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Late gadolinium enhancement in Brugada syndrome: a marker for subtle underlying cardiomyopathy?

Short Title: Late enhancement in Brugada syndrome

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Abstract

Background

There is increasing evidence that the Brugada ECG pattern is a marker of subtle structural heart disease.

Objective

We characterised Brugada syndrome (BrS) patients using cardiovascular magnetic resonance (CMR) with late gadolinium enhancement (LGE).

Methods

BrS was diagnosed according to international guidelines. 26% BrS patients carried SCN5A mutations. CMR data from 78 BrS patients were compared with 78 healthy controls (44±15 vs 42±14 years; p=0.434 and 64% vs 64% male; p=1.000).

Results

Right ventricular (RV) ejection fraction was slightly lower (61±8% vs 64±5%; p=0.004) and RV end-systolic volume slightly greater (31±10mL/m^2 vs 28±6mL/m^2; p=0.038) in BrS compared with controls. These values remained within the normal range. LGE was demonstrated in 8% BrS patients (left ventricular (LV) midwall LGE in 5%) but not in controls (p=0.028). In BrS patients with midwall LGE there were no other features of cardiomyopathy at the time of CMR but genetic testing and follow-up has revealed a desmoplakin mutation in one patient and evolution of T-wave inversion throughout all precordial ECG leads in another. Neither patient fulfils diagnostic criteria for arrhythmogenic right ventricular cardiomyopathy.

Conclusion

Some BrS patients have LV midwall LGE consistent with an underlying cardiomyopathic process. Even cases without LGE show greater RV volumes and reduced RV function. These findings lend further support to the presence of subtle structural abnormalities in BrS. The BrS pattern with LGE may serve as early markers for evolution of a cardiomyopathic phenotype over time. CMR is a potentially useful adjunct investigation in the clinical evaluation of BrS.

Keywords

Brugada syndrome; Cardiac magnetic resonance; Cardiomyopathy; Late gadolinium enhancement; Arrhythmogenic right ventricular cardiomyopathy

Introduction

The Brugada syndrome (BrS) is an inherited arrhythmia syndrome characterised by ST-segment elevation in the right precordial ECG leads. It is associated with ventricular fibrillation (VF) and sudden cardiac death (SCD) in the absence of overt structural heart disease.(1)

There is, however, increasing evidence to suggest that the Brugada ECG pattern is a marker of subtle cardiac structural abnormalities. Histopathological analysis of sudden death victims with prior electrocardiograms (ECG) suggestive of BrS has demonstrated right ventricular (RV) fibro-fatty infiltration similar to arrhythmogenic right ventricular cardiomyopathy (ARVC).(2) In some BrS patients, abnormalities including conduction delay and QRS fragmentation have been seen during electrophysiological studies. Combined the impression is of an overlap with subtle cardiomyopathy.(2–12)

Data from cardiac imaging is sparse. Cardiovascular magnetic resonance (CMR) studies have produced conflicting results with some showing increased cardiac dimensions and reduced ventricular function in BrS patients compared with controls and others showing no apparent difference.(13–16) It appears that BrS patients carrying *SCN5A* mutations have greater ventricular volumes and lower ejection fractions compared with mutation negative BrS patients and healthy subjects.(16,17) In non-ischemic cardiomyopathies including dilated cardiomyopathy and hypertrophic cardiomyopathy, arrhythmogenesis has been associated with presence of late gadolinium enhancement (LGE) representing

focal myocardial fibrosis on CMR.(18,19) Systematic assessment for myocardial fibrosis in BrS has not been performed and therefore we sought to characterise a cohort of patients using the CMR LGE technique.

Methods

Patient characteristics

Patients with Brugada syndrome (BrS) were identified from a database at St George's Hospital, London. All fulfilled international diagnostic criteria with: a type 1 BrS ECG pattern demonstrated in ≥1 ECG lead (V_1-V_3) in the 2nd, 3rd or 4th intercostal space in the presence or absence of a sodium channel blocking agent.(20) These patients were under follow-up in the inherited heart disease clinic and had conventional investigation according to a standard diagnostic algorithm including 15 lead ECG, signal averaged ECG (SAECG), echocardiography, exercise testing, 12 lead Holter monitoring and ajmaline provocation testing.(21) Patients were considered symptomatic if there was a history of cardiac arrest or unexplained syncope with a negative tilt test result. A family history of sudden cardiac death was recorded if sudden death had occurred in a first degree relative <45 years old.(22) A spontaneous type 1 ECG pattern was recorded when the type 1 ECG pattern was seen in the absence of a sodium channel blocker. The SAECG was considered abnormal for late potentials when ≥2 of the following were demonstrated: filtered QRS duration ≥114ms; duration of the terminal QRS <40μV ≥38ms; and root mean square voltage of the terminal 40ms ≤20μV. Genotyping for sodium channel mutations (*SCN5A*) was performed as part of routine clinical care.

Healthy controls of a similar age and sex were identified from research databases. These were individuals without known cardiac risk factors, prior history of cardiac disease or

family history of inherited heart disease. The study was approved by the Local Research Ethics Committee.

Cardiovascular magnetic resonance analysis

Since 2010 patients diagnosed with BrS at St George's Hospital have had CMR as part of the investigative algorithm. All BrS patients with complete CMR datasets were included in the study. There were 7 patient exclusions (2 had incomplete scans due to claustrophobia and 5 were not given gadolinium). The final population comprised 78 BrS patients (44±15 years; 64% male). These were compared with 78 healthy controls (42±14 years; 64% male). CMR scans were performed at St George's Hospital and Royal Brompton Hospital, London, according to a standard protocol.(23) Cine images were performed using a steady state free precession sequence in three long axis and continuous short axis views covering the entire left ventricle (LV) and RV from base to apex. The LGE images were obtained in the same views using an inversion recovery sequence 10 minutes following administration of gadolinium (0.1mmol/kg). Studies were performed at 1.5 Tesla (Siemens Avanto; 40%) and 3.0 Tesla (Philips Achieva; 60%) field strength. Raw DICOM CMR data was obtained and de novo analysis was performed using dedicated software with valve plane tracking (CMR-tools 2012, Cardiovascular Imaging Solutions, London, UK). Measurements were made according to international guidelines (atrial areas from the horizontal long axis view, ventricular volumes including papillary muscles as myocardium from the short axis stack). (24) Atrial areas, ventricular volumes and mass were indexed to body surface area. Presence or absence of LGE was

recorded independently by two operators (AC and RB) and patterns of LGE were described. When there was disagreement the images were reviewed by a third operator (LA) and a consensus was reached. The presence of CMR fat infiltration within the myocardium was not specifically assessed or recorded as its identification has been shown to be of limited value in ARVC and was therefore less likely to be of utility in BrS.(25)

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics 22 (SPSS Inc., Chicago, Illinois, USA). Continuous variables are expressed as means ± standard deviation and categorical variables as percentages. Continuous variables were tested for normality using the Shapiro-Wilk test. Comparisons between groups were carried out using an unpaired t-test after controlling for equality of variances with the Levene's test, Kruskal Wallis test or chi squared/Fisher's exact test where appropriate. A two-tailed p value <0.05 was considered significant.

Results

Patient characteristics

BrS patients and healthy controls were similar in age (44±15 years vs 42±14 years; p=0.434) and gender (males 64% vs 64%; p=1.000). Their clinical characteristics are shown in table 1.

Cardiovascular magnetic resonance analysis

Brugada syndrome patients and normal controls

Right ventricular ejection fraction (RVEF) was lower (61±8% vs 64±5%; p=0.004) and RV end systolic volume (RVESV) was greater (31±10mL/m^2 vs 28±6mL/m^2; p=0.038) in BrS patients compared with healthy controls. There were no significant differences in other size or function measurements between cohorts. Overall LGE was demonstrated in 6 (8%) BrS patients (45±15 years; 83% male) and no healthy controls (table 2). LGE was found in patients studied at both 1.5T and 3.0T field strengths. Following exclusion of patients with LGE, RVEF remained lower (61±8% vs 64±5%; p=0.008) and RVESV greater (31±10mL/m^2 vs 28±6mL/m^2; p=0.026) in BrS patients compared with controls.

Brugada syndrome patients with and without SCN5A mutations

Right atrial (RA) area (12±2cm^2/m^2 vs 10±2cm^2/m^2; p=0.010), RV end diastolic volume (RVEDV) (78±18mL/m^2 vs 74±12mL/m^2; p=0.038), LV end diastolic volume (LVEDV) (74±14mL/m^2 vs 71±11mL/m^2; p=0.019) and LV end systolic volume (LVESV) (27±6mL/m^2 vs 24±6mL/m^2; p=0.024) were greater in patients with *SCN5A* mutations

compared to those without. Overall there was a trend towards greater cardiac dimensions and lower ventricular function in patients with *SCN5A* mutations, although this did not reach statistical significance across all variables (table 3).

Patterns of late gadolinium enhancement in Brugada syndrome

Where LGE was present in patients with BrS, it was found most frequently in the LV midwall (4 patients; 5%). The distribution was varied and included septal and inferolateral locations as well as multiple locations within one patient (figure 1 and table 4). LGE was also found at the RV insertion points but was not seen in the RV myocardium.

Clinical characteristics of patients with LV midwall late gadolinium enhancement

There were four patients with midwall LV LGE (figure 1 and table 4). All were asymptomatic. Patients 1 and 2 were siblings with ajmaline induced type 1 ECG pattern and a family history of sudden cardiac death (SCD) during sleep (son of patient 1). Patient 3 had ajmaline induced type 1 ECG pattern with a family history of SCD at rest (sister). Patient 4 had a spontaneous type 1 ECG pattern with a family history of SCD (uncle). At the time of CMR assessment patient 1 had T wave inversion in ECG leads V_1 and V_2 but no other features of cardiomyopathy. All four patients had otherwise unremarkable ECGs and SAECGs, normal transthoracic echocardiograms and no significant arrhythmias on exercise testing or Holter monitoring. *SCN5A* mutation analysis was negative in patient 2 (therefore not repeated in her brother patient 1),

patient 3 and patient 4. In patient 3 further genetic testing has revealed a mutation in the desmoplakin gene.

Follow-up

Two patients (3%) were lost to follow-up but the remaining 76 patients have been followed up for 31±21 months. Two patients (3%), both of whom presented initially with VF cardiac arrest, had further VF events shocked appropriately by their implantable cardioverter-defibrillators. Two patients (3%) without prior arrhythmia developed non-sustained ventricular tachycardia without haemodynamic compromise. Two patients (3%) developed sinus node disease and three patients (4%) developed atrial fibrillation. One further patient died secondary to septicaemia. None of these had LGE on their presenting CMR. Of the four patients (5%) with BrS and midwall LGE, followed for 45±15 months, one developed T wave inversion across all precordial ECG leads after 25 months (patient 2; figures 2 and 3), but none suffered a SCD event, VF or any other arrhythmia. Follow-up for the remaining patients has been unremarkable.

Discussion

This study demonstrated an increased prevalence of myocardial fibrosis in BrS patients compared with healthy controls. BrS patients with midwall LGE had strong family histories of sudden cardiac death but were asymptomatic and during a short follow-up presence of LGE did not appear to predict arrhythmic events. The presence of LGE was therefore not associated with arrhythmogenesis or a personal risk of sudden death.

Previous CMR studies of BrS patients have not focused on LGE assessment. Analysis of a smaller cohort failed to demonstrate evidence of LGE.(15) Rudic et al. found LV subepicardial LGE in 1/60 BrS patients consistent with healed myocarditis and compatible with the patient's past medical history.(16) Van Hoorn et al. found LGE in 3/40 SCN5A mutation positive and 3/98 SCN5A mutation negative BrS patients but the location, pattern and relevance of LGE was not specified.(17)

Our data demonstrated mildly reduced RV systolic function (RVEF) and mildly increased RV systolic volume (RVESV) in BrS patients compared with controls. However these values remained within the normal range. These findings are similar to other CMR studies in BrS where lower RVEF and increased RVESV as well as greater RV outflow tract dimensions have been reported.(13,14,16) There are minor differences in absolute values for volumes and function between studies which likely reflect use of different software analysis programs and methods for tracing the endocardial borders (including or excluding papillary muscle mass) but results of the comparisons are similar.

From previous data it appears that increased atrial and ventricular dimensions and reduced ventricular function in BrS may be driven by patients with *SCN5A* mutations.(16,17) There were greater cardiac dimensions and reduced ventricular function in our *SCN5A* mutation positive BrS patients compared with their mutation negative counterparts. However this difference was not significant for all variables which likely reflects the smaller number of patients carrying an SCN5A mutation in this cohort.

Clinical implications in patients with BrS

RV insertion point LGE is found in patients with hypertrophic cardiomyopathy but may also be found in normal individuals and is of unclear clinical significance.(26) Midwall LGE is associated with pathology. In our BrS patients midwall LGE was similar to that seen in non-ischemic cardiomyopathies and myocarditis.(27) These patients were diagnosed with BrS based on current guidelines.(20) All of the patients with midwall LGE therefore fulfilled diagnostic criteria for BrS and during comprehensive clinical evaluation none of these patients demonstrated a cardiomyopathy phenotype at the time of CMR. There was T wave inversion in ECG leads V_1 and V_2 in one patient but otherwise all four patients had unremarkable ECGs and SAECGs, normal transthoracic echocardiograms and no significant arrhythmias on exercise testing or Holter monitoring. This is potentially important as current practice does not include CMR in the routine clinical evaluation of BrS, particularly if the echocardiogram is normal and the

ECG does not suggest structural abnormalities.(20,21) Underlying cardiomyopathy may therefore be missed. During subsequent short follow-up the ECG in one patient has evolved to demonstrate T wave inversion across all precordial leads and further genetic testing in another patient revealed a desmoplakin mutation. Both of these are major criteria for ARVC, but these patients exhibit no other Task Force features of this condition and as yet neither fulfils diagnostic criteria for definite ARVC.(28)

Repolarization abnormalities vs conduction slowing in BrS

There are two competing hypotheses for the mechanism of ST-segment elevation and ventricular arrhythmia in BrS: the repolarization and the conduction slowing theories. The repolarization theory suggests that unopposed action of the I_{to} current in RV epicardium leads to dispersion of repolarization allowing re-entry and initiation of arrhythmia. The conduction slowing theory suggests that delayed conduction in the RVOT facilitates re-entry and subsequent arrhythmia. Although the repolarization theory has received most support from the scientific community, there is increasing evidence to suggest that the BrS ECG pattern is a marker of subtle structural heart disease.(2–12) It appears that BrS requires subtle structural abnormalities with sodium channel dysfunction, and the role of SCN5A mutations is likely modulatory. (29)

Prior to the original description of BrS, a case series of patients with idiopathic VF and right precordial ST-segment elevation documented RV structural abnormalities.(30) Subsequent histopathological studies in sudden death cases with prior ECGs suggestive

of BrS have demonstrated evidence of fibro-fatty infiltration in the RV. This suggested an overlap of BrS with ARVC.(2) Our group previously used histopathological morphometric quantification of collagen and connexin 43 (Cx43) and identified a higher collagen and lower Cx43 content in the RVOT of sudden arrhythmic death syndrome (SADS) cases with an associated familial diagnosis of BrS compared with controls.(3) This was correlated with *in vivo* evidence of conduction delay. In addition, endomyocardial biopsies from living patients with BrS have demonstrated a variety of structural changes including lymphocytic myocarditis, myocyte hypertrophy, mild fibrosis and fatty infiltration.(4,5)

Left ventricular midwall LGE in BrS

BrS is usually regarded as a disease of the RV and RVOT, but here fibrosis was demonstrated within the LV myocardium. This is in keeping with histopathology from SADS/BrS cases where higher collagen content was demonstrated in LV as well as RV myocardium.(3) The lack of RV LGE on CMR may reflect the difficulties associated with imaging the thin walled RV myocardium using current clinical techniques, as opposed to excluding the presence of fibrosis.(25) We agree with others who have hypothesized that RV fibrosis, undetectable using current imaging technology, is also present in these patients and explains the BrS ECG phenotype.(11,12,29) Our data therefore lend support to the depolarization hypothesis and the presence of subtle structural abnormalities in patients with BrS.

It is possible that the LV midwall LGE in these patients reflects healed myocarditis although there was nothing in their medical histories to suggest this. Similar patterns of LGE found in two siblings make a genetic cause more likely. This suggests a degree of phenotypic overlap between BrS and inherited cardiomyopathies and LGE may serve as an early marker for evolution of a subtle but more clinically appreciable cardiomyopathic phenotype over time. When patients with LGE were excluded, BrS patients still exhibited mildly reduced RV systolic function (RVEF) and mildly increased RV systolic volumes (RVESV), and in these patients diffuse underlying fibrosis may therefore be more relevant.

Study Limitations

This is a retrospective study which utilised two different MRI scanners. There were small numbers of BrS patients with LV LGE myocardial fibrosis. RV LGE was not seen, but given the inherent difficulties associated with CMR imaging of the thin walled RV myocardium, the absence of RV LGE does not exclude RV fibrosis. Overt structural abnormalities were not seen in the majority of BrS patients and subtle anomalies and diffuse fibrosis may be more relevant. LGE cannot image diffuse interstitial fibrosis and other CMR techniques (T1 mapping) may therefore be considered in future studies.(31)

Conclusion

Some BrS patients have left ventricular midwall LGE consistent with an underlying cardiomyopathic process. Even cases without LGE show greater RVESV and lower RVEF on average. These findings lend further support to the presence of subtle structural abnormalities in BrS and the depolarization hypothesis. LGE may serve as an early marker for evolution of a cardiomyopathic phenotype over time. CMR is a potentially useful adjunct investigation in the clinical evaluation of BrS.

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Figures

Figure 1 Cardiovascular magnetic resonance imaging in Brugada syndrome (BrS). The left sided panel demonstrates extensive late gadolinium enhancement (LGE) in a 45 year old male patient (patient 1) with BrS. Patchy midwall LGE is demonstrated in the mid and apical lateral wall, basal and apical inferolateral wall of the left ventricle and the mid anteroseptum. The centre panel demonstrates midwall LGE in the mid inferoseptum of his 53 year old sister (patient 2) who also has BrS. The right sided panel demonstrates midwall LGE in the basal and mid septum and anteroseptum of an unrelated 40 year old man (patient 3) with BrS who was subsequently found to have a desmoplakin gene mutation, a Task Force criterion for arrhythmogenic right ventricular cardiomyopathy.

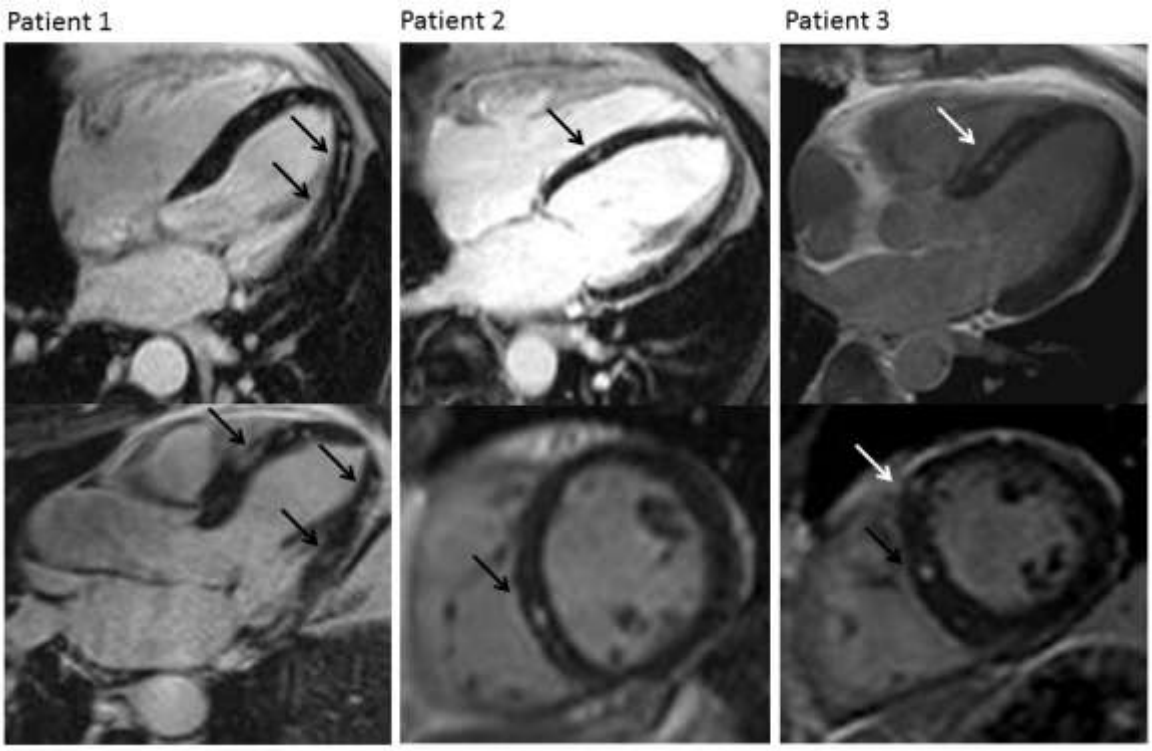


Figure 2 Electrocardiograms during diagnostic ajmaline testing in a 53 year old lady (patient 2) with Brugada syndrome (BrS). At peak ajmaline there is a characteristic type 1 BrS pattern with coved ST elevation ≥0.2mV and T wave inversion in leads V23 (V2 in the 3rd intercostal space) and V22 (V2 in the 2nd intercostal space).

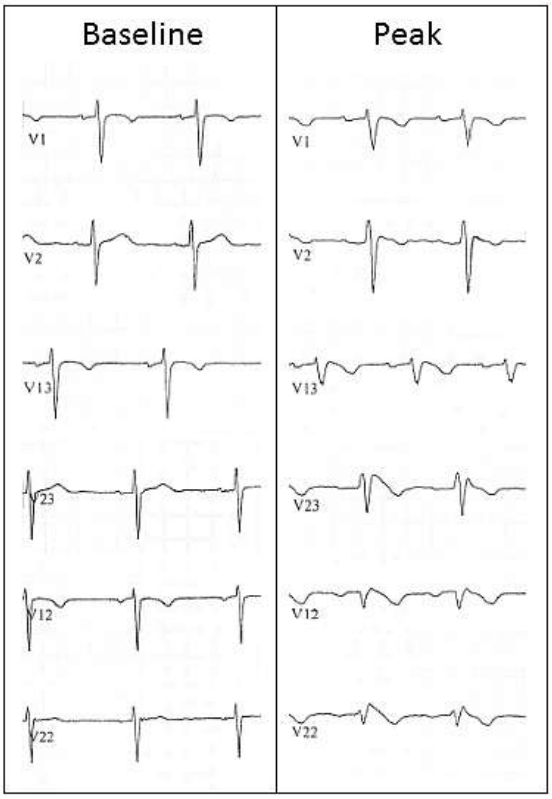
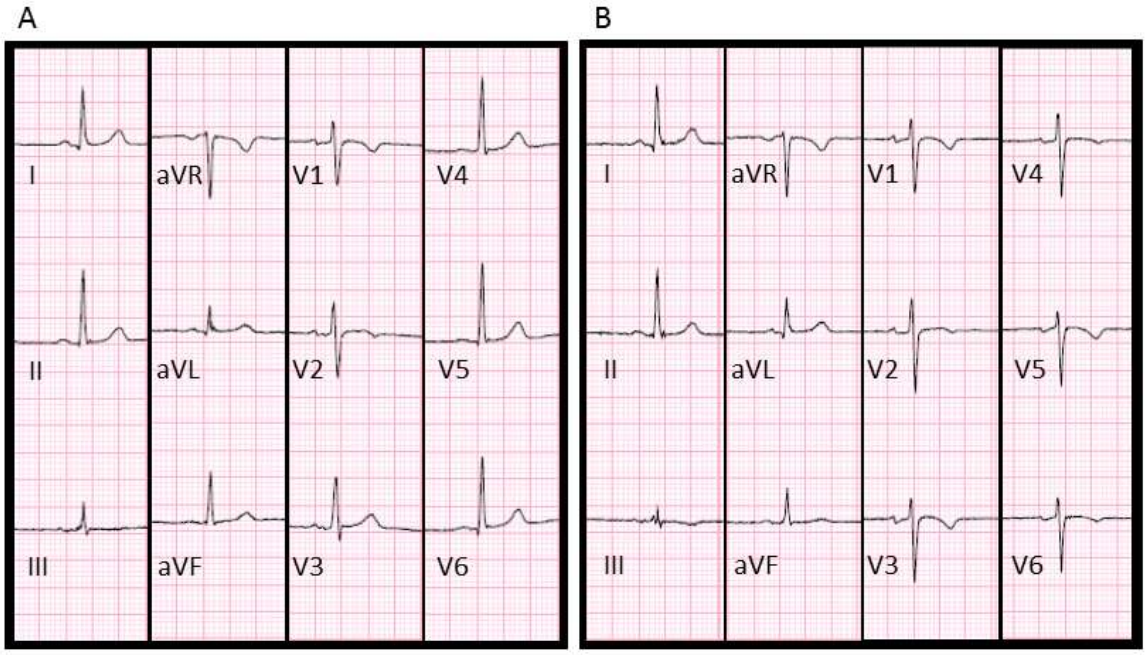


Figure 3 Resting electrocardiograms from a 53 year old lady (patient 2) with Brugada syndrome. Panel A demonstrates her presenting ECG with T wave inversion in leads V_1 and V_2, a minor criterion for arrhythmogenic right ventricular cardiomyopathy (ARVC). Panel B demonstrates her ECG after two years of follow-up with T wave inversion throughout all precordial leads, a major Task Force criterion for ARVC.



Tables

Table 1 Demographic and clinical characteristics of Brugada syndrome patients and healthy controls.

	Brugada patients (n=78)	Healthy controls (n=78)
Age	44±15	42±14
Sex (male; %)	64	64
Syncope (%)	19	0
Cardiac arrest (%)	9	0
Spontaneous type 1 BrS ECG (%)	23	0
SCN5A mutation presence (%)	26	NA
Family history SCD <45 years (%)	49	0
Abnormal SAECG (%)	33	0

BrS, Brugada syndrome; ECG, electrocardiogram; SCN5A, gene encoding the cardiac sodium channel; SCD, sudden cardiac death; SAECG, signal averaged electrocardiogram; NA, not applicable

Table 2 Comparison of cardiovascular magnetic resonance findings in patients with Brugada syndrome and healthy controls.

	Brugada patients (n=78)	Healthy controls (n=78)	p-value
LA area (cm^2/m^2)	12±2	11±2	0.275
LVEDV (mL/m^2)	74±13	76±13	0.260
LVESV (mL/m^2)	26±7	27±6	0.139
LVEF (%)	65±5	64±5	0.328
LV mass (g/m^2)	57±13	56±13	0.401
RA area (cm^2/m^2)	11±2	11±2	0.423
RVEDV (mL/m^2)	78±16	76±13	0.622
RVESV (mL/m^2)	31±10	28±6	**0.038**
RVEF (%)	61±8	64±5	**0.004**
LGE presence (n)	6 (8%)	0	**0.028**

LA, left atrium; RA, right atrium; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volume; LVEF, left ventricular ejection fraction; RVEDV, right ventricular end diastolic volume; RVESV, right ventricular end systolic volume; RVEF, right ventricular ejection fraction; LGE, late gadolinium enhancement

Table 3 Comparison of cardiovascular magnetic resonance findings in Brugada syndrome patients with and without SCN5A mutations.

	Brugada with SCN5A mutation (n=20)	Brugada without SCN5A mutation (n=34)	p-value
LA area (cm^2/m^2)	12±2	11±2	0.227
LVEDV (mL/m^2)	74±14	71±11	**0.019**
LVESV (mL/m^2)	27±6	24±6	**0.024**
LVEF (%)	64±5	66±5	0.079
LV mass (g/m2)	55±16	58±12	0.408
RA area (cm^2/m^2)	12±2	10±2	**0.010**
RVEDV (mL/m^2)	78±18	74±12	**0.038**
RVESV (mL/m^2)	32±11	29±9	0.166
RVEF (%)	59±10	61±7	0.387
LGE presence (n)	0	3	n/a

LA, left atrium; RA, right atrium; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volume; LVEF, left ventricular ejection fraction; RVEDV, right ventricular end diastolic volume; RVESV, right ventricular end systolic volume; RVEF, right ventricular ejection fraction; LGE, late gadolinium enhancement

Table 4 Patterns of late gadolinium enhancement in Brugada syndrome patients and their associated clinical characteristics.

Patient	Sex	Age	Symptoms	Spont type 1 ECG	FHx SCD	SCN5A mutation	LGE pattern
1	M	45	None	No	Yes	Untested	Midwall Mid and apical lateral wall, basal and apical inferolateral wall, mid anteroseptum (figure 1)
2	F	53	None	No	Yes	No	Midwall Mid inferoseptum (figure 1)
3	M	40	None	No	Yes	No	Midwall Basal and mid septum/anteroseptum (figure 1)
4	M	60	None	Yes	Yes	No	Midwall Basal inferolateral
5	M	54	None	No	Yes	Untested	Basal inferior RV insertion point
6	M	19	None	No	No	Untested	Basal anterior RV insertion point

ECG, electrocardiogram; FHx SCD, family history of sudden cardiac death; SCN5A, gene encoding the cardiac sodium channel; LGE, late gadolinium enhancement