The Brugada ECG Pattern

A Marker of Channelopathy, Structural Heart Disease, or Neither? Toward a Unifying Mechanism of the Brugada Syndrome

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In 1992, Brugada and Brugada introduced a new clinical entity characterized by right precordial ST-segment elevation followed by a negative T-wave and a high incidence of ventricular fibrillation (VF) in the absence of structural heart disease. The typical ECG anomaly is currently known as the Brugada ECG pattern and the conglomerate of features as the Brugada syndrome. Over the years, the Brugada syndrome has been recognized as an important cause of sudden cardiac death in young men, especially in Southeast Asia, and has attracted much attention from researchers and clinicians alike. This has led to substantial progress in identification of modulating factors of the Brugada ECG pattern, the associated ventricular arrhythmias, and in the risk stratification of patients. However, the development of effective therapeutic strategies has lagged behind. Currently, symptomatic treatment with implantable cardioverter-defibrillators (ICDs) is the mainstay in the prevention of sudden cardiac death, although it is costly and associated with a high risk of complications.

The pathophysiological mechanism of the Brugada syndrome remains elusive, and no single causal factor appears to link all patients. The Brugada ECG pattern is modulated by genetic mutations and pharmacological agents that alter the function of ion channels active during the early phases of the action potential. Furthermore, signs of right ventricular structural abnormalities are often found in patients with Brugada syndrome. The aim of this study is to review the available literature on the Brugada syndrome in an attempt to provide a unifying hypothesis of the mechanism of the Brugada syndrome. This unifying hypothesis should be able to explain the ECG pattern, the arrhythmogenic mechanism, their modulation by ion channels, and the relation of structural abnormalities to the Brugada syndrome.

Is the Brugada Syndrome a Channelopathy?
The Brugada syndrome was introduced shortly after the first demonstration of statistical linkage between the long-QT syndrome (LQTS) and a gene locus. Since then, genetic mutations that alter ion channel functions and prolong the QT duration have been linked with the LQTS. These observations defined the LQTS as a channelopathy. In analogy with the LQTS, a hereditary pattern was suspected in half the Brugada syndrome cases. Additionally, no structural heart disease was demonstrated, suggesting that the Brugada syndrome also was a channelopathy. Over the years, this analogy was substantiated by further observations of similarity with the LQTS.

Genetics
Genetic mutations that alter ion channel functions have been identified in patients with Brugada syndrome. The first identified mutations were located in SCN5A, the gene encoding the α-subunit of the cardiac sodium channel, leading to reduced cardiac sodium current (I\text{Na}). The prevalence of SCN5A mutations is ~20% and is higher in patients with than without a family history of Brugada syndrome. Recently, mutations in GPD1L, a gene probably involved in the transportation of cardiac sodium channels to the membrane and in SCN1B and SCN3B, encoding β-subunits of sodium channels, have also been associated with the Brugada syndrome. However, these mutations are rare among patients. A mutation in KCNE3 has been associated with the Brugada syndrome in 1 family. This gene encodes MiRP2, a β-subunit of several potassium channels. Mutations in CACNA1C and CACNB2b, genes encoding the α1-L and β2b-subunits of the L-type calcium channel, which reduce the L-type calcium current (I\text{CaL}), have been associated with the Brugada phenotype in combination with a relatively short QT interval.

Modulators of the Brugada ECG Pattern and Arrhythmias
The Brugada ECG pattern can vary spontaneously and can even disappear temporarily. Before VF, the Brugada ECG pattern becomes more prominent and is often accompanied by shortly coupled premature ventricular complexes (PVCs) that initiate VF. Interestingly, the origin of these PVCs appears to depend on whether patients carry an SCN5A mutation. In patients without an SCN5A mutation, most PVCs have left...
bundle-branch block morphology and probably originate from the right ventricle. In SCN5A mutation carriers, PVC morphologies are more diverse and often have right bundle-branch block morphology in line with a left ventricular origin.20 Like in the LQTS,21 the Brugada ECG pattern and ventricular arrhythmias appear to have specific triggers. The Brugada ECG pattern is usually more pronounced at night or at rest22 and after large meals,23 when most VF episodes and sudden deaths in the Brugada syndrome also occur.22,23,24 Fluctuations in heart frequency during Holter monitoring have suggested that increased vagal activity precedes VF.19 Also, 123I-MIBG SPECT imaging has shown that cardiac norepinephrine uptake is reduced in patients with Brugada syndrome.25 However, it is unclear whether this represents reduced neuronal uptake or regional denervation and whether it underlies the vagal modulation of the Brugada syndrome. Febrile illness can also augment or provoke the Brugada ECG pattern and trigger arrhythmias.26 Therapeutic hypothermia after resuscitation for VF concealed the Brugada ECG pattern28 and can be beneficial in the treatment of electrical storms.32

Responsiveness to Pharmacological Agents
Like the QT-prolongation in LQTS, the Brugada ECG pattern can be augmented or provoked by pharmacological agents such as sodium channel blockers (class 1A and 1C), β-blockers, and acetylcholine.28 Paradoxically, the class 1A sodium channel blocker quinidine reduces the Brugada ECG pattern29 and inducibility of VF.30 Besides blocking sodium channels, quinidine has vagolytic effects and blocks several potassium currents.31 Likewise, isoproterenol can attenuate the Brugada ECG pattern28 and can be beneficial in the treatment of electrical storms.32

The Canine Right Ventricular Wedge Preparation
The canine right ventricular wedge preparation has provided mechanistic support for the Brugada syndrome as a repolarization-related disorder.33 The transient outward current (Ito) is larger in subepicardial than in subendocardial myocytes.34 In this preparation, the subepicardial abundance of Ito in combination with slow pacing rates, sodium channel blockade, and acetylcholine led to loss of the action potential dome and early completion of repolarization in the right ventricular subepicardium but not the subendocardium. This transmural repolarization gradient caused ST-segment elevation on a transmural pseudo-ECG and was suggested to underlie the ST-segment elevation of the Brugada ECG pattern (Figure 1, loss of action potential dome, solid line). Other subepicardial myocytes have a prolonged action potential and were suggested to underlie the negative T-wave of the Brugada ECG pattern (Figure 1, loss of action potential dome, dashed line).

This “transmural dispersion of repolarization” hypothesis also tentatively provides a mechanism for initiation of VF in the Brugada syndrome. The repolarization gradient causes an electrotonic transmural current from sites with normal to sites with early repolarization, flowing during phase 2 of the action potential. This current was suggested to initiate action potentials at sites of early repolarization (phase 2 reentry). Spontaneous extrasystoles in the canine right ventricular wedge preparation originate from sites of early repolarization.35 In this model, quinidine and isoproterenol attenuate the Brugada ECG pattern by blocking of Ito or increase in Icalc, respectively, thereby restoring the balance between repolarizing and depolarizing currents during phase 1 of the action potential and preventing subepicardial loss of the action potential dome.33

Limitations to the Concept of the Brugada Syndrome as a Channelopathy
The causality between loss-of-function mutations in SCN5A and the Brugada syndrome has been questioned.35 Only ≈20% of patients carry an SCN5A mutation,9 and the prevalence in those without a family history is even lower.10 If the Brugada syndrome were a congenital channelopathy, the overwhelming part of patients should carry mutations. However, no hereditary pattern is evident in most index patients.9,10 Still, de novo mutations or a multifactorial genetic background could underlie the Brugada syndrome. Ideally, such a complex hereditary origin of a syndrome is demonstrated by twin studies. So far, only 1 report of an identical male twin with the Brugada syndrome has been published, and, of these twins, only 1 brother manifested the Brugada syndrome.36

Second, unlike the SCN5A mutations in LQT3,37 no statistical linkage has been demonstrated between loss-of-function
SCN5A mutations and the Brugada syndrome in families affected by both. In these families, 8 of the 62 individuals with the Brugada ECG pattern did not carry the familial SCN5A mutation. Third, the hypothesized loss of action potential dome as cause of the Brugada syndrome has not been confirmed in patients. In 2 studies, unipolar electrograms from the epicardium of the right ventricular outflow tract demonstrated no early repolarization during the ST-segment. Similarly, monophasic action potentials recorded at the right ventricular epicardium during open heart surgery demonstrated no loss of dome or early repolarization. Also, arrhythmias appeared to originate from the subendocardium rather than from the subepicardium during a mapping study. Finally, sodium channel blockers do not provoke the Brugada ECG pattern in healthy individuals or in all SCN5A mutation carriers. These findings suggest that other factors besides a reduced sodium channel function are essential for the Brugada syndrome.

**Is the Brugada ECG Pattern a Marker of Structural Heart Disease?**

Before the description of the Brugada syndrome, Martini et al presented 3 patients with idiopathic VF and right precordial ST-segment elevation. One of these patients demonstrated what was later to be called the Brugada ECG pattern. In contrast with Brugada and Brugada, structural right ventricular abnormalities were found on careful reevaluation of these patients. This led the authors to suggest that right ventricular structural abnormalities underlie the Brugada syndrome. Since then, signs of right ventricular structural abnormalities were found in more studies on patients with the Brugada ECG pattern. Conversely, the Brugada ECG pattern can also be provoked in patients with cardiac structural changes.

**Histopathological Studies**

Corrado et al identified 13 young sudden cardiac death victims who retrospectively showed the Brugada ECG pattern. Twelve of them demonstrated structural heart disease consistent with arrhythmogenic right ventricular cardiomyopathy (ARVC). In an autopsy series of patients of southeast Asian descent with sudden unexpected death syndrome later shown to overlap with the Brugada syndrome, structural right ventricular hypertrophy or dilatation, and a variety of conduction system abnormalities occurred in almost every case. In 2 reports, deceased index patients of families affected by sudden cardiac death and the Brugada ECG pattern ARVC was demonstrated at autopsy. Furthermore, in a long-term follow-up study of patients with Brugada syndrome, the only sudden death victim showed ARVC at autopsy despite rigorous investigation at time of diagnosis. However, gross structural abnormalities are unlikely to be always present because retrospectively screened autopsy reports of 11 sudden death victims in families affected by Brugada syndrome did not mention structural heart disease.

To date, 2 systematic studies on endocardial biopsies in patients with Brugada syndrome are available. Frustaci et al demonstrated abnormalities in all 18 patients undergoing endocardial biopsy. Lymphocytic myocarditis and atypical cardiomyopathic alterations (hypertrophy and diffuse vacuolization) were the most common findings. Zumbagen et al demonstrated moderate changes such as hypertrophy, mild fibrosis, and fatty infiltration in endocardial biopsies of most patients. In both studies, fibrofatty infiltration consistent with ARVC was demonstrated in only several cases.

**Functional and Anatomic Imaging Studies**

Using computed tomography, Takagi et al have described wall motion abnormalities of mainly the right ventricular outflow tract in 19 of 27 Brugada syndrome patients and focal aneurysmal changes in another 2 patients. Both functional and structural disorders can underlie wall motion abnormalities. However, fibrosis or fatty infiltration was demonstrated in endocardial biopsies in 4 of 13 patients. MRI in 20 Brugada syndrome patients demonstrated a larger right ventricular outflow tract area compared with control subjects and a high intramyocardial T1 signal suggestive for fatty infiltration in 4 patients. Recently, a more elaborate MRI study also identified right ventricular wall motion abnormalities and increased right ventricular end-systolic and inflow tract diameters in Brugada syndrome patients. On echocardiography, right ventricular contraction is delayed by sodium channel blockade in Brugada syndrome compared with control patients, indicative for subtle structural abnormalities or altered functional properties of the right ventricle.

**Electrophysiologic Studies**

Late potentials on signal averaged ECGs are common in Brugada syndrome, especially in symptomatic patients. Late potentials are associated with structural heart disease and are found after myocardial infarction or in ARVC. In the Brugada syndrome, late potentials probably have a subepicardial origin because they coincided with late activation in epicardial but not endocardial electrograms of the right ventricular outflow tract. Furthermore, fragmentation of QRS complexes in the right precordial leads are found in the majority of Brugada syndrome patients with a spontaneous Brugada ECG pattern. Fragmented QRS complexes result from discontinuous activation and, like late potentials, are common after myocardial infarction and in ARVC. Moderate conduction abnormalities were found in Brugada syndrome patients in right ventricular endocardial stimulation and mapping studies. Unipolar electrograms of Brugada syndrome patients contained more fractionation and more right ventricular activation delay after shortly coupled premature stimuli than of control patients. Activation delay on shortly coupled premature stimuli has been demonstrated to depend on the arrangement of structural discontinuities in the myocardium.

The Brugada ECG pattern can also be provoked in patients with cardiac conditions characterized by overt structural abnormalities. In a study by Chiale et al, ajmaline provoked the Brugada ECG pattern and shortly coupled PVCs in 7 of 101 patients in the early stage of Chagas disease. Likewise,
Limitations of the Concept of the Brugada ECG Pattern as a Marker of Structural Heart Disease

The main argument against the concept of the Brugada ECG pattern as a marker of structural heart disease is that signs of structural abnormalities are not found in all patients. Furthermore, the structural abnormalities demonstrated are often subtle and not specific for a disease process and patients do not meet the diagnostic criteria for ARVC, either at the time of diagnosis or at follow-up.60

In short, the classification of the Brugada syndrome as a channelopathy or as marker of structural heart disease is currently not justified. Therefore, the challenge remains to unify the functional modulation and signs of structural abnormalities in a hypothesis on the mechanism of the Brugada syndrome.

A Unifying Hypothesis of the Brugada Syndrome: Two Conspiring Factors

Thus far, 2 explanted Langendorff-perfused hearts of sodium channel mutations carriers have been studied and provided alternative hypotheses of the Brugada syndrome in which decreased cardiac excitability by sodium current reduction and right ventricular structural abnormalities conspire. The first heart was of a Brugada syndrome patient undergoing cardiac transplantation for intolerable ICD discharges for VF.42 No transmural gradient of repolarization was found and when VF was induced by programmed stimulation the first reentrant activation originated from subendocardial, not subepicardial, myocardium. Marked activation delay was observed in the right ventricle, which contained abundant fibrous and adipose tissue. As long as a part of the right ventricle is not activated, a potential gradient exists. Therefore, reentrant activation may circle these sites of conduction block and cause reentry if activation distal to the site of block is sufficiently delayed. Colors depict direction of activation.

The second heart came from a loss-of-function mutation carrier in SCN5A, undergoing cardiac transplantation for end-stage heart failure in dilated cardiomyopathy.69 In this heart, sodium channel blockade provoked right-sided ST-segment elevation on a pseudo-ECG. Neither early repolarization nor late activation was found as a cause of the ST-segment elevation. However, the ST-segment elevation did coincide with loss of local activation at the basal right ventricular subepicardium, which contained fibrosis and fatty infiltration.69 Fibrosis and fatty infiltration form barriers that can create sites of sudden expansion of the myocardium. At the site of “tissue expansion,” few myocytes have to produce the depolarizing current to excite a large mass of neighboring myocytes and conduction may fail (current-to-load mismatch). Therefore, we suggested that excitation failure by current-to-load mismatch causes the ST-segment elevation and that modest activation delay at neighboring sites causes the negative T-wave of the Brugada ECG pattern (Figure 1, excitation failure). The modeling part of this study has supported the feasibility of this hypothesis.69

Success of action potential propagation in structural discontinuous myocardium depends on the tissue architecture69,70 and on the current available for propagation, which is modulated by \( I_{Na} \), \( I_{CaL} \), and \( I_{to} \) (Figure 2). The tissue architecture can be asymmetrical and may result in unidirectional block and in reentrant arrhythmias without the need of an extrasystole by a focal mechanism. According to these conduction hypotheses, isoproterenol attenuates the Brugada ECG pattern by increasing the \( I_{CaL} \), thereby preventing conduction block under current-to-load mismatch conditions.71,72 Likewise, reduction of \( I_{to} \) benefits conduction as demonstrated at the Purkinje-ventricular junction and in simulation studies.73 In a case report, quinidine reversibly eliminated late potentials and attenuated the Brugada ECG pattern, probably because it blocks the repolarizing \( I_{to} \). Therefore, both increase in \( I_{CaL} \) and blockade of \( I_{to} \) may attenuate the Brugada ECG pattern and the associated arrhythmias by preventing conduction block caused by current-to-load mismatch.

The question arises of why these conduction abnormalities preferentially occur at the right ventricular subepicardium. The embryological origin (contribution of the second heart field, neural crest cells) of the right ventricle differs from left ventricle and has been suggested to predispose the right ventricle to arrhythmias in adulthood.75,76 The adult right
Figure 3. Hypothesized relation between loss-of-function mutations in SCN5A, right ventricular structural abnormalities, and the Brugada ECG pattern. Right precordial ST-elevation in the presence (red line) or absence (black line) of loss-of-function mutations in SCN5A are indicated in the graph. Level of structural abnormalities that will be recognized as structural heart disease is indicated by a vertical dashed line, ST-segment elevation sufficient for the diagnosis of the Brugada syndrome is indicated by a horizontal dashed line. In the presence of a loss-of-function mutation in SCN5A, fewer structural abnormalities are required for the development of the Brugada ECG pattern.

Ventricular subepicardium contains most structural discontinuities. The collagen content is markedly higher in the right than the left ventricle in patients without cardiovascular disease\textsuperscript{77} and fatty infiltration—predominately the right ventricular subepicardium—and can be identified in 85% of subjects and even more so in elderly subjects.\textsuperscript{78} Second, the right ventricular subepicardium may have the lowest redundancy in current available for conduction. In guinea pigs, the right ventricle contains fewer sodium channels than the left ventricle.\textsuperscript{79} The expression of cardiac sodium channels is lower at the subepicardium than the subendocardium in mice, which results in a reduced action potential upstroke velocity.\textsuperscript{80} The subepicardium in humans also has a higher \(I_{\text{Na}}\)\textsuperscript{34} which may reduce the safety of conduction.\textsuperscript{79} This makes the right ventricular subepicardium more sensitive to sodium channel blockade. Finally, the subepicardial basal right ventricle is the last activated part of the heart,\textsuperscript{81} limiting the chance of excitation via secondary routes in case of conduction block.

In these conduction hypothesis, fewer structural discontinuities are required for the development of the Brugada ECG pattern if the depolarizing current is reduced by, for example, SCN5A mutations\textsuperscript{69} (Figure 3). If we accept that most structural abnormalities are acquired throughout life, we understand the rarity of the Brugada ECG pattern or the arrhythmias is mechanism in patients with structural abnormalities (eg, excitation failure) than in patients without structural abnormalities (eg, loss of action potential dome). In this case, diagnostics based on the Brugada ECG pattern will increase the prevalence of structural abnormalities in the Brugada syndrome. Different mechanisms probably will have different modulating factors and result in different ventricular arrhythmias.

As in the Brugada syndrome, sodium channel blocking agents can provoke the Brugada ECG pattern in patients with conditions characterized by severe structural abnormalities such as ARVC\textsuperscript{68} and Chagas disease\textsuperscript{67} but not in healthy individuals.\textsuperscript{9,43} Therefore, a presentation bias cannot be the sole cause of the association between the Brugada syndrome and structural abnormalities.

Different Patients, Different Mechanisms

The Brugada ECG pattern may be caused by a different mechanism in patients with structural abnormalities (eg, excitation failure) than in patients without structural abnormalities. Late potentials have a higher prevalence in patients with syncope or aborted sudden death than in asymptomatic patients.\textsuperscript{57} Furthermore, symptomatic Brugada syndrome patients with fragmented QRS complexes are at increased risk of recurrent VF.\textsuperscript{61} However, fibrosis and fatty replacement in endocardial biopsies,\textsuperscript{51} late potentials,\textsuperscript{57} and fragmented QRS complexes\textsuperscript{61} are also common in asymptomatic patients. Furthermore, sodium channel blockade can frequently provoke the Brugada ECG pattern in patients with conditions characterized by severe structural abnormalities such as ARVC\textsuperscript{68} or Chagas disease\textsuperscript{67} but not in healthy individuals.\textsuperscript{9,43} Therefore, a presentation bias cannot be the sole cause of the association between the Brugada syndrome and structural abnormalities.

Presentation Bias

A higher incidence of arrhythmias in patients with structural abnormalities can lead to a presentation bias in the clinic and overrepresentation of structural abnormalities in the Brugada syndrome in literature. Signs of structural abnormalities in the Brugada syndrome are associated with a higher risk of arrhythmias. Late potentials have a higher prevalence in patients with syncope or aborted sudden death than in asymptomatic patients.\textsuperscript{57} Furthermore, symptomatic Brugada syndrome patients with fragmented QRS complexes are at increased risk of recurrent VF.\textsuperscript{61} However, fibrosis and fatty replacement in endocardial biopsies,\textsuperscript{51} late potentials,\textsuperscript{57} and fragmented QRS complexes\textsuperscript{61} are also common in asymptomatic patients. Furthermore, sodium channel blockade can frequently provoke the Brugada ECG pattern in patients with conditions characterized by severe structural abnormalities such as ARVC\textsuperscript{68} or Chagas disease\textsuperscript{67} but not in healthy individuals.\textsuperscript{9,43} Therefore, a presentation bias cannot be the sole cause of the association between the Brugada syndrome and structural abnormalities.

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As in the Brugada syndrome, sodium channel blocking agents can provoke the Brugada ECG pattern in patients with conditions characterized by severe structural abnormalities such as ARVC\textsuperscript{68} and Chagas disease.\textsuperscript{67} In these patients, similar non–pause-dependent, shortly coupled PVCs can accompany the Brugada ECG pattern\textsuperscript{67,84} and initiate similar polymorphic ventricular tachycardias that deteriorate in VF\textsuperscript{84} as in patients with the Brugada ECG pattern without structural heart disease.\textsuperscript{19} Likewise, sudden cardiac death in ARVC patients with the Brugada ECG pattern also appears to occur in the setting of increased vagal tone such as during sleeping or at rest.\textsuperscript{9,49}

Therefore, no difference in modulating factors of the Brugada ECG pattern, triggers, or ventricular arrhythmias have been identified between patients with or without gross structural abnormalities. Thus, it is unlikely that the mechanism of the Brugada ECG pattern or the arrhythmias is different between these conditions.
A Single Cause of the Brugada ECG Pattern and Structural Abnormalities

A third alternative explanation is that structural abnormalities and the Brugada ECG pattern stem from a single cause without the structural abnormalities being a prerequisite for the Brugada ECG pattern. Support for such a relation can be found in mice with haploinsufficiency in SCN5A who develop fibrosis on aging. Therefore, the mechanism causing fibrosis is unknown. Long-term toxicity studies with flecainide in rodents did not result in cardiac fibrosis. Therefore, development of fibrosis may depend on sodium channel dysfunction during early development. Recently, Sato et al demonstrated that plakophilin-2 colocalizes with the cardiac sodium channel at the intercalated disc and that reduction in plakinitt-2 expression results in reduced I Na of isolated neonatal rat cardiomyocytes. Mutations in the gene encoding plakophilin-2 (PKP2) have been associated with ARVC. Hence, PKP2 mutations may cause structural abnormalities and reduce I Na. However, most Brugada syndrome patients do not carry a mutation in SCN5A or plakophilin-2, and such a common cause has not yet been identified.

Structural Changes Secondary to the Mechanism of the Brugada ECG Pattern

On echocardiography, Brugada syndrome patients demonstrated delayed onset of right ventricular contraction that increased after flecainide and correlated well with the ST-segment amplitude of the Brugada ECG pattern. Therefore, a single mechanism probably underlies the delayed contraction and Brugada ECG pattern. This delayed contraction may increase the right ventricular wall stress and over time cause structural abnormalities. However, progression or development of structural abnormalities during follow-up is rare in Brugada syndrome patients. Furthermore, in preexisting conditions characterized by structural abnormalities (ARVC or Chagas disease), sodium channel blockade also often provokes the Brugada ECG pattern. Therefore, structural abnormalities probably are essential for and not secondary to the mechanism of the Brugada ECG pattern.

Conclusion

Structural abnormalities probably are intrinsic to the Brugada syndrome, and limited sensitivity of our diagnostic modalities may render these structural discontinuities difficult to distinguish from normal. None of the proposed mechanisms of the Brugada syndrome and the Brugada ECG pattern stem from a single cause without the structural abnormalities being a prerequisite for the Brugada ECG pattern. Support for such a relation can be found in mice with haploinsufficiency in SCN5A who develop fibrosis on aging. Thus far, the mechanism causing fibrosis is unknown. Long-term toxicity studies with flecainide in rodents did not result in cardiac fibrosis. Therefore, development of fibrosis may depend on sodium channel dysfunction during early development. Recently, Sato et al demonstrated that plakophilin-2 colocalizes with the cardiac sodium channel at the intercalated disc and that reduction in plakinitt-2 expression results in reduced I Na of isolated neonatal rat cardiomyocytes. Mutations in the gene encoding plakophilin-2 (PKP2) have been associated with ARVC. Hence, PKP2 mutations may cause structural abnormalities and reduce I Na. However, most Brugada syndrome patients do not carry a mutation in SCN5A or plakophilin-2, and such a common cause has not yet been identified.

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Disclosures

None.


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