Both arrhythmogenic right ventricular cardiomyopathy (ARVC) and Brugada syndrome (BS) are inherited conditions, which distinctively affect the RV and predispose to arrhythmic sudden cardiac death (SCD).1,2 Although ARVC is a heart muscle disorder characterized by loss of RV myocardium with fibrofatty substitution which constitute a part of the substrate for malignant ventricular arrhythmias,3,5 BS is a primary electrical heart disease, and the ventricular electrical instability is not directly related to widespread, major structural myocardial changes.6–8

Since the first description of BS in 1992, problems on nosographic definition, pathogenetic relationship, and differential diagnosis with ARVC have emerged on the basis of common phenotypic manifestations mostly related to the predominant RV involvement with right precordial ECG repolarization abnormalities, RV (outflow tract [OT]) conduction disturbances, and RV ventricular arrhythmias degenerating into ventricular fibrillation (VF).3,10 Moreover, because of the concealed nature of structural changes, which may fall under the resolution power of routine imaging techniques, such as echocardiography, angiography, and magnetic resonance imaging6,7; in contrast, patients with ARVC characteristically show RV morphofunctional changes, such as global dilatation, bulgings/aneurysms, and wall motion abnormalities.23,24

The ECG pattern of BS is characterized by a high take-off of the ST-segment and predispose to phase 2 reentry (or local electrical reentry around fibrofatty tissue).4,5 Fibrofatty myocardial replacement accounts for a right intraventricular conduction defect and predisposes to a scar-related VT similar to that observed in the postmyocardial infarction setting. In contrast, patients with BS typically have no signs of overt structural heart disease detectable by imaging techniques, such as echocardiography, angiography, and magnetic resonance imaging6; in contrast, patients with ARVC characteristically show RV morphofunctional changes, such as global dilatation, bulgings/aneurysms, and wall motion abnormalities.23,24

At variance with ARVC that is a genetic heart muscle disorder of intercellular junctions resulting from mutations of desmosomal and sodium channel proteins.12–21 Whether ARVC and BS actually have a common pathogenetic denominator remained unsolved by past clinical and pathologic studies. However, recent experimental studies have renewed the interest in identifying the mechanisms responsible for the overlapping disease phenotype by demonstrating a subcellular inter-relationship caused by a cross talk between desmosomal and sodium channel proteins.12–21

This article reviews the available clinical, imaging, electrophysiologic, and pathologic evidence of the overlapping phenotype between ARVC and BS and reweaves the scientific discussion about the possible pathogenetic link between these 2 conditions on the basis of significant insights coming from recent studies of molecular biology. The purpose is to put into perspective the debate on this controversial issue, without claiming to draw definite conclusions.

ARVC Versus BS

According to traditional diagnostic criteria, ARVC and BS are distinct clinical entities. ARVC demonstrates substantial differences from BS with respect to involved genes, underlying cardiomyopathic changes, autonomic and antiarrhythmic drug modulation of ECG abnormalities, circumstances and mechanisms of arrhythmias and outcome (Table).

At variance with ARVC that is a genetic heart muscle disorder of intercellular junctions resulting from mutations of desmosomal genes, BS is a channelopathy caused by defects in genes coding for sodium channel, calcium channel, potassium channel, or channel-interacting proteins. Mutations in SCN5A, encoding the cardiac predominant sodium channel α-subunit, are found in ≤30% of patients with BS, whereas other mutant genes are uncommon.22

Patients with BS typically have no signs of overt structural heart disease detectable by imaging techniques, such as echocardiography, angiography, and magnetic resonance imaging6; in contrast, patients with ARVC characteristically show RV morphofunctional changes, such as global dilatation, bulgings/aneurysms, and wall motion abnormalities.23,24

The ECG pattern of BS is characterized by a high take-off and downsloping ST-segment elevation (coved-type morphology) followed by T-wave inversion in V1 and V2/V3, whereas right precordial T-wave inversion in ARVC is usually preceded by no or mild upward ST-segment11 (Figure 1).

The most common arrhythmic event in patients with ARVC is a monomorphic ventricular tachycardia (VT) with a left bundle branch block pattern, most likely resulting from a macroreentry around fibrofatty tissue.4,5 Fibrofatty myocardial replacement accounts for a right intraventricular conduction defect and predisposes to a scar-related VT similar to that observed in the postmyocardial infarction setting. In contrast, patients with BS, a genetically induced sodium channel loss of function has been proposed to lead to loss of the epicardial action potential dome and transmural/epicardial dispersion of repolarization, which, in turn, could induce elevation of the ST-segment and predispose to phase 2 reentry (or local
reexcitation) leading to rapid polymorphic VT, which can degenerate into VF (repolarization theory)\(^7,8\) (Figure 2). On the contrary, impaired conduction in the RVOT in BS may in itself provoke or contribute to inhomogeneous repolarization to trigger malignant arrhythmic events (depolarization theory).\(^25\)

Ventricular arrhythmias in patients with ARVC are facilitated by catecholamines and mostly occur during or immediately after exercise; accordingly, participation in competitive sports has been associated with an increased risk for SCD.\(^26\) Instead, in patients with BS, ST-segment elevation and arrhythmias are characteristically enhanced by vagotropic agents or \(\beta\)-adrenergic blockers, and cardiac arrest has been documented to occur usually at rest or during sleep.\(^7,8\) Unlike ARVC, the ECG abnormalities in patients with BS can vary considerably from time to time, until complete transient normalization, mostly because of variable influences of autonomic nervous system over the time.\(^27\) Administration of sodium channel blockers such as flecainide, ajmaline, and procainamide can accentuate or unmask ST-segment elevation in patients with BS, whereas it usually does not affect ventricular repolarization in patients with ARVC.\(^6,28\)

Finally, the clinical course of both conditions may be complicated by VF leading to SCD mostly occurring in young adults, whereas RV or biventricular heart failure distinctively occur in patients with ARVC as a consequence of progression of the underlying structural myocardial abnormalities over time.\(^1,3,4,7,27,29\)

**Phenotypic Overlap Between ARVC and BS**

Review of the literature demonstrates scientific evidence that features of both ARVC and BS may occur in some patients.

**Clinical Features**

Previous clinical studies demonstrated a phenotypic overlap between the ARVC and BS. In 1986, Martini et al\(^30\) described 6 patients who experienced VF and had clinical evidence of underlying structural abnormalities of the RV; 3 of them exhibited a Brugada-like ECG pattern. Tada et al\(^31\) reported RV morphofunctional abnormalities and histologic abnormalities consistent with ARVC in 5 of 6 Japanese men with a clinical and ECG diagnosis of BS. Corrado et al\(^32\) reported an Italian family with Brugada-like ST-segment elevation, RV cardiomyopathic changes at echocardiography, and diagnostic

<table>
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AD indicates autosomal dominant; AR, autosomal recessive; ARVC, arrhythmogenic right ventricular cardiomyopathy; LAD, left axis deviation; LV, left ventricle; RBBB, right bundle branch block; RV, right ventricle; TWI, T-wave inversion; VF, ventricular fibrillation; and VT, ventricular tachycardia.
of sodium channel blockers. Although epsilon waves were uncommon (6 of 47 patients with BS), other conduction abnormalities such as a terminal QRS activation delay >55 ms were detected in 40% of cases. Moreover, late potential on signal-averaged ECG was identified by Ikeda et al in the majority of patients with BS, despite using more restrictive cutoff values than those proposed by the revised Task Force diagnostic criteria for ARVC. Of interest, the presence of late potential was an independent predictor of life-threatening events with most significant correlation on multivariable analysis. Morita et al recorded a fragmented QRS characterized by multiple spikes within the QRS complex in 43% of basal ECG of patients with BS. This ECG pattern reflected a local epicardial activation delay and was significantly more often found in the patient subgroup who experienced VF (VF subgroup 85%, syncope subgroup 50%, and asymptomatic subgroup 34%; P<0.01). The QRS fragmentation was confirmed to be an independent risk indicator (hazard ratio, 4.94; 95% confidence interval 1.54–15.8; P=0.007) in a large cohort of patients prospectively investigated in the Programmed Electrical Stimulation Predictive Value (PRELUDE) study.

Intracardiac electrophysiologic studies using epicardial and endocardial mapping have consistently confirmed signs of ventricular conduction delay, mostly involving the RVOT in the form of fragmented electrograms and late potentials. These electrogram recordings are typically observed in patients with ARVC as an expression of a discontinuous conduction through the diseased RV myocardium. According to some authors, these findings support the depolarization theory that explains ECG abnormalities and life-threatening ventricular arrhythmias of BS as the result, at least in part, of an intraventricular conduction defect in the RVOT. Such a delayed conduction is presumably caused by relatively mild structural abnormalities, such as histologic myocardial fibrosis, which may not become evident using conventional imaging techniques. Most compelling evidence in favor of this substrate derives from electrophysiologic mapping and ablation procedures in patients with BS, showing that elimination of fragmented electrograms and late potentials in the RVOT resulted in normalization of ST-segment elevation and noninducibility of VT/VF.

Clinicopathologic Features
The largest clinicopathologic study on SCD victims with an ECG pattern of right precordial ST-segment elevation was obtained by reviewing a series of 273 young (<35 years) SCD victims of who were enrolled in the Registry of the Veneto Region of Italy from 1979 to 1998. Among 96 SCD with an available ECG, 13 (14%; 12 men and 1 woman; mean age, 24 years) showed ST-segment elevation in leads V1 to V3, either isolated (9 cases) or associated with right bundle branch block (4 cases). At autopsy, all these victims had pathologic features consistent with ARVC (92%) except 1, who had no evidence of structural heart disease. Compared with the 19 SCD victims with ARVC and no ST-segment elevation from the same series, those with ARVC and right precordial ST-segment elevation significantly more often died suddenly at rest or during sleep showed serial ECG changes over time (Figure 3A) and had polymorphic VT. These findings provide
Figure 3. Electrocardiographic and histopathologic findings in 2 sudden death victims with overlapping phenotype of arrhythmogenic right ventricular cardiomyopathy (ARVC) and Brugada syndrome (BS). **Top.** A 35-year-old man who died suddenly at rest. Baseline 12-lead ECG showing first-degree AV block and a coved-type Brugada ECG (A). Note the serial changes over years of right precordial repolarization abnormalities with transient near-normalization (B). Panoramic histological view of right ventricular (RV) free wall showing transmural myocardial loss with fatty replacement, mostly involving subepicardial and midmural layers (C). At higher magnification, histological examination of RV myocardium shows tiny interstitial fibrosis in the setting of myocardial atrophy and fatty tissue (D). **Bottom.** A 27-year-old patient who died suddenly while sleeping. Baseline 12-lead ECG showing a coved-type Brugada ECG (A). Day-to-day changes of right precordial ST-segment pattern, which exhibits maximum displacement upward on March 22, 1996 (B). Panoramic histological view of RV myocardium disclosing full-thickness fibrofatty myocardial replacement (C). Adapted from Corrado et al.45
compelling evidence that ARVC may present with phenotypic features typically observed in BS.

Pathogenetic Hypotheses
The clinical, imaging, histopathologic, electrophysiologic, and pathologic evidence of a possible overlap between ARVC and BS raises the question on which pathogenetic mechanisms underlie such an interaction.

In the past, the phenocopy theory was proposed based on postmortem histopathologic findings of patients with a mixed phenotype. According to this theory, the Brugada-like ECG and Brugada arrhythmias found in some patients with ARVC are because of pathologic changes that give rise to a structural epicardial–endocardial heterogeneity of repolarization in the RV wall, which in turn may account for a voltage gradient–dependent ST-segment elevation and arrhythmias because of local reexcitation, electrical mechanisms similar to those responsible of ECG repolarization changes and arrhythmias of BS (Figure 3B).45

The overlapping phenotype has been alternatively explained by a genetic theory of double genetic defects leading to the coexistence of both ARVC and Brugada phenotypes or genetically defective cardiac sodium channel secondarily inducing myocyte death and leading to structural cardiomyopathic changes over time that resemble those observed in patients with ARVC.46

More recently, new insights from molecular biology and genetic studies demonstrated molecular and cellular mechanisms of interaction between desmosomes and sodium channel at the intercalated disc, which support the concept that ARVC and BS are not 2 separate entities.

Experimental Cell and Animal Studies
It is noteworthy that intercalated disc is the host of multiple molecular complexes capable of interacting with each other. Electron microscopy images show the proximity at the intercalated disc of mechanical junctions (desmosomal proteins and adherens junctions/area composita), gap junctions, and sodium channel complexes, suggesting the likelihood of mutual interactions between constituting proteins such as plakophilin-2 (PKP2), connexin 43, and Na$_{v}$,1.5 (ie, the major subunit of the cardiac sodium channel), respectively. These molecules populate adhesion/excitability nodes (mininodes of Ranvier) holding the connexome, a protein-interacting network where multiple molecules work together to coordinate excitability, cell coupling, and cell adhesion in the heart (Figure 4).14

Experimental studies have provided solid scientific data that a molecular cross talk exists between desmosomes and both voltage-gated sodium channels and gap junction proteins at intercalated discs. Particularly, cell and animal models studies have shown that the loss of expression of desmosomal proteins may affect the integrity of the voltage-gated sodium channels resident in the cardiac intercalated disc, leading to an alteration of the amplitude and kinetics of sodium current. Using a combination of conventional biochemistry, patch clamp, and optical mapping experiments, Sato et al.15 showed for the first time that PKP2 associates with Na$_{v}$,1.5, and that knockdown of PKP2 expression alters the properties of the sodium current and the velocity of action potential propagation in cultured cardiomyocytes. Biochemical analysis demonstrated that PKP2 communoprecipitates not only with connexin 43 but also with Na$_{v}$,1.5. Voltage clamp study revealed that the loss of PKP2 expression also leads to a decrease in amplitude and a shift in voltage-gating kinetics of the sodium current in adult cardiac myocytes. Optical mapping showed that PKP2 knockdown associates with a significant decrease in conduction velocity in cardiac cell monolayers and an increased propensity to reentrant arrhythmias, likely resulting from the combination of decreased electric coupling and impaired sodium current density.15

A subsequent study showed that the cytoskeletal adaptor protein Ankyrin-G (AnkG) may play a key role in allowing for the interaction between 3 molecular components previously considered independent: the desmosome, the gap junction, and the sodium channel complex.16 A mouse model with PKP2 haploinsufficiency (PKP2-Hz), which mimics the clinical situation of patients harboring truncating mutations (with an expected <50% of PKP2 availability), was used to investigate in vivo the modulation of sodium current amplitude by defective desmosomal proteins in the murine heart.17 The mouse model did not show signs of structural cardiomyopathy. Na$_{v}$,1.5 protein abundance was not altered and yet the

Figure 4. Diagrammatic representation of the relationship between desmosomes, gap junctions, and sodium channels at the intercalated discs. The connexome is a protein-interacting network where these molecules work together to coordinate excitability, cell coupling, and cell adhesion in the heart. The loss of expression of desmosomal proteins may induce electrical ventricular instability by a concomitant sodium channel dysfunction with current reduction, as a consequence of the cross talk between these molecules at the intercalated discs. Adapted from Sato et al.16
amplitude of sodium current in isolated ventricular cardiomyocytes was significantly decreased. Moreover, there was a shift in gating and sodium current kinetics when compared with wild-type cardiomyocytes. These findings indicate that genetically mediated partial loss of PKP2 was able to affect sodium current amplitude, similarly to what was demonstrated in cells after total loss of PKP2 expression.

To investigate the predisposition of hearts deficient in PKP2 to drug-induced arrhythmic events, the PKP2-Hz mouse model was challenged with flecainide (ie, a class 1C sodium channel-blocker antiarrhythmic drug). All treated animals showed an increased sensitivity to flecainide-induced atrial and ventricular conduction prolongation, with marked increased P wave, PR and QRS interval duration and increased conduction velocity in Langendorff-perfused isolated hearts. Of importance, flecainide injection in vivo caused ventricular arrhythmias and some cases of SCD in PKP2-Hz animals but not in the wild-types. These results demonstrated that PKP2 haploinsufficiency reduces sodium current in murine myocardium and may render the heart susceptible to sodium channel–dependent life-threatening arrhythmias, similar to those that precipitate SCD in patients with BS.

The relationship between desmosomal integrity and the structure or function of the sodium channel complex has been confirmed by other studies from different laboratories. Gomes et al reported that patients with ARVC harboring desmoplakin mutations showed regional conduction delay and heterogeneous Na1.5 distribution. In a collaborative immunohistochemistry study on heart samples from patients with ARVC, Noorman et al showed that in most cases, Na1.5 was reduced at the intercalated disc, even if the distribution of the N-cadherin signal remained normal. Reduced sodium current amplitude has been observed in PKP2-deficient HL-1 cells (cardiac muscle cell line) and in induced pluripotent stem cell–derived cardiomyocytes from a patient with PKP2 deficiency.

Rizzo et al studied transgenic mice with cardiac over-expression of mutant desmoglein-2-N271S (Tg-NS/L) before and after the onset of cell death and replacement fibrosis. Before the onset of myocyte necrosis, epicardial mapping in Langendorff-perfused hearts showed prolonged ventricular activation time, reduced longitudinal and transversal conduction velocity, and reduced action potential upstroke velocity because of a lower sodium current density in mice overexpressing a mutation in desmoglein-2. Of interest, spontaneous ventricular arrhythmias, including short run of VT, occurred in mice aged ≥6 weeks that had histopathologic evidence of myocyte necrosis; instead, younger mice showed an increased arrhythmia inducibility by extrastimuli or burst pacing, but no spontaneous arrhythmias.

Recently, Asimaki et al confirmed that Zebrafish ventricular myocytes expressing genetically defective phakoglobin showed a 70% to 80% reductions in sodium current density. It is noteworthy that serious cardiomyopathies with severe structural abnormalities may develop secondarily a nonspecific sodium channel dysfunction with current reduction. The experimental evidence overwhelmingly supports the notion that modifications in desmosomal proteins can affect the sodium current even in the absence of a structural disease, or of a cellular environment compatible with that of a fibrotic heart. The concept is further supported by the observation that the majority of patients with overlapping phenotype reported in the literature were affected by an early or minor variant of ARVC not fulfilling International Task Force criteria for diagnosis of definitive ARVC and, thus, unlikely to induce a secondary sodium channel dysfunction.

**Figure 5.** PKP2 mutations associate with Brugada syndrome and with reduced sodium current. **Top left,** Representative ECG showing ST-segment elevation, diagnostic for Brugada syndrome, in 1 of the 5 patients carriers of missense mutations on the PKP2 gene, and correspondent electropherograms showing the specific amino acid substitution R635Q. **Bottom left,** Sodium current amplitude recorded in HL-1 cells silenced for PKP2 (PKP2-knockdown) transfected with the mutant (red), an empty vector (blue), or wild-type PKP2 (black). **Right,** Pedigree of the family showing cosegregation between the PKP2 mutation and the clinical Phenotype. Hx indicates history; and SD, sudden death. Adapted from Cerrone et al.
Molecular Genetic Studies in Humans
Among 38 Dutch patients with BS in whom SCN5A were previously excluded, Koopmann et al were unable to demonstrate mutations in a variety of other candidate genes including desmosomal genes plakoglobin and plakophilin-2. The authors concluded that the studied candidate genes are unlikely to be major causal genes of BS. Studying a larger patient population, Cerrone et al discovered 5 single amino acid substitutions in 5 unrelated patients by direct sequencing the PKP2 gene in a cohort of 200 patients with clinical diagnosis of BS and no mutations on the most prevalent genes. This missense variant in PKP2 was proved to affect the cardiac sodium current, by using an HL-1 cell line, stably silenced for the endogenous PKP2; in the absence of PKP2, these cells showed a decrease in the native sodium current (Figure 5). Moreover, cells transiently transfected with the PKP2 mutants associated with the Brugada phenotype showed significantly decrease of sodium current, when compared with cells transfected with wild-type PKP2. Similar results were obtained using a line of human induced pluripotent stem cell–derived cardiomyocytes from a patient lacking PKP2 at the cell membrane. In these cells, sodium current increased on transfection with wild-type PKP2, whereas transfection with one of the PKP2 mutants associated with BS was not able to restore normal sodium current. These genotype–phenotype correlation data demonstrated that missense mutations in PKP2 can induce a Brugada phenotype by a decreased cardiac sodium current.

Clinical Implications
The clinical impact of the interaction between desmosomal gene mutations and sodium current is an emerging area of interest that offers arguments of discussion and has the potential to generate further scientific investigations. One clinical implication is that screening of desmosomal gene mutation should be considered as a part of the algorithm of molecular genetic testing of patients with BS, when the genotype is negative for other predominant genes associated with BS. Clinical manifestations of ARVC usually develop during adolescence and young adulthood and are preceded by a long preclinical phase (concealed ARVC), during which SCD has been reported to occur unexpectedly as the first manifestation of the disease. It has been suggested that fatal events occurring before overt structural myocardial changes may be caused by a primarily electrical mechanism, as a consequence of the cross talk of genetically defective desmosomal proteins with the voltage-gated sodium channel complex, leading to reduced sodium current and arrhythmogenic mechanisms similar to those in BS. Previous experimental studies consistently showed that pure electrical abnormalities induced by genetically defective desmosomal proteins created a predisposing arrhythmogenic myocardial milieu, with induction of arrhythmias exclusively in the presence of additional triggers such as drug challenge or electrical pacing in the experimental setting. These data suggest that sodium channel dysfunction secondary to defective desmosomal proteins is unlikely to be sufficient to generate spontaneous arrhythmias; rather, it may contribute to the arrhythmogenesis in the early stage of a developing ARVC structural phenotype (Figure 6). In this regard, it has been recently reported that phenotypic expression was a prerequisite for malignant ventricular arrhythmias and SCD in a cohort of ARVC desmosomal gene mutation carriers prospectively investigated. Arrhythmic events during a long-term follow-up (8.5 years) occurred in desmosomal gene mutation carriers who fulfilled morphofunctional International Task Force diagnostic criteria and showed major risk factors.
Corrado et al  ARVC vs Brugada Syndrome
desmosomal gene mutation carriers without a definite ARVC phenotypic expression had an uneventful clinical course, with the exception of a 15-year-old desmoplakin gene mutation carrier with previously normal ECG and echocardiographic findings who died suddenly 2 years later while sleeping. Postmortem evaluation in this SCD victim demonstrated the presence of an epicardial scar in the inferolateral LV region. This finding suggests that lethal ventricular arrhythmias during the concealed phase of ARVC, other than the expression of a subcellular arrhythmogenic mechanism, may be the result of the low sensitivity of routine clinical tests such as ECG and echocardiography for detection of early/minor arrhythmogenic phenotypic substrates, such as an isolated epicardial scar of the left ventricle, for which detection requires more sophisticated imaging technology such as contrast-enhanced cardiac magnetic resonance. These data were recently confirmed by the study of Te Riele et al showing an ARVC-causing compound DSG-2 gene mutations (1253_1257insATGA, E418fsX419; 2983_2987delGG, G995fsX1014). The patients developed a definite ARVC phenotype with T-wave inversion in right precordial leads (D), RV dilatation/dysfunction (E) with biventricular late gadolinium enhancement at postcontrast sequences on cardiac magnetic resonance (not shown).

A better understanding of the role of sodium current in desmosomal disease is crucial to guide antiarrhythmic therapy with sodium channel blockers in patients affected with ARVC. The knowledge that ARVC and BS may share mechanisms of ventricular arrhythmias mediated by a sodium channel dysfunction may have important pharmacogenetic implications on the response to sodium channel blockers of patients with ARVC, in terms of either therapeutic efficacy or adverse effects. The complex molecular cross talk between desmosomes and sodium channel invites to great caution in using class IC antiarrhythmic agents to treat symptomatic ventricular arrhythmias in patients with ARVC because of the inherent proarrhythmic risk of these drugs to enhance conduction disturbances and repolarization heterogeneity by further reduction of the sodium current. Whether an aggressive antiarrhythmic approach with implantable defibrillator represents a more appropriate prevention strategy in the subset of patients with ARVC, and Brugada-like right precordial ST-segment elevation and polymorphic VT needs to be assessed by future prospective studies.

Sodium channel blockers (including flecainide acetate in Europe) are also currently used as a diagnostic tool in patients with suspect of BS, with the aim to provoke the occurrence of the diagnostic ECG changes by further stressing the sodium channel function. Krishan and Antzelevitch and Antzelevitch and Yan showed a synergism between intramyocardial conduction defect and heterogeneous repolarization in giving rise to arrhythmic activity in canine ventricle. In some patients with ARVC, the reduction in sodium current leading to dispersion of repolarization may contribute importantly to the induction and maintenance of reentrant activity in association with delayed intraventricular conduction. Figure 7. Effects of flecainide test in a 16-year-old patient with compound DSG-2 gene mutations. Pharmacologic sodium channel block test was interrupted after infusion of 50 mg of flecainide acetate because of the occurrence of enormous QRS widening/J wave (A) followed by AV block (B), and ventricular fibrillation (C). The patients survived thanks to an extracorporeal membrane oxygenation device that was promptly applied after unsuccessful cardiopulmonary resuscitation and repeated DC shocks caused by ventricular fibrillation relapses leading to electromechanical dissociation. Subsequent genotyping showed an ARVC-causing compound DSG-2 gene mutations (1253_1257insATGA, E418fsX419; 2983_2987delGG, G995fsX1014). The patients developed a definite ARVC phenotype with T-wave inversion in right precordial leads (D), RV dilatation/dysfunction (E) with biventricular late gadolinium enhancement at postcontrast sequences on cardiac magnetic resonance (not shown).
As a corollary, flecainide would be expected to aid in the evaluation of an increased arrhythmia risk or progression to cardiomyopathy in desmosomal gene mutation carriers by unmasking a concomitant sodium channel dysfunction with current reduction secondary to desmosomal gene mutation. However, anecdotal experience of using flecainide challenge in patients with desmosomal gene-related ARVC warns about the risk of potentially lethal arrhythmic complications (Figure 7). The exaggerated response of patients with ARVC to flecainide is in keeping with the observation that sodium current deficiency induced by desmosomal gene defects increases the susceptibility to flecainide-induced arrhythmias in experimental animals.

Conclusions
This article has proposed the controversial topic on the relationship between ARVC and BS for scientific discussion in light of the results of recent studies of biology and genetics that provide new insights on the existence of a pathogenetic link at molecular level. Accordingly the overlapping phenotype may be explained by the emerging theory that ARVC and BS are not completely different conditions, but the ends of a spectrum of structural myocardiobal abnormalities and sodium current deficiency that share a common origin as diseases of the connexome.

Future experimental and clinical studies are needed to better define the molecular basis and to assess the clinical impact of overlapping phenotypes in terms of prevalence, arrhythmic risk stratification, and therapeutic approaches for prevention of SCD.

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Relationship Between Arrhythmogenic Right Ventricular Cardiomyopathy and Brugada Syndrome: New Insights From Molecular Biology and Clinical Implications
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