Brugada Syndrome and Arrhythmogenic Cardiomyopathy: Overlapping Disorders of the Connexome?

Yael Ben-Haim, MD[1,2], Angeliki Asimaki, PhD[1,2], Elijah R. Behr, MBBS, MD[1,2]

1. Institute of Molecular and Clinical Sciences, St. George's University of London, London, United Kingdom
2. Cardiology Clinical Academic Group, St. George's University Hospitals NHS Foundation Trust, London, United Kingdom

Corresponding author:

Prof. Elijah R. Behr

Cardiology Clinical Academic Group

Institute of Molecular and Clinical Sciences

St. George's University of London

Cranmer Terrace

London, SW17 0RE

Tel. +44 (0)20 8725 2994

Fax: +44 (0)20 8725 3416

Email: ebehr@sgul.ac.uk

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Introduction

Arrhythmogenic cardiomyopathy (ACM) and Brugada syndrome (BrS) are inherited diseases characterized by an increased risk for arrhythmias and sudden cardiac death (SCD). Possible overlap between the two was suggested soon after the description of BrS. Since then, various studies focusing on different aspects have been published pointing to similar findings in the two diseases. More recent findings on the structure of the cardiac cell-cell junctions may unite the pathophysiology of both diseases and give further evidence to the theory that they may in part be variants of the same disease spectrum. In this review, we aim to summarise the studies indicating the pathophysiological, genetic, structural, and electrophysiological overlap between ACM and BrS.

Keywords: Arrhythmogenic cardiomyopathy; Brugada syndrome; genetics; connexome

Definitions and diagnosis of arrhythmogenic cardiomyopathy and Brugada syndrome

Arrhythmogenic cardiomyopathy was first described in 1982 as arrhythmogenic right ventricular dysplasia in a series of patients with right ventricular arrhythmias, electrocardiogram (ECG) changes in right ventricular (RV) precordial leads, and extensive fibro-fatty replacement of their RV myocardium.[1] With better characterization of the disease the name evolved to arrhythmogenic right ventricular cardiomyopathy (ARVC) and, with identification of left dominant and biventricular disease, to the broader term arrhythmogenic cardiomyopathy (ACM).[2] Since clinical, imaging, and pathological findings may not be present in all patients, a criteria system was proposed for its diagnosis and developed together with the understanding of the disease.

The first task force diagnostic criteria for ARVC was published in 1994 and proposed that a diagnosis is fulfilled by the presence of criteria of different types including structural, electrophysiological, and clinical features.[3] While these criteria had high specificity, their sensitivity was low, and family members or patients with early disease could not always be identified. In 2010, as more cases were

described and the pathology, genetics and clinical course of the disease were clearer, a modification of these criteria was proposed in order to increase their sensitivity (Figure 1).[4] The last ACM consensus statement published in 2019 broadened the spectrum of cardiomyopathies under the ACM diagnostic banner and included all heart muscle disorders not caused by ischaemia, hypertension, or valvular disease that have a final common pathway of arrhythmia. This definition includes systemic, inflammatory and genetic disorders, with ARVC among them.[5]

Ten years after the description of ACM, Brugada syndrome was first described as a primary arrhythmia syndrome associated with sudden cardiac death (SCD) and characterized by right precordial lead ST elevation unrelated to ischaemia, electrolyte disturbance, or structural heart disease.[6] Since its publication an increasing number of cases were identified and in 2002 diagnostic criteria were published. With further elaboration in 2005, the criteria relied upon the type 1 Brugada ECG pattern, coved ST elevation with T wave inversion, either appearing spontaneously or with sodium channel blocker challenge (i.e. with ajmaline, flecainide, procainamide, or pilsicainide) in at least two right precordial leads, together with at least one clinical criterion. A lone ECG pattern without any clinical symptoms was considered 'idiopathic Brugada ECG pattern'.[7, 8] The 2013 consensus statement was more lenient, however, and only ECG criteria were needed for the diagnosis.[9] This liberalisation was felt to have resulted in over diagnosis of BrS, especially with regards to drug induced Brugada ECG pattern, as a positive ajmaline test can be seen in over a quarter of patients with atrioventricular nodal re-entry tachycardia (AVNRT).[10]

Finally, in 2016 a diagnostic score system, the Shanghai score, was proposed (Figure 1). Here, similar to previous recommendations, BrS can be diagnosed in the presence of a spontaneous type 1 Brugada ECG pattern. However, if the type 1 pattern was unmasked with a pharmacological challenge or with fever, then clinical history, family history, and genetic criteria, each with a different weight, are needed in order to establish the diagnosis.[11] Recognising that a type 1 Brugada ECG pattern might be provoked by environmental and non-genetic factors, the expert group suggested the diagnosis of a Brugada ECG phenocopy. This phenocopy should be considered when asymptomatic individuals without a family history of sudden death or BrS demonstrate a Brugada ECG pattern in the context of an identifiable

underlying condition and that ECG pattern does not repeat after the resolution of that underlying condition.[11]

Previous case series and reports of possible overlap

While BrS was first thought to be a primary electrical disease without structural abnormalities and ACM a heart muscle disease, there was a growing number of reports of possible overlap between the two conditions. The idea that BrS and ACM may in fact be variants of the same entity can be found as early as 1988 when *Nava et al* published a case with what is now considered a type 1 Brugada ECG pattern and evidence of conduction delay in the right ventricle.[12] A year later the same group reported six patients with idiopathic ventricular fibrillation, one of them with similar ECG pattern and right ventricular structural abnormalities.[13] In 1993, one year after BrS was first described, two papers were published suggesting that the new entity, was in fact a form of ACM.[14, 15] As a response to these publications, *Brugada et al* wrote a letter clarifying that the two diseases are not to be confused, as BrS is not associated with any structural abnormalities.[16]

However, cases of overlapping ECG features of the two diseases continued to be published, with case reports of patients with ACM demonstrating BrS ECG pattern,[17-19] and a relatively high incidence of epsilon like waves (Figure 1) in BrS patients.[20] In addition, there have been reports of structural abnormalities in BrS patients that are similar to those found in ACM patients.[21, 22]

Genetic overlap and the concept of the connexome

Cardiac myocytes adhere to each other through the intercalated discs (IDs): highly complex, specialised protein structures that provide mechanical adhesion and electrical continuity. The ID contains a number of protein sub-complexes. Of those, desmosomes and fascia adherens junctions, that together form the area composita, are involved in maintaining mechanical adhesion, while gap junctions and ion channel complexes are involved in generating action potentials and conducting electrical signals (Figure 2).[23-25] Until recently, it was thought that each of these junction types was structurally and functionally distinct. Recent evidence, however, has challenged this belief. It is now largely believed that these sub-complexes in fact act as a single structural and functional entity, which has become known as the

connexome.[26, 27] Different proteins contribute to the interaction between these sub-complexes. In the area composita, plakophilin 2 (PKP2) and α-T-catenin interact and offer a link between desmosomes and fascia adherens junctions. Gap junctions are made of hexamers of connexin 43 (Cx43). Their trafficking and localisation in the membrane is regulated by N cadherin and beta catenin, both of which are fascia adherens proteins. Desmosomal proteins desmoplakin (DSP) and PKP2 interact with Cx43 as well, aiding its stabilisation in the membrane. PKP2 interacts with Cx43 either directly or through the scaffolding protein Ankyrin G. The voltage gated sodium channel complex has many interacting proteins responsible for its trafficking and stabilisation (see below), among them Ankyrin G and PKP2 have an important role. Cx43 contributes to $Na_V1.5$ stability in the membrane as well.[26] This evidence has altered the way we view diseases associated with pathogenic variants in the ID. And it has added more weight to the theory that ACM and BrS are indeed variants of the same disease process; a disease of the connexome.

Over 50% of patients diagnosed with ACM harbour one or more pathogenic variants in genes encoding for proteins of the desmosome.[28] The first ACM-causing gene identified was *JUP*, which codes for the armadillo protein plakoglobin. The *JUP* pathogenic variant was found in patients with Naxos disease, a rare, recessive form of ACM where the cardiomyopathy is inherited along with cutaneous abnormalities.[29] Following the identification of this first pathogenic variant, all cardiac desmosomal genes were subsequently implicated in ACM; this included the cadherin proteins desmocollin-2 (*DSC2*) and desmoglein-2 (*DSG2*), the armadillo protein plakophilin 2 (*PKP2*) and the plakin protein desmoplakin (*DSP*). Collectively, all these studies coined the term 'a disease of the desmosome'.[30] It is estimated that approximately 40% of patients diagnosed with ACM have pathogenic variants in the *PKP2* gene. Even though it was recently suggested that several *PKP2* variants are not pathogenic and in fact exist in healthy members of the larger population, *PKP2* remains the most commonly affected gene in ACM.[26, 31]

The desmosome has an active role in mechanical adhesion. This is why these 'bridges' are predominantly found in tissues subjected to increased mechanical stress such as the heart and the epidermis.[32] It is postulated that pathogenic variants in desmosomal components lead to a decrease in the force of cell-cell adhesion causing cell dissociation, apoptosis and eventually replacement by fat

and scar; the major pathognomonic feature of ACM.[33] Indeed, electron microscopy studies in myocardial samples from ACM patients show evidence of loss of cell-cell adhesion.[34, 35]

Despite its annotation as 'a disease of the desmosome', ACM has also been associated with rare variants in non-desmosomal genes such as N-cadherin (*CDH2*), desmin (*DES*), α-catenin (*CTNNA3*), phospholamban (*PLN*), the cardiac ryanodine receptor (*RyR2*), filamin C (*FLNC*), transmembrane protein 43 (*TMEM43*) and the transforming growth factor 3β (*TGFβ3*).[26, 30, 36, 37] Even if they are not desmosomal proteins though, the majority of the above have a role in cell-cell adhesion. Desmin is the molecular link through which desmoplakin anchors the cytoskeleton.[38] N-cadherin is a major component of the fascia adherens junctions.[39] Filamin C also maintains mechanical integrity as it tethers the sarcomeres to the cell membrane.[40] Additionally, pathogenic variants in α-catenin disrupt the function and localisation of PKP2 while *TGF3β* codes for a pro-inflammatory mediator, which regulates the expression of desmosomal genes.[41-43]

TMEM43 and *PLN* have no known role in mechanical adhesion. *TMEM43*, however, promotes adipogenesis through the peroxisome proliferator-activated receptor-γ (PPARγ), a transcription factor dysregulated in several experimental models of ACM.[44-46] Finally, *PLN* is involved in maintaining the calcium signalling in the heart and it is well established that dysregulation in calcium dynamics can promote apoptosis, fibrogenesis and arrhythmias.[47]

RyR2 was the first ion channel protein to be implicated in ACM pathogenesis.[48] It is more commonly known for underlying another myocardial disease, the channelopathy catecholaminergic polymorphic ventricular tachycardia (CPVT).[49] Subsequent studies, however, suggested that the pathogenic *RyR2* variant-carrying ACM patients might have been misdiagnosed CPVT patients.[31]

Most of the aforementioned genes are the subject of an ongoing evaluation by the ClinGen Resource[50] to assess their true clinical significance in ACM. Other than *PKP2* (see below), they have never been implicated in the pathogenesis of BrS. Recently, however, several publications have shown rare variants in *SCN5A* in ACM families.[51] *SCN5A* codes for the major subunit of the cardiac sodium channel ($Na_V1.5$), and also appears to locate in ion channel complexes at the ID, as well as other regions of the cell membrane.[52] It is also the most important gene in BrS.[53] Pathogenic *SCN5A* variants are found in 20-25% of BrS patients and to date more than 300 pathogenic variants have been identified.[26, 54, 55] Yet

in large families harbouring pathogenic *SCN5A* variants, genotype negative relatives can exhibit BrS phenotype, indicating that the variant is not always required to cause the disease.[56] Thus although BrS is a heritable disease, it is not a strict Mendelian disorder and robust evidence supports the role of common genetic variation underlying its aetiology.[57]

Most of the other genes implicated in BrS pathogenesis encode cardiac ion channel proteins, adding to the belief that BrS was exclusively a channelopathy. Many have a role in regulating the function of the sodium channel. *SCN1B*, *SCN2B* and *SCN3B* encode for the β-subunits of the sodium channel controlling its function. *SCN10A* codes for $Na_v1.8$, a neuronal sodium channel, which has been postulated to modulate the expression of $Na_v1.5$ and the electrical function of the heart. Pathogenic variants in Glycerol-3-Phosphate Dehydrogenase 1 Like (*GPD1L*), can reduce the cell surface expression levels and the inward peak sodium current (I_{Na}) of $Na_V1.5$. Finally, pathogenic variants in RAN Guanine Nucleotide Release Factor (*RANGRF*) impair the trafficking of $Na_v1.5$ leading to I_{Na} reduction and manifestation of a Brugada phenotype.[54]

A small subset of BrS patients were found to harbour putative pathogenic variants in genes encoding non-sodium channels. These included *KCNE3*, *KCNJ8*, *KCND3* and *KCNE*, which encode voltage-gated potassium channels as well as *CACNA1C*, *CACNB2B* and *CACNA2D1*, which encode calcium-dependent channels. *HCN4*, the gene responsible for the potassium/sodium hyperpolarisation-activated cyclic nucleotide-gated channel 4, has also been implicated in BrS. Another BrS implicated gene, transient receptor potential cation channel subfamily M member 4 protein (*TRPM4*), allows sodium entry into the cell causing membrane depolarization and regulates calcium dynamics.[54]

However, despite the scientific endeavour spent investigating these additional genes, only a small proportion of probands harbour them, and other than *SCN5A*, their supportive genetic linkage, population frequency and functional data are insufficiently robust to support their usage for clinical genetic testing following re-evaluation by the ClinGen Resource.[58] Furthermore, statistical burden testing of all putative genes has only associated *SCN5A* with BrS.[59]

Intriguingly, however, the first non-ion channel gene to be implicated in BrS was *PKP2*. *Cerrone et al*. first identified *PKP2* variants in 5 out of 200 otherwise genotype negative patients and families with a BrS diagnosis.[60] Following this discovery, *Peters* presented a case report of a patient with an ACM-BrS

'hybrid' phenotype with a missense variant in *PKP2*.[61] The following year, another case report was published describing a patient with a clear BrS phenotype and pathogenic variants in both the *PKP2* and *DSP* genes.[62] In support of these genetic findings, cell culture models lacking *PKP2* show significantly decreased I_{Na} current.[63] These studies have supported the genetic basis of the hypothesis that ACM and BrS may in fact share a common pathway of disruptions in the connexome.[27]

Gap junction remodelling overlap

A growing body of literature shows a clear dependence of gap junctions on the correct formation and maintenance of mechanical junctions.[64] With this in mind, the first study published showing gap junction remodelling in the hearts of patients with Naxos disease was not surprising.[65] Interestingly, signal for the major gap junction protein Cx43 was significantly reduced at the IDs in both right and left ventricular samples including areas that appeared to be histologically unremarkable.[65] A subsequent paper showed gap junction remodelling in the heart of a 7-year old child with Naxos disease who had died of myelodysplasia. In this case, Cx43 was re-localised from junctional to intracellular sites in total lack of structural changes.[66] Gap junction remodelling has since been identified in much larger series of ACM patient samples.[67-69] Shifting of Cx43 signal from the IDs is not a specific finding for ACM and has been reported in several other cardiomyopathies. However, in other diseases it tends to occur late; after the heart has been significantly remodelled. In contrast, in ACM it occurs early, preceding structural changes suggesting that it might be playing a primary role in the highly arrhythmogenic nature of this disease.[64, 65]

More interesting, however, was the finding that Cx43 signal can be reduced at the IDs also in hearts from patients with a clear BrS diagnosis.[70] This study not only introduced an additional pathway potentially contributing to the arrhythmic burden in BrS but also added further weight to the overlap theory between the two diseases.

Inflammation overlap

Inflammation was recognised as a feature of ACM ever since the disease was first described by pathologists.[71] Autopsy studies show that myocardial inflammation in the form of T-cell infiltrates is present in over two thirds of the cases.[72] In a different set of studies, the innate component of inflammation also appeared to be activated in ACM with cardiac myocytes themselves secreting high

levels of pro-inflammatory mediators.[73] A more recent study proved that inflammation is not a consequence of the apoptosis and fibrofatty replacement characterizing ACM. Instead, it is a driving force of the disease pathogenesis and blocking a major inflammatory pathway appears to mitigate the disease in several experimental models.[74]

More recently, however, inflammation has become part of the BrS spectrum as well. *Frustaci et al* were the first to report evidence of histological myocarditis in 77% of BrS patients examined.[75] Parvovirus B19 myocarditis was next found in an additional 4 BrS patients who presented with ventricular tachycardia (VT).[76, 77] Finally, *Pieroni et al* showed histological evidence of myocardial inflammation in 80% of 30 BrS patients examined and a strong association between inflammation and abnormal electrical mapping.[78]

These, however, are not the first studies to associate inflammation with apparently electrical heart disease. In a cross-sectional study conducted in 2013, cardiac conduction abnormalities were diagnosed in up to 33% of 210 patients with the inflammatory condition ankylosing spondylitis (AS). These consisted mostly of atrioventricular block and prolonged QT duration, with one patient showing pacemaker-dependence and an additional 7 patients complete heart block.[79] In 2014, *Adlan et al* showed a link between pro-inflammatory cytokines and QT interval in patients with rheumatoid arthritis (RA). Their results supported that lower cytokine levels can protect against QT prolongation in RA.[80] The detection of inflammation in BrS extends the histopathological similarities between the two diseases. It is not currently known, however, whether inflammation is a driving pathogenic force in BrS or whether a BrS background increases susceptibility to myocarditis.

Structural changes

Macroscopically, ACM hearts can be grossly normal, show single or multiple aneurysms, or have biventricular dilation with multiple free wall aneurysms.[2] Histology shows segmental fibrofatty replacement of the myocardium, which is one of the characteristic findings in ACM and is one of the criteria for its diagnosis. An autopsy study of sudden cardiac death victims found that both ventricles were affected in 70% of cases with a much lower incidence of lone left ventricular (LV) or RV disease.[81]

Overlapping structural abnormalities with ACM have been described in BrS patients. A study of 16 family members, 8 of whom had BrS, demonstrated that RV structural abnormalities and conduction system abnormalities were the prevalent underlying structural substrates in patients with ECG changes consistent with BrS.[21] In addition to the histologic studies mentioned above that demonstrated inflammatory changes in BrS patients,[75, 78] findings of RV fatty infiltration and fibrosis have been described as well.[22, 70, 82]

Imaging studies

Ventricular dilation and regional wall motion abnormalities are key features in ACM and are readily assessed by echocardiography and cardiac magnetic resonance imaging (CMR). RV longitudinal strain imaging may detect subclinical systolic dysfunction.[83] CMR may also show myocardial fat and late gadolinium enhancement (LGE) as a marker for ventricular wall fibrosis.[5]

Ventricular structural and functional abnormalities have been demonstrated in imaging studies using different modalities in BrS patients as well. Echocardiography using tissue Doppler, longitudinal strain, and myocardial performance index, performed in BrS patients with positive sodium channel blocker test have shown that a positive drug test coincides with delay in the onset of RV contraction, significantly reduced RV longitudinal strain, and increased myocardial performance index (MPI).[84, 85] Furthermore, BrS patients were found to have higher mechanical dispersion on echocardiography than controls, a finding that was more prominent among patients with previous life-threatening arrhythmias.[86] Wall motion abnormalities in the right ventricular outflow tract (RVOT) and inferior RV wall were also demonstrated in a study using electron beam computed tomography (CT) in BrS patients.[87] Later, CMR studies further confirmed the presence of structural and functional changes in the RV, showing a high incidence of RVOT abnormalities in as many as 67% of the patients with increased RVOT dimensions and lower right ventricular ejection fraction (RVEF).[88, 89] These functional abnormalities were more frequent in the BrS group compared to controls, but not as frequent as they were in the ARVC group.[89] Structural changes appear to be more prominent in patients with spontaneous type 1 ECG pattern compared with patients with drug-induced type 1 ECG pattern, and in patients with a pathogenic *SCN5A* variant.[89, 90] Among patients with a pathogenic *SCN5A* variant there is a correlation with the type of pathogenic variant and functional changes; patients that have a

truncating *SCN5A* variant, considered to cause a more significant $Na_V1.5$ current reduction, tend to have lower ejection fractions.[91]

LGE, which correlates with ventricular wall fibrosis and is prominent in ACM, was demonstrated in 8% of BrS patients by *Bastiaenan el al*, most frequently in the LV midwall.[92] While this may be evidence of prior myocarditis, as has been described previously in BrS patients,[75-78] two patients with LGE later exhibited features associated with ACM, one with widespread T wave inversion, and the other harbouring a pathogenic *DSP* variant. This interesting observation may further support the overlap between the two diseases, with a possible link to disease mechanism.

Electrophysiological overlap

The cellular and structural changes in ACM and BrS are reflected in the ECG with depolarization and repolarization abnormalities.[93-95] Overlapping ECG patterns and clinical characteristics were demonstrated in different case series previously. In 2001 *Corrado et al* reported a subpopulation of ACM patients that displayed the type 1 Brugada ECG pattern in a study of young sudden cardiac death victims. These ACM patients with Brugada ECG pattern had clinical characteristics that were more typical for BrS patients than ACM patients, with sudden death occurring more at rest with a lower proportion of competitive athletes amongst them. In addition, their ECGs were more likely to show dynamic repolarization changes and polymorphic ventricular tachycardia (PMVT).[17] Similarly, patients meeting all or most criteria for both diagnoses with BrS ECG pattern as well as epsilon-like waves and structural changes were later described.[18, 19] This is in line with studies showing a positive ajmaline test in 16% of ACM patients tested and a relatively high incidence of epsilon-like waves among BrS patients.[20, 96] It is important to recognise, however, that 4.5% of otherwise healthy individuals were found to have a positive ajmaline test.[10] A retrospective study of BrS patients with ICD demonstrated that 4.2% of the patients that received appropriate ICD intervention experienced monomorphic VT (MVT).[97] This shows that BrS may cause MVT as well as PMVT, a finding that is more frequently seen in ACM. These reports suggest the possibility that the two conditions may be different phenotypes of a similar underlying disease process.

Ventricular arrhythmias in ACM are thought to be caused primarily by macro-re-entry caused by ventricular structural changes. In addition, as mentioned previously, it is clear now that gap junction and ion channel remodelling has an important part in arrhythmogenesis in ACM.[67-69] This explains the relatively high incidence of arrhythmias in structurally normal hearts in the early stage of the disease.[64, 65] As for BrS, there are two competing theories regarding its arrhythmic mechanism. The 'repolarization theory' suggests that reduced sodium current and unopposed potassium current in the RV epicardium lead to loss of the action potential dome causing a transmural voltage gradient with dispersion of repolarization that allows phase 2 re-entry. On the other hand, the 'depolarization theory' suggests that delayed conduction in the RVOT facilitates re-entry.[84, 98-100]

Different electrophysiological studies including signal averaged electrocardiogram (SAECG), unipolar and bipolar mapping studies and epicardial mapping studies, demonstrated similar findings in both diseases. These findings tended to be localised to the RVOT in BrS patients, consistent with the findings in imaging studies.

Electrophysiological similarities include late potentials (LPs) on SAECG that have been described in both ACM and BrS patients. LPs are considered to reflect delayed myocardial activation in areas with scar or channelopathic changes causing conduction delay. Previous studies have shown LPs in BrS patients originate from the epicardial RVOT,[100, 101] their presence supports the 'depolarization theory' for the arrhythmogenesis in BrS. CARTO maps of BrS patients did not show any conduction block, but the activation duration was significantly longer in BrS patients with type 1 ECG pattern, and increased after ajmaline provocation in patients with initial type 2 ECG pattern.[99] In addition, non-contact endocardial mapping revealed considerable conduction delay in the RVOT compared to the rest of the RV, also consistent with the depolarization theory.[102] The fact that both diseases show fractionated electrograms supports the idea that structural derangement is at least a part of the mechanism for ECG and arrhythmic findings.

Endocardial electroanatomical voltage mapping studies in ACM have demonstrated that bipolar low voltage areas correlated with areas of myocyte loss and fibrofatty replacement on endomyocardial

biopsy (EMB).[103] This correlation between electroanatomical findings and pathological abnormalities was shown in BrS patients as well. *Pieroni et al* demonstrated low voltage endocardial areas in most patients with BrS that always included the RVOT. The common histology finding was myocardial inflammation and fibrosis and low voltage areas were larger in patients with inflammation on EMB compared to those without.[78] There seemed to be a correlation between low voltage areas and higher arrhythmic risk in both diseases.[78, 104]

Epicardial findings in patients with ACM and BrS are similar as well. In 2009 *Garcia et al* published the results of epicardial mapping studies in ACM patients. They showed low voltage areas in the epicardium overlying the endocardial low voltage areas and more extensive than the endocardial low voltage area,[105] consistent with previous autopsy series.[71] An even greater difference between endo and epicardium electrocardiograms was shown by *Nademanee et al* in BrS patients. Patients had normal endocardial electrocardiograms over the RVOT endocardium and abnormal low amplitude and delayed electrograms over the anterior RVOT epicardium with similar characteristics to those in ACM patients.[106] These epicardial areas of abnormal low amplitude and delayed electrograms were then correlated with fibrosis on myocardial biopsies at open heart ablation procedures.[70] *Brugada et al* later showed that the size of these low voltage areas increased after flecainide administration.[107] These areas were also the site of electromechanical abnormalities.[108]

Implications

Whilst we have detailed many overlapping features of ACM and BrS, these diseases can have different natural histories and outcomes (e.g. patients with ACM may go on to develop heart failure, which is not part of the BrS phenotype; sodium channel blockers can exacerbate BrS phenotype but could be useful in some ACM patients).[109] Nonetheless, we propose that both are distinct phenotypes that share, in part, a common pathophysiology of the connexome that manifests a wide spectrum of phenotypic expression. From a clinical perspective, systematic prospective research into the implications of the overlap between ACM and BrS will be required to understand any impact on patient management. For instance, BrS patients with structural abnormalities might be more suitable for ablation therapy.

Conclusions

Better understanding of the pathophysiologic and genetic basis of ACM and BrS supports the possibility of a shared underlying disease process with overlapping but distinct phenotypes. This has been demonstrated by clinical, structural and electrophysiological studies (Figure 3). The connexome, that includes mechanical junctions, gap junctions, and ion channels, may serve as a common pathway for the diseases. Dysfunction of any one of its components will cause a 'disease of the connexome' that may manifest as ACM or BrS clinically depending on other determinants including genetic background. *PKP2* and *SCN5A* variation have been demonstrated in both diseases which further links their origin to the connexome, although this is only identified in a minority. Findings from imaging and electrophysiological studies demonstrate similar abnormalities but these differ in their distribution between the two disorders, further emphasising the possibility that they are different phenotypes but with the same common disease process.

Additional studies are necessary to verify if ACM and BrS form a spectrum of diseases of the connexome, and what affects specific phenotype development and risk for SCD. This will require deeper understanding of the molecular pathways disrupted in the two diseases, as well as further genomic and functional investigation of the impact of common and rare genetic variation on disease extent and location with translation to the patient phenotype.

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Figure Legends

Figure 1.

Shanghai score for diagnosis of Brugada syndrome and Modified Task Force criteria for diagnosis of ARVC showing the diagnostic categories for the diagnosis of each disease. ARVC, arrhythmogenic right ventricular cardiomyopathy; BrS, Brugada syndrome; BSA, body surface area; ECG, electrocardiogram; echo, echocardiogram; LBBB, left bundle branch block; MRI, magnetic resonance imaging; PLAX, parasternal long-axis; PSAX, parasternal short-axis; RBBB, right bundle branch block; RV, right ventricular; RVEDV, right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; RVOT, right ventricular outflow tract; SAECG, signal-averaged electrocardiogram; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia. Adapted from *Antzelevitch et al.*[11], *Markus et al*[4].

Figure 2.

The connexome. Intercalated discs (IDs) provide mechanical adhesion and electrical continuity to cardiac myocytes and include four sub-complexes. Desmosomes and fascia adherens junctions together form the area composita and maintain cellular mechanical adhesion. Gap junctions and ion channel complexes generate and conduct action potentials. These four sub-complexes are believed to act as a single functional entity, the connexome. The sub-complexes include plakophilin 2 (PKP2) and α-catenin that interact and offer a link between desmosomes and fascia adherens junctions; desmosomal proteins desmoplakin and PKP2 interact with connexin 43 (Cx43) directly or through the scaffolding protein Ankyrin G (ANK3), aiding to its stabilisation in the membrane; ANK3 and PKP2 assist the trafficking and stabilisation of the α and β subunits of $Na_V1.5$ along with Cx43.

Figure 3.

Arrhythmogenic cardiomyopathy and Brugada syndrome overlap. The gene most commonly implicated in ACM is *PKP2* (40% of patients) and pathogenic variants have also been identified in BrS patients. Pathogenic variants in *SCN5A* are the main finding in BrS patients (20%) and have also been associated with ACM. Common genetic variation has only been associated with BrS. Decreased

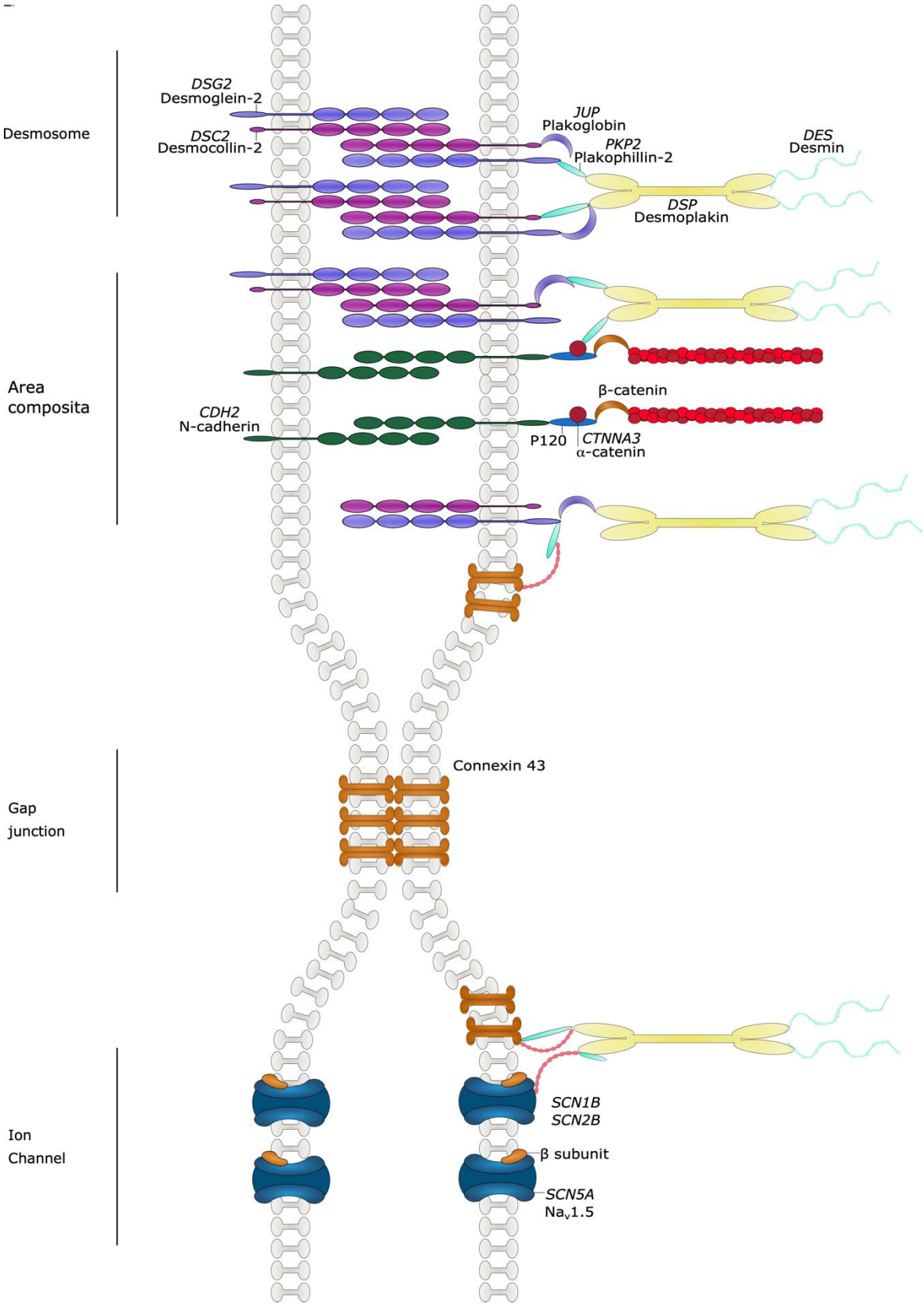
$Na_V1.5$ current and gap junction remodelling are common functional features. These cellular changes associate with histological, structural, functional and electrophysiological abnormalities, which are mild and restricted to the RVOT in BrS and can be progressive and global in ACM. Depolarization and repolarization abnormalities associate with ECG manifestations. *LGE in RV and LV. Cx43, connexin 43; EF, ejection fraction; LGE, late gadolinium enhancement; LP, late potential; LVA, low voltage areas; RVOT, right ventricular outflow tract; RWMA, regional wall motion abnormalities; VT, ventricular tachycardia.

Figures

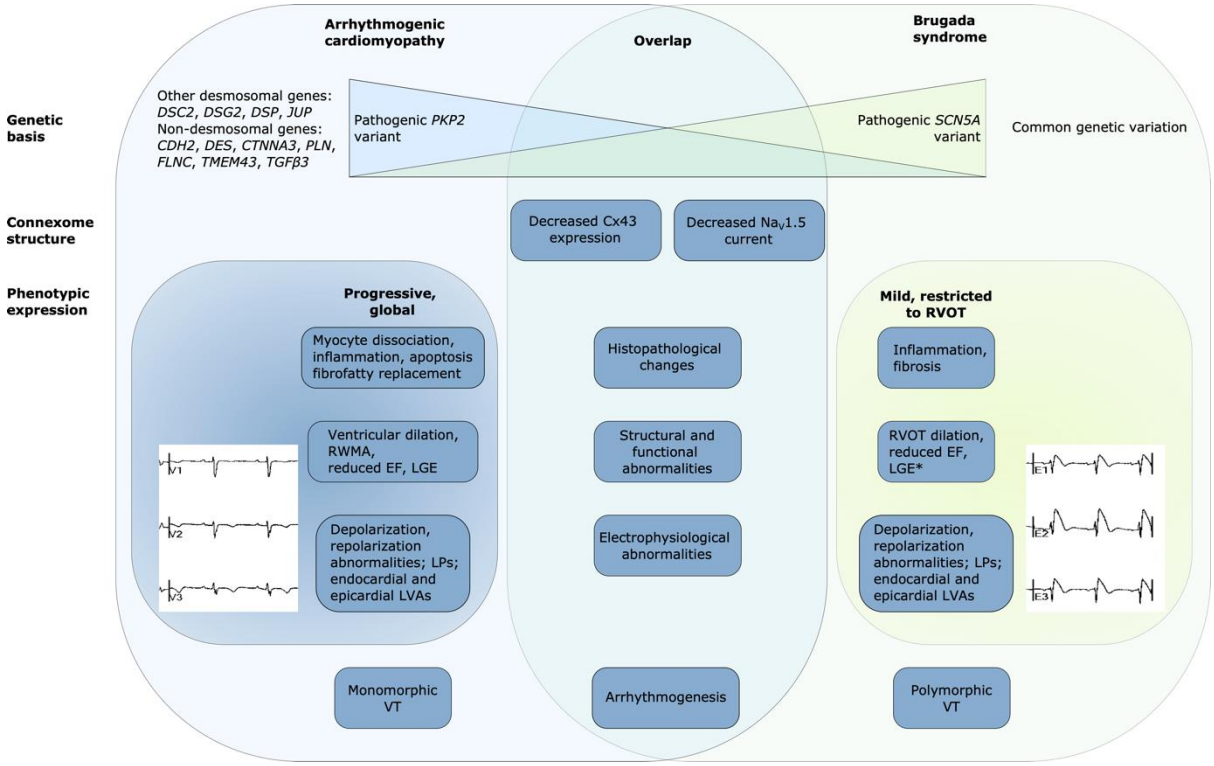
Figure 1

Shanghai Score		Modified Task Force Criteria for ARVC	
	Points	Major	Minor
ECG			
A. Spontaneous type 1 Brugada ECG pattern at nominal or high leads B. Fever-induced type 1 Brugada ECG pattern at nominal or high leads C. Type 2 or 3 Brugada ECG pattern that converts with provocative drug challenge	3.5 3 2	Repolarization abnormalities	
		Inverted T waves in right precordial leads (V_1,V_2, and V_3) or beyond in individuals >14 years of age (in the absence of complete RBBB QRS≥120ms)	A. Inverted T waves in leads V_1 and V_2 in individuals >14 years of age (in the absence of complete RBBB) or in V_4, V_5, or V_6 B. Inverted T waves in leads V_1, V_2, V_3, and V_4 in individuals >14 years of age in the presence of complete RBBB
		Depolarization/conduction abnormalities	
		Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V_1 to V_3)	A. Late potentials by SAECG in ≥1 of 3 parameters in the absence of QRS duration of ≥110ms on the standard ECG: 1) Filtered QRS duration (fQRS) ≥114ms 2) Duration of terminal QRS <40μV (low-amplitude signal duration) ≥38ms 3) Root-mean-square voltage of terminal 40ms ≤20μV B. Terminal activation duration of QRS≥55ms measured from the nadir of the S wave to the end of the QRS, including R' in V_1, V_2, or V_3 in the absence of complete RBBB
Clinical history			
A. Unexplained cardiac arrest or documented VF/polymorphic VT B. Nocturnal agonal respirations C. Suspected arrhythmic syncope D. Syncope of unclear mechanism/unclear aetiology E. Atrial flutter/fibrillation in patients <30 years of age without alternative aetiology	3 2 2 1 0.5	Arrhythmias	
		Non-sustained or sustained VT of LBBB with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)	A. Non-sustained or sustained VT of RV outflow configuration, LBBB morphology with inferior axis (positive QRS in II, III, and aVF and negative in lead aVL) or of unknown axis B. >500 ventricular extrasystoles per 24 hours (Holter)
Family history			
A. First- or second-degree relative with definite BrS B. Suspicious SCD (fever, nocturnal, Brugada aggravating drugs) in a first- or second-degree relative C. Unexplained SCD <45 years of age in first- or second-degree relative with negative autopsy	2 1 0.5	A. ARVC confirmed in a first-degree relative who meets current task force criteria B. ARVC confirmed pathologically at autopsy or surgery in a first-degree relative	A. History of ARVC in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current task force criteria B. Premature sudden death (<35 years of age) due to suspected ARVC in a first-degree relative C. ARVC confirmed pathologically or by current task force criteria in second-degree relative
Genetic test result			
A. Probable pathogenic variant in BrS susceptibility gene	0.5	C. Identification of a pathogenic variant categorized as associated or probably associated with ARVC in the patient under evaluation *part of 'Family history' criteria	
Structural alterations and ventricular dysfunction			
		Echo	
		Regional RV akinesia, dyskinesia, or aneurysm and 1 of the following (end-diastole): 1) PLAX RVOT ≥32mm (PLAX/BSA ≥19mm/m^2) 2) PSAX RVOT ≥36mm (PSAX/BSA ≥21mm/m^2) 3) Fractional area change ≤33%	Regional RV akinesia, dyskinesia, or aneurysm and 1 of the following (end-diastole): 1) PLAX RVOT ≥29 to <32mm (PLAX/BSA ≥16 to <19mm/m^2) 2) PSAX RVOT ≥32 to <36mm (PSAX/BSA ≥18 to <21mm/m^2) 3) Fractional area change >33 to ≤40%
		MRI	
		Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following: 1) Ratio RVEDV/BSA ≥110mL/m^2 (male), ≥100mL/m^2 (female) 2) RVEF ≤40%	Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following: 1) Ratio RVEDV/BSA ≥100 to <110mL/m^2 (male), ≥90 to <100mL/m^2 (female) 2) RVEF >40 to ≤45%
		RV angiography	
		Regional RV akinesia, dyskinesia, or aneurysm	
Tissue characterization of wall			
		Endomyocardial biopsy showing fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement and with: Residual myocytes <60% by morphometric analysis (or <50% if estimated)	Endomyocardial biopsy showing fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement and with: Residual myocytes 60% to 75% by morphometric analysis (or 50% to 65% if estimated)
*Award points once for highest score within each category; **Score requires at least one ECG finding Probable/definite Brugada syndrome: ≥3.5 points Possible Brugada syndrome: 2-3 points Non-diagnostic: <2 points		ARVC diagnosis: Definite: 2 major, or 1 major and 2 minor, or 4 minor criteria from different categories Borderline: 1 major and 1 minor, or 3 minor criteria from different categories Possible: 1 major, or 2 minor criteria from different categories	

Figure 2


Desmosome
DSG2
Desmoglein-2
DSC2
Desmocollin-2
JUP
Plakoglobin
PKP2
Plakophillin-2
DES
Desmin
DSP
Desmoplakin
Area
composita
CDH2
N-cadherin
β-catenin
P120
CTNNA3
α-catenin
Gap
junction
Connexin 43
Ion
Channel
SCN1B
SCN2B
β subunit
SCN5A
Nav1.5

1 Figure 3


Arrhythmogenic cardiomyopathy
Overlap
Brugada syndrome
Genetic basis
Other desmosomal genes: DSC2, DSG2, DSP, JUP
Non-desmosomal genes: CDH2, DES, CTNNA3, PLN, FLNC, TMEM43, TGFβ3
Pathogenic PKP2 variant
Pathogenic SCN5A variant
Common genetic variation
Connexome structure
Decreased Cx43 expression
Decreased Na$_v$1.5 current
Phenotypic expression
Progressive, global
Myocyte dissociation, inflammation, apoptosis fibrofatty replacement
Ventricular dilation, RWMA, reduced EF, LGE
Depolarization, repolarization abnormalities; LPs; endocardial and epicardial LVAs
Histopathological changes
Structural and functional abnormalities
Electrophysiological abnormalities
Mild, restricted to RVOT
Inflammation, fibrosis
RVOT dilation, reduced EF, LGE*
Depolarization, repolarization abnormalities; LPs; endocardial and epicardial LVAs
Monomorphic VT
Arrhythmogenesis
Polymorphic VT

2