wave syndromes.

Keywords

Cardiac arrhythmias; Sudden cardiac death; Early repolarization syndrome; Brugada syndrome; Idiopathic Ventricular fibrillation

J Wave Syndromes: Clinical characteristics

The electrocardiographic J wave was first described in 1938[1] in an ECG recorded from an accidentally frozen human. It was referred to as the Osborn wave for many years after being reported by Osborn in hypothermic dogs in 1953.[2] The appearance of prominent J wave in humans is encountered in cases of hypothermia,[3-5] hypercalcemia[6, 7] and more recently has been suggested as a marker for a substrate capable of generating life-threatening ventricular

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arrhythmias.[8] In humans, the J wave more commonly appears as a J point elevation, with part of the J wave buried inside the QRS.

An early repolarization (ER) pattern on the ECG was first described in 1936 by Shipley and Hallaran , who studied four-lead ECGs of 200 healthy young men and women and described J deflection as slurring or notching of the terminal part of QRS complex and considered it as a normal variant.[9] In subsequent years, ST segment elevation was added to these electrocardiographic manifestations and the complex was designated “early repolarization” based on the presumption that early repolarization was responsible,[10] although no data were available to support this assertion. Experimental data in support of the hypothesis was first advanced with the identification of the cellular basis for the J wave in 1996.[11]

An ER pattern in the ECG, consisting of a distinct J wave or J point elevation, a notch or slur of the terminal part of the QRS and an ST segment elevation, is generally found in healthy young males and has traditionally been viewed as benign.[12, 13] In 2000, we challenged this view on the basis of experimental data showing that an ER pattern in the canine coronary-perfused wedge preparation predisposes to the development of polymorphic ventricular tachycardia and fibrillation (VT/VF).[8, 14, 15]

Validation of this hypothesis was provided eight years later in the New England Journal of Medicine by Haïssaguerre et al.,[16] and a letter to the editor by Nam et al.[17] These reports together with numerous additional case control and population based studies provided clinical evidence that there is an increased prevalence of ER pattern, particularly in the inferior and infero-lateral leads, among patients with a history of idiopathic ventricular fibrillation, thus confirming a link between ER pattern in the ECG and life-threatening cardiac arrhythmias. (see also[18, 19] for review).

The poorer prognosis of subjects with inferior or infero-lateral ER was confirmed in numerous population based studies. (see also[18, 19] for references). We recently suggested a classification scheme for ER (Table 1).[8] An ER pattern manifest exclusively in the lateral precordial leads was designated as Type 1; this form is prevalent among healthy male athletes and is thought to be associated with a relatively low level of risk for arrhythmic events. ER pattern in the inferior or infero-lateral leads was designated as Type 2; this form is thought to be associated with a moderate level of risk. Finally, an ER pattern appearing globally in the inferior, lateral and right precordial leads was labeled Type 3; this form is associated with the highest level of risk and in some cases has been associated with electrical storms.[8] Type 3 ER may at times be very similar to that of Type 2, exhibiting infero-lateral ER, except for brief periods immediately before the development of VT/VF when pronounced J waves are also observed in the right precordial leads (see[20] for an example). BrS represents a fourth variant in which ER is limited to the right precordial leads.

Genetics Basis for the J wave Syndromes

BrS has been associated with mutations in twelve different genes, accounting for approximately 40% of probands. Greater than 300 mutations in *SCN5A* ($Na_v1.5$, BrS1) have been reported by centers worldwide accounting for 11-28% of BrS probands. Mutations in *CACNA1C* ($Ca_v1.2$, BrS3), *CACNB2b* ($Ca_v\beta2b$, BrS4) and *CACNA2D1* ($Ca_v\alpha2\Delta$, BrS9) are reportedly found in ~13% of probands. Mutations in glycerol-3-phophate dehydrogenase 1-like enzyme gene (*GPD1L*, BrS2), *SCN1B* (β_1-subunit of Na channel, BrS5), *KCNE3* (MiRP2; BrS6), *SCN3B* (β3-subunit of Na channel, BrS7), *KCNJ8* (BrS8) and *KCND3* (BrS10) are more rare. Mutations in these genes lead to loss of function in I_{Na} and I_{Ca}, as well as to a gain of function in I_{to} or I_K-ATP. MOG1 was recently described as a new partner of $Na_V1.5$, playing a role in its regulation, expression and trafficking. A missense

mutation in MOG1 was also associated with BrS (BrS11). Mutations in sarcolemmal membrane-associated protein (SLMAP), a protein of unknown function localizing at T-tubules and sarcoplasmic reticulum, has recently been associated with BrS (BrS12). Preliminary reports indicate an important association with *SCN10A*, a neuronal sodium channel that co-associates with *SCN5A,* with a yield as high as 20%. Mutations in *KCNH2* and *KCNE5,* although not causative, have been identified as capable of modulating the substrate for the development of BrS. Loss-of-function mutations in *HCN4* causing a reduction in the pacemaker current, I_f, have the potential to unmask BrS by reducing heart rate.[21] (see [18] for references).

The familial nature of ER pattern has been demonstrated in a number of studies.[22-24] ER pattern and ERS have been associated with mutations in 6 genes. Consistent with the findings that I_K-ATP activation can generate an ER pattern in canine ventricular wedge preparations, a rare variant in *KCNJ8*, responsible for the pore forming subunit of the I_K-ATP channel, has been reported in a patients with ERS as well as BrS.[25-27] Loss of function mutations in the α1 and β2 and α2δ subunits of the cardiac L-type calcium channel (*CACNA1C, CACNB2, and CACNA2D1*) have been uncovered in patients with ERS.[28] The most recent addition to the genes associated with ERS is *SCN5A*, the gene that encodes the α subunit of the cardiac sodium channel.[29] Interestingly, it appears that The *SCN5A* mutations are associated with a Type 3 ERS in which a J point or ST segment elevations is present in the right precordial leads as well as in the inferior and lateral leads under baseline conditions or following a sodium block challenge.[29]

It is noteworthy that only a small fraction of identified genetic variants in the numerous genes associated with BrS and ERS have been investigated functionally to elucidate establish causality or a plausible contribution to pathogenesis. Very few have been studied in genetically engineered animal model or native cardiac cell. Computational strategies have been developed to predict the functional consequences of mutations, but none of these methods have been rigorously tested. The lack of functional or biological validation of mutation effects remains the most severe limitation of genetic test interpretation.[30] This limitation is further extended to those cases in which a susceptibility gene has been identified on the basis of a single proband and with the absence of familial segregation data.

Ionic and Cellular Mechanisms

The J wave in the ECG is inscribed as a consequence of the presence of a prominent I_{to}-mediated action potential notch in epicardium, but not endocardium giving rise to a transmural voltage gradient.[31, 32] Direct evidence in support of this hypothesis derives from data first reported using the arterially-perfused canine ventricular wedge preparation.[11]

Factors that augment or reduce I_{to} or that speed or slow the kinetics of the current can importantly modify the manifestation of the J wave on the ECG. Whether augmented by exposure to hypothermia, I_{Ca} and I_{Na} blockers or I_{to} agonists such as NS5806 or reduced by I_{to} blockers such as 4-aminopyridine, quinidine or premature activation or, changes in the magnitude of the epicardial AP notch parallel those of the J wave.[33, 34]

Brugada Syndrome

The proposed cellular mechanism for the Brugada syndrome is summarized in Fig. 1. Most studies support the hypothesis that the Brugada syndrome results from amplification of heterogeneities intrinsic to the early phases of the action potential among the different transmural cell types. An increase in net repolarizing current due to either a decrease of inward currents such ands I_{Na} or I_{Ca} or an increase of outward current such as I_{to} or I_K-ATP, accentuates the notch leading to augmentation of the J wave or appearance of ST segment

elevation. A further increase in net repolarizing current can result in partial or complete loss of the action potential dome, leading to a transmural voltage gradient that manifests as an accentuated J wave or an ST segment elevation.[15, 33, 34] In regions of the myocardium exhibiting a prominent I_{to}, such as the epicardium of the right ventricle, marked accentuation of the action potential notch gives rise to a coved-type ST segment elevation diagnostic of BrS. Additional outward shift of the net current active during the early phase of the AP can lead to loss of the AP dome (APD), thus creating a dispersion of repolarization between epicardium and endocardium as well as within epicardium, between the region at which the dome is lost and regions at which it is maintained. The transmural dispersion is responsible for the development of ST segment elevation and the creation of a vulnerable window across the ventricular wall, whereas the epicardial dispersion give to phase 2 reentry, which provides the extrasystole that captures the vulnerable window, thus precipitating VT/VF. The VT is usually polymorphic, resembling a very rapid form of Torsade de Pointes.

Recent studies have suggested that delayed conduction or abnormal depolarization in the right ventricular outflow tract provides the principal substrate of the ST segment elevation or J waves associated with BrS.[35, 36] The repolarization vs. depolarization hypotheses controversy has been documented as a published debate.[37] Our group has performed thousands of experiments in several different models of Brugada syndrome involving both loss of inward current and gain of outward currents. In none of these have we or anyone else working with similar models ever found evidence that the electrocardiographic or arrhythmic manifestations of BrS are based principally on conduction delay.

Apparently compelling data in support of delayed conduction in the RVOT as the basis for BrS was recently provided by Nademanee and co-workers.[36] Using a bipolar electrogram applied to the epicardial surface of the RVOT, these authors recorded late potentials, in some cases appearing as a continuous fractionated electrogram. This activity was interpreted as indicating delayed conduction over the anterior aspect of the RVOT epicardium. Catheter ablation over this abnormal region of the RVOT resulted in normalization of the Brugada ECG pattern over a period of up to 3 months and prevented induction of VT/VF as well as spontaneous recurrence of VT/VF episodes. Signal averaged ECG (SAECG) recordings have also demonstrated late potentials in patients with the Brugada syndrome, especially in the anterior wall of the right ventricular outflow tract (RVOT).[38-44]

Although late potentials of the type described by Nademanee et al. are traditionally ascribed to conduction delays secondary to structural defects, in cases of BrS they are more likely to arise from a delayed second upstroke of the epicardial action potential in the RVOT or as a consequence of concealed phase 2 reentry.[37, 40, 45] It is noteworthy that wall motion abnormalities have also been detected in BrS patients[46]. Although such contractile abnormalities are commonly considered pathognomonic of structural disease, in the setting of BrS, they are likely to be the result of loss of the action potential dome in the right ventricular epicardium.[40, 47] Loss of the dome is expected to lead to contractile dysfunction because calcium entry into the cells is greatly diminished and sarcoplasmic reticulum calcium stores are depleted.

The rate-dependence of the ST segment elevation in BrS has been suggested to be helpful in discriminating between the repolarization and depolarization hypotheses.[45] If the ST segment elevation is due predominantly to delayed conduction in the RVOT, acceleration of the rate would be expected to further aggravate conduction and thus accentuate the ST segment elevation in the ECG. If, on the other hand, ST segment elevation or the BrS phenotype is secondary to accentuation of the epicardial action potential notch, acceleration of the rate would be expected to normalize the ECG, by reducing the action potential notch and restoring the action potential dome in RV epicardium. This occurs because the transient

outward current, which is at the heart of this mechanism, is slow to recover from inactivation and is less available at faster rates.

Although there are relatively few reports of the effects of pacing, most investigators in the field agree that there is a tendency for the Brugada ECG to normalize during an increase in heart rate consistent with the repolarization hypothesis.[48-50] There are however also reports of ST segment elevation or J point elevation with exercise. Amin et al. recently reported J point elevation in BrS patients (both SCN5A+ and SCN5A−) during exercise.[51] The principal difference between studies showing a decrease vs. increase of the J point in response to exercise appears to be the presence of a prominent ST segment elevation at baseline in the former.

In BrS cases in which ST segment elevation is accompanied by notching of the QRS, suggesting major conduction delay in the RV, exercise-induced acceleration of rate leads to further fragmentation of the QRS, but to a *normalization* of the ST segment elevation in all right precordial leads.[37] These findings suggest that the ST segment elevation is due to a repolarization defect and not to the clearly apparent depolarization defect responsible for the fragmentation of the QRS. Fragmentation of the QRS is associated with increased mortality and arrhythmic events in patients with coronary artery disease as well as patients with arrhythmogenic right ventricular cardiomyopathy and Brugada syndrome.[52]

Finally, Kurita et al. placed monophasic action potential (MAP) electrodes on the epicardial and endocardial surfaces of the right ventricular outflow tract (RVOT) in patients with the Brugada syndrome and demonstrated an accentuated notch in the epicardial response, thus providing direct support for the repolarization hypothesis in humans.[53, 54]

Additional support for the repolarization hypothesis derives from the demonstration that quinidine normalizes ST segment elevation and ***suppresses*** late potentials recorded in patients with Brugada syndrome.[55-57] These effects of the drug are presumably due to inhibition of I_{to} leading to reduction of the epicardial action potential notch and normalization of the repolarization heterogeneities. If the ST segment elevation or the late potentials were due to delayed conduction, quinidine-induced I_{Na} inhibition would be expected to accentuate their appearance.

It is noteworthy that experimental models displaying major conduction delays have been developed by exposing wedge preparations to global ischemia.[58, 59] Progressive delay in these models leads to a gradual prolongation of the R wave and inversion of the T wave. The ECG at first glance resembles a BrS phenotype, but with closer inspection it is clear that the depolarization hypothesis does not lead to an ST segment elevation, but rather to an R wave prolongation. The marked conduction delay is due to a discontinuity in conduction in the deep subepicardium. Conduction under these conditions is exquisitely sensitive to rate, with acceleration leading to block and inexcitability. This is a common characteristic of ischemia-induced tombstone morphology of the ECG, induced by coronary spasm.[60] but is not characteristic of BrS A similar phenomenon is observed in right ventricular wedge preparations following exposure to hyperkalemic conditions.[61]

Also of interest is the observation that magnetocardiograms recorded from patients with complete RBBB generate currents from the RVOT to the upper left chest that are opposite from those recorded in patients with Brugada syndrome.[62]

While the available data, both basic and clinical, point to the repolarization hypothesis, i.e., transmural voltage gradients that develop secondary to accentuation of the epicardial notch, at times leading to loss of the action potential dome, as the predominant mechanism underlying the Brugada syndrome ECG signature and arrhythmogenesis, there is no doubt

that in some cases, particularly those associated with sodium channel loss of function, conduction slowing may contribute to the development of arrhythmias. There are also likely to be cases in which a conduction defect may predominate.[63, 64]

In patients with BrS, the appearance of prominent J waves is limited to the leads facing the right ventricular outflow tract where I_{to} is most prominent. The prominent I_{to} in right ventricular epicardium provides for a net outward current, which promotes the appearance of the J wave in this region of the ventricular myocardium. In the case of ERS, the appearance of prominent J waves is generally limited to the inferior and lateral precordial ECG leads, pointing to heterogeneities in left ventricular (LV) myocardium as the cause.

Early Repolarization Syndrome

Early repolarization pattern is characterized by J point elevation, J waves with and without ST segment elevation and slurring of the terminal part of the ECG in inferior limb and lateral precordial leads. These electrocardiographic manifestations of ER can be recapitulated in the coronary-perfused LV wedge preparation. Figure 2 illustrates the diversity of ECG phenotypes generated by different configurations of the epicardial action potential notch and varying degrees of transmural conduction in coronary-perfused canine left ventricular wedge preparations. These range from a J point elevation to slurring of the terminal part of the QRS, distinct J waves with and without ST segment elevation as well as gigantic J waves, appearing as an ST segment elevation, which often give rise to polymorphic VT. The distinctive ER patterns all result from “early repolarization” of the epicardial action potential and reflect the dynamicity that could be observed clinically in select patients with ER or ERS. These observations provide justification for the long-standing nomenclature and question the need for narrow or overly restrictive definitions of ER pattern.[65-67]

The ionic and cellular mechanisms involved in generating ER patterns in the ECG appear to be similar to those responsible for BrS. A net outward shift of current due to reduction of I_{Ca} or I_{Na} or augmentation of I_K-ATP have been shown to underlie ER, giving rise to J point elevation and distinct J waves with and without ST segment elevation.

Our working hypothesis is that an outward shift in repolarizing current due to a decrease in sodium or calcium channel currents or an increase in I_{to}, I_K-ATP, I_K-ACh, or other outward currents gives rise to the J wave syndromes (Figure 3). The phenotype depends on the part of the heart that is principally affected and the ion channels involved. The J wave syndromes can be viewed as a spectrum of disorders involving accentuation of the epicardial action potential notch in different regions of heart, leading to the development of prominent J waves that predispose to the development phase 2 reentry, which serves to trigger VT/VF.[8]

Clinical Manifestations of J Wave Syndromes

In both BrS and ERS, the manifestation of the J wave or ER is dynamic, with the most prominent ECG changes appearing just before the onset of VT/VF. (see also[18, 19] for references). Other ECG characteristics of ERS also closely match those of BrS, including the presence of accentuated J waves, ST segment elevation, pause and bradycardia-dependence, short coupled extrasystole-induced polymorphic VT/VF. Suppression of the ECG features by isoproterenol or pacing in ER patients further supports the notion that they share common underlying electrophysiologic abnormalities with BrS patients.[20] However, salient diagnostic features of BrS such as provocation by sodium channel blockers or positive signal averaged ECG are rarely observed in these ERS patients.[17, 20] An exception to this rule appears to apply to ERS associated with SCN5A mutations.[29] Kawata and coworkers recently showed that sodium channel blockers attenuate ER in patients with both

ERS apparently due to slowing of transmural conduction so that J point shifts to a lower position on the terminal part of the QRS.[68] The principal difference between ERS and BrS is the myocardial region associated with the highest arrhythmogenic risk; it is the right ventricular outflow tract (RVOT) in the case of BrS and the inferior region of the left ventricle in ERS (Table 2).

Of note, experimental studies have also provided evidence in support of the hypothesis that accentuated J waves associated with the early phases of ischemia may also be due to an accentuation of the action potential notch in epicardium, but not endocardium.[69]

Differentiating J waves Caused by Depolarization vs. Repolarization Abnormalities

It is noteworthy that perturbation in the terminal part of the QRS that are generally referred to as J waves can arise from either repolarization or depolarization abnormalities. When due to depolarization defects, it often appears as a notch interrupting the descending limb of the QRS, with little or no ST segment elevation. Depolarization defects contributing to apparent J waves on the descending limb of the QRS or “terminal QRS distortion” can occur in the setting of bundle branch block, peri-infarction block, or severe ischemia in the Sclarovsky-Birnbaum system.[70].

One way to distinguish between the two mechanisms is to examine the effect of rate or atrial premature responses. When due to delayed conduction, the notched appearance should become accentuated with acceleration of rate or prematurity, and when due to repolarization problems, the amplitude of the J wave should diminish. These different responses are due to the fact that delayed conduction almost invariably becomes more accentuated at faster rates or with prematurity, whereas the I_{to}-mediated APN diminishes due to insufficient time for the I_{to} to reactivate.

Summary and Conclusion

Idiopathic ventricular tachycardia and fibrillation (VT/VF) have been associated with the appearance of prominent J waves for over three decades. Accentuated J waves characterize both Brugada and early repolarization syndromes prompting their designation as J wave syndromes. An early repolarization (ER) pattern, characterized by J point elevation, slurring of the terminal part of the QRS and in some cases ST segment elevation, although considered a benign electrocardiographic manifestation until a decade ago, has more recently been shown to be associated with increased risk for life-threatening arrhythmias, named early repolarization syndrome (ERS). Experimental data as well as numerous clinical case-control and population-based association studies have advanced evidence that an ER pattern in the inferior or infero-lateral leads is associated with increased risk for development of life-threatening arrhythmias. ERS and Brugada syndrome (BrS) share similar electrocardiographic features, clinical outcomes, risk factors as well as a common arrhythmic platform related to amplification of I_{to}-mediated J waves. Although BrS and ERS differ with respect to the magnitude and lead location of abnormal J wave manifestation, they are thought to represent a continuous spectrum of phenotypic expression, termed J wave syndromes. The two syndromes have been shown to be associated with gain of function mutations in genes that encode outward currents, such as I_{to} and I_K-ATP, or in loss of function mutations in genes that encode inward currents such as I_{Ca} and I_{Na}, thus producing an outward shift in the balance of current active during the early phases of the action potential. In the case of epicardium, this results in an accentuation of the action potential notch, which underlies the manifestation of J waves and apparent ST segment elevation. Although the vast majority of subjects presenting with ER patterns are not

believed to be at increased risk, the challenge ahead is to identify the small subset of patients who are at risk.

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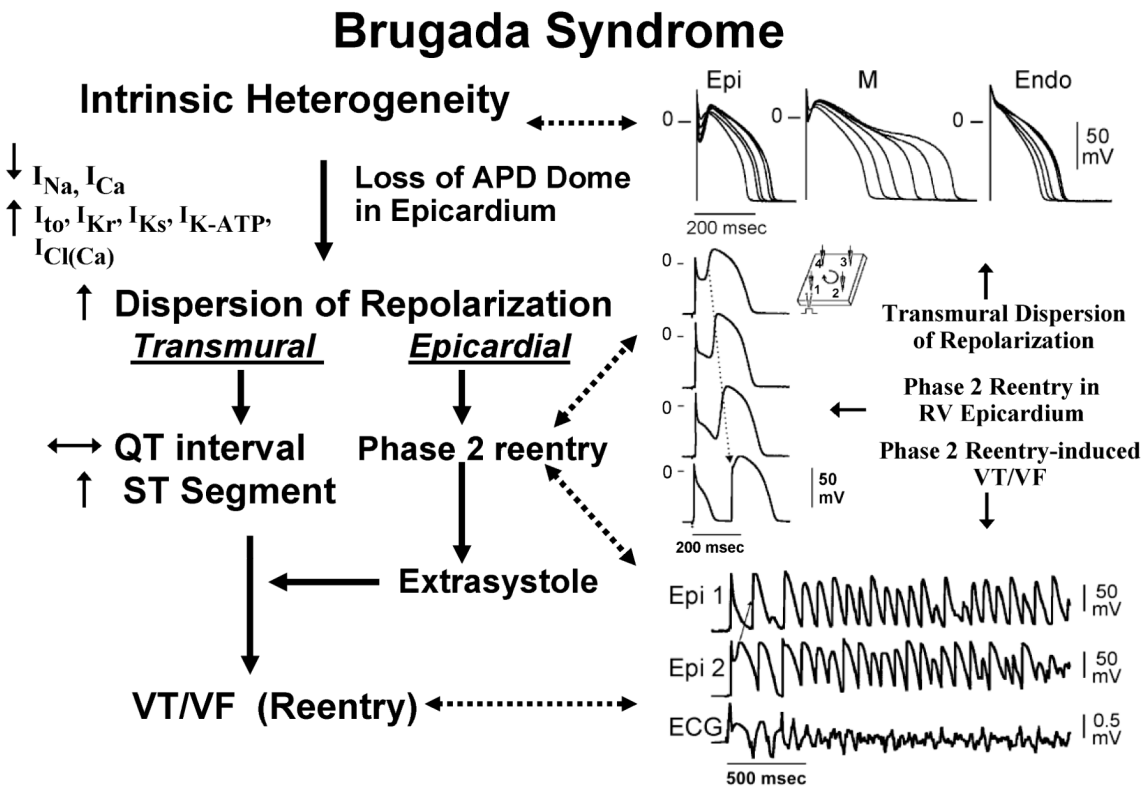

Figure 1.

Proposed mechanism for the Brugada syndrome. A shift in the balance of currents serves to amplify existing heterogeneities by causing loss of the action potential dome at some epicardial, but not endocardial sites. A vulnerable window develops as a result of the dispersion of repolarization and refractoriness within epicardium as well as across the wall. Epicardial dispersion leads to the development of phase 2 reentry, which provides the extrasystole that captures the vulnerable window and initiates VT/VF via a circus movement reentry mechanism. Modified from [76], with permission.

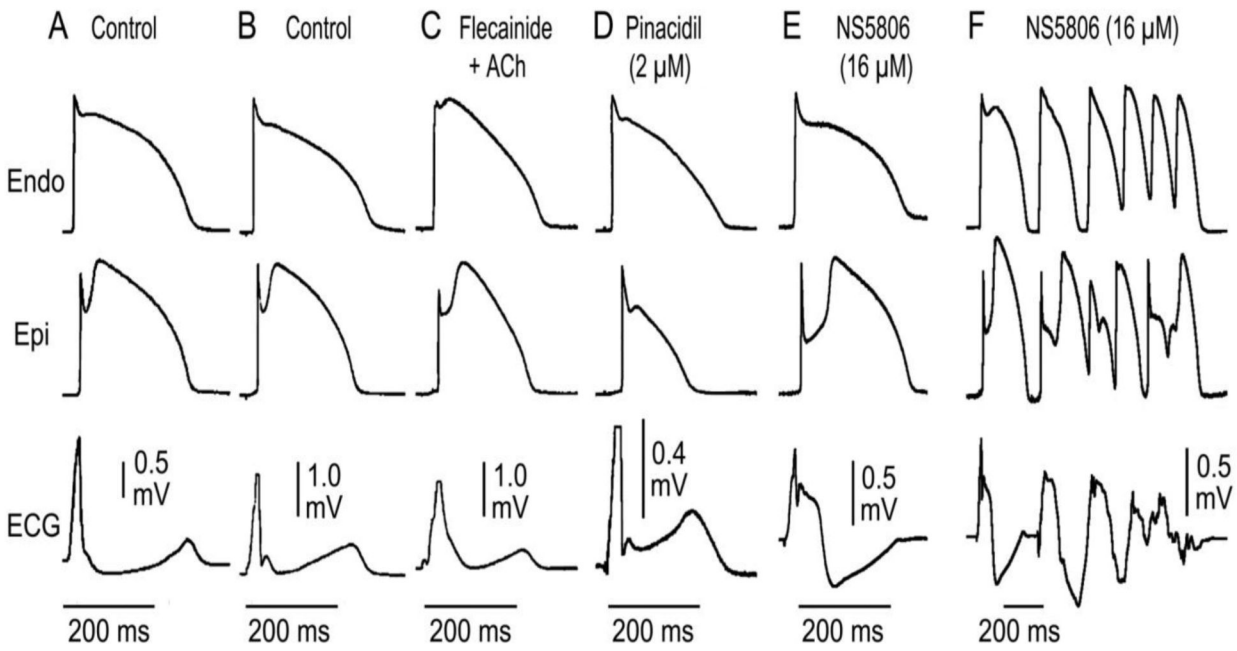

Figure 2.

Diverse manifestations of early repolarization pattern. Each panel shows transmembrane action potentials recorded from the epicardial and endocardial regions of arterially-perfused canine left ventricular wedge preparations and a transmural ECG simultaneously recorded. Under the conditions indicated, early repolarization of the epicardial action potential result in different configurations of the action potential notch giving rise to diverse electrocardiographic manifestations of ERP. The six panels illustrate the cellular basis for a J point elevation, a distinct J wave, slurring of the terminal part of the QRS, combined J wave, J point and ST segment elevation, and a gigantic J wave appearing as an ST segment elevation, which gives rise to polymorphic VT. Modified from [77], with permission.

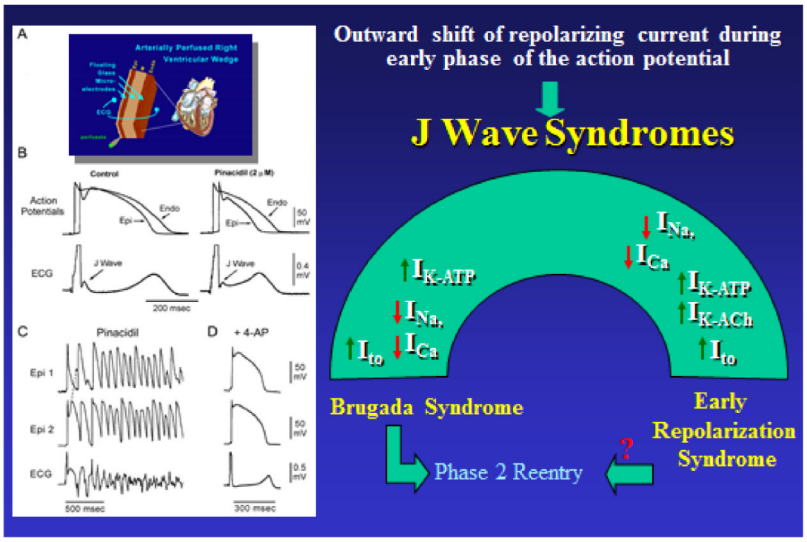

Figure 3.

Ionic and Cellular basis for the early repolarization syndrome. **Left panel**: **A:** Schematic of Coronary-perfused wedge preparation **B:** Simultaneous recording of transmembrane action potentials (APs) from epicardial (Epi) and endocardial (Endo) regions and a transmural ECG in an isolated arterially perfused canine ventricular wedge. A J wave in the transmural ECG is manifest due to the presence of an AP notch in epicardium but not endocardium. Pinacidil (2 μM), an ATP-sensitive potassium channel opener, causes depression of the AP dome in epicardium, resulting in ST segment elevation in the ECG resembling the ERS. **C:** I_K-ATP activation in the canine right ventricular wedge preparation using 2.5 uM pinacidil produces heterogeneous loss of the AP dome in epicardium, resulting in ST segment elevation, phase 2 reentry and ventricular tachycardia or ventricular fibrillation (VT/VF) (BrS phenotype). **D:** The I_{to} blocker, 4-aminopyridine (4-AP), restored the Epi AP dome, reduced both transmural and Epi dispersion of repolarization, normalized the ST segment and prevented phase 2 reentry and VT/VF in the continued presence of pinacidil. (Modified from [8], with permission). **Right panel:** Schematic depicting our working hypothesis of the ionic mechanism underlying the J wave syndromes. An outward shift in repolarizing current due to a decrease in sodium or calcium channel currents or an increase in I_{to}, I_K-ATP or I_K-ACh, or other outward currents gives rise to accentuated J waves associated with the Brugada syndrome and early repolarization syndrome. Both are thought to be triggered by closely-coupled phase 2 reentrant extrasystoles, but in the case of ERS a Purkinje source of ectopic activity is also suspected. (Modified from [8], with permission)

Table 1

J-wave Syndromes: Similarities and Differences

	J Wave Syndromes					
	Inherited				Acquired	
	ER in lateral leads ERS Type 1	**ER in inferior or infero-lateral leads ERS Type 2**	**Global ER ERS Type 3**	**Brugada Syndrome**	**Ischemia-mediated VT/VF**	**Hypothermia-mediated VT/VF**
Anatomic Location	Antero-lateral left ventricle	Inferior left ventricle	Left and right ventricles	Right ventricle	Left and right ventricles	Left and right ventricles
Leads Displaying J point/ J-wave	I, V4-V6	II, III, aVF	Global	V1-V3	Any of 12 leads	Any of 12 leads
Response of J wave /ST Elevation to: Bradycardia or pause Na+ channel blockers	↑ ↓ →	↑ ↓ →	↑ ↓ →	↑ ↑	N/A N/A	N/A N/A
Sex Dominance	**Male**	**Male**	**Male**	**Male**	**Male**[71,72]	Either gender
VT/VF	Rare Common in healthy athletes[12, 13, 34]	Yes[16,73]	Yes, Electrical storms[17, 74]	Yes	Yes	Yes
Response of to Quinidine: J wave /ST elevation VT/VF	↓ ↓	↓ ↓	↓ ↓	↓ ↓	Limited data	↓ [75]
Response of to Isoproterenol: J wave /ST elevation VT/VF	↓ ↓	↓ ↓	Limited data	↓ ↓	N/A	N/A

ER= early repolarization; ERS=early repolarization syndrome; N/A=not available; VF=ventricular fibrillation; VT=ventricular tachycardia. Modified from [8], with permission.

Table 2

Features Common to Brugada and Early Repolarization Syndromes and Possible Underlying Mechanisms

	BrS	ERS	Possible Mechanism(s)
Region Associated with highest arrhythmic risk	RVOT	Inferior myocardium	Increased levels of I_{to}
Male Predominance	Yes (75%)	Yes (80%)	Testosterone modulation of ion currents underlying the epicardial AP notch
Average age of first event	~35-40	42	
Dynamicity of ECG	High	High	Autonomic modulation of ion channel currents underlying early phases of the epicardial AP
VT/VF trigger	Short-coupled PVC	Short-coupled PVC	Phase 2 reentry
Ameliorative response to quinidine	Yes	Yes	Inhibition of Ito and possible vagolytic effect
Ameliorative response to Isoproterenol and cilostazol	Yes	Yes	Increased ICa and faster heart rate
Ameliorative response to pacing	Yes	Yes	Reduced availability of I_{to} due to slow recovery from inactivation
Vagally-mediated accentuation of ECG pattern	Yes	Yes	Direct effect to inhibit I_{Ca} and indirect effect to increase I_{to} (due to slowing of heart rate)

RVOT=right ventricular outflow tract, AP=action potential; PVC=premature ventricular contraction