Longitudinal Assessment of Structural Phenotype in Brugada Syndrome Using Cardiac Magnetic Resonance Imaging

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ABSTRACT

Background: Despite historically being considered a channelopathy, subtle structural changes have been reported in Brugada Syndrome (BrS) on histopathology and cardiac magnetic resonance (CMR) imaging. It is not known if these structural changes progress over time.

Objectives: To assess if structural changes in BrS evolve over time with serial CMR assessment and investigate the utility of parametric mapping techniques to identify diffuse fibrosis in BrS.

Methods: Patients with a diagnosis of BrS based on international guidelines and normal CMR at least 3 years prior to the study period, were invited to undergo repeat CMR. CMRs were analysed de novo and compared at baseline and follow-up.

Results: Eighteen patients with BrS (72% male and mean age at follow-up 47.4 ± 8.9 years) underwent serial CMR with an average of 5.0 ± 1.7 years between scans. No patients had late gadolinium enhancement (LGE) on baseline CMR but 4 (22%) developed LGE on follow-up, typically localised to the RV side of the basal septum. RV end-systolic volume (RV-ESV) increased over time (p=0.04) and was associated with a trend towards reduction in RV ejection fraction (RV-EF) (p=0.07). Four patients showed a reduction in RV-EF >10%. There was no evidence of diffuse myocardial fibrosis observed on parametric mapping.

Conclusions: Structural changes may evolve over time with development of focal fibrosis, evidenced by LGE on CMR in a significant proportion of patients with BrS. These findings have implications for our understanding of the pathological substrate in BrS and the longitudinal evaluation of patients with BrS.
KEYWORDS:

Brugada Syndrome; cardiac magnetic resonance; cardiomyopathy; fibrosis; late gadolinium enhancement.
INTRODUCTION

Brugada syndrome (BrS) is an inherited heart disease characterised by an ECG signature of downsloping ST elevation with T-wave inversion in the right precordial leads and a risk of malignant ventricular arrhythmia. BrS has primarily been considered a channelopathy due to its signature ECG phenotype, the absence of ubiquitous structural disease and its association with pathogenic variants in the SCN5A gene. However, structural abnormalities in BrS are increasingly appreciated. Histopathological changes including fibrosis, fatty infiltration, inflammatory infiltrates, and increased collagen deposition have been described in patients with BrS. Structural changes have also been observed with cardiac magnetic resonance (CMR) imaging, which is the gold standard for right ventricular assessment and non-invasive detection of replacement fibrosis. Newer parametric mapping techniques allow more detailed tissue characterisation for subtle changes such as diffuse fibrosis, but these have not been specifically studied in BrS.

In inherited cardiomyopathies such as hypertrophic cardiomyopathy, disease penetrance has been shown to be age-related. Indeed, the extent of structural abnormalities in HCM, including focal myocardial scar, can progress over time and these changes correlate with clinical outcomes. In BrS, first arrhythmic events most often occur in the 3rd or 4th decade of life and structural abnormalities identified on non-invasive imaging may correlate with arrhythmic events. Hence, it is important to assess whether the structural abnormalities in BrS emerge or progress over time.

In this exploratory study, we sought to identify if the structural changes in patients with BrS develop or progress over time on serial CMR imaging. The secondary aim was to
investigate if newer parametric mapping CMR techniques may detect diffuse fibrosis in BrS.
METHODS

Patient selection:
Patients who fulfilled diagnostic criteria for BrS, 2mm coved-type ST segment elevation spontaneously or after provocation with sodium channel blocker, were recruited from the Genetic Heart Disease Clinic at Royal Prince Alfred Hospital, Sydney, Australia. Patients with BrS were invited to participate if they had undergone CMR imaging more than 3 years prior demonstrating normal ventricular volumes and absence of myocardial scar, and if there were no contraindications to repeat scanning such as an implantable cardioverter-defibrillator (ICD). Notably, no patients screened for inclusion were excluded due to abnormal baseline volumes or baseline LGE, in keeping with the subclinical volumetric changes described in BrS and low rate of LGE previously described. Demographic and clinical information were collected from patient records. Patients with no history of cardiac arrest or syncope were considered asymptomatic and a family history of sudden cardiac death (SCD) was noted if a first- or second-degree relatives died suddenly under the age of 45 years. The study adhered to Helsinki Declaration guidelines, was approved by the local research ethics committee (X15-0061) and informed consent was obtained from all participants.

CMR acquisition:
Baseline MRI scans were obtained for de novo analysis. Follow-up CMR scans were performed using a 1.5T (Phillips) scanner and the imaging protocol included steady-state free precession (SSFP) cine acquisitions of both ventricles from base to apex in the vertical long-axis, four-chamber (4Ch), and the short-axis (SAX) views. Segmented phase-sensitive inversion recovery sequences (Imaging parameters: TR= 3.6ms; TE= 1.2ms; flip angle=15°; slice thickness=5mm; FOV = 370mm, acquired
during a single breath hold) were used to identify focal myocardial scar 10 min post
administration of intravenous contrast (0.2 mmol/kg of Gadobutrol, Gadovist). A look-
locker sequence was used to determine the null point of normal remote myocardium.
Significant enhancement was defined as occurring at 5 standard deviations above the
null point. Parametric mapping was performed for tissue characterisation on follow-up
scans (required sequences were not available at the time of baseline scanning). Native
T1 times were computed in the interventricular septum and haematocrit was measured
immediately prior to scanning using a point-of-care device for extracellular volume
(ECV).

CMR analysis:

Image analysis was performed using Horos version 3.3 (Horos Project) and OsiriX 12.
Presence or absence of LGE was reported independently by two level 3 EACVI/SCMR
reporters. Native T1 times and ECV were compared to the local reference range
(native T1 = 968-1076ms and ECV <28%). Left ventricular (LV) and right ventricular
(RV) volumes and ejection fractions were calculated using Simpson’s method after
manually contouring the endocardial surface at end-diastole and end-systole in
sequential cine short-axis slices. Ventricular volumes were compared to reference
standards for age and sex, according to standard recommendations. A change in
ejection fraction (EF) ≥10 percentage points was considered a significant change over
time. This cut-off was chosen on the basis of the reported reproducibility of EF
measurements, and consensus definitions of left ventricular impairment in the cardio-
oncology setting. Right ventricular outflow tract (RVOT) volume was assessed on
short axis images by manual segmentation in end-diastole. For consistency, the
inferior border of the right ventricular outflow tract was taken at 90 degrees from the
LV/RV insertion points or RV/aortic junction as appropriate. The superior border was defined at the level of the pulmonary valve. RVOT volume was derived using Simpson’s method. RVOT volume was measured twice on all scans and the mean volume is reported. RVOT volume was then calculated on a random selection of 20% of CMRs by a second observer for the appraisal of interobserver variability.

Statistical analysis:

SAS Studio (SAS Institute Inc., Cary, NC) and GraphPad Prism version 9.1 (GraphPad Software, LLC) were used for statistical analysis. Descriptive statistics of continuous variables are reported as means and standard deviations and categorical variables as counts and percentages of available data. Continuous variables were tested for normality using the Shapiro-Wilk test and compared using two-tailed, paired t-tests. Statistical significance was defined as p<0.05. The data underlying this article will be shared on reasonable request to the corresponding author.
RESULTS

Patient characteristics

The clinical characteristics of the cohort are reported in Table 1. The majority of participants were male (72%) and the average age at time of follow-up scan was 47.4 ± 8.9 years. Given the exclusion of patients with ICDs, all patients were asymptomatic. Nine (50%) patients had a spontaneous type 1 BrS ECG pattern, 2 (11%) patients had a history of fever-induced type 1 pattern while 7 (39%) had only had a type 1 BrS ECG documented during a sodium channel blocker challenge. Three patients had a pathogenic or likely pathogenic SCN5A variant (patient WC1 - c.1936delC, patient AOL1 - c.4086delG, and patient TD3 had a previously described balanced translocation interrupting SCN5A).19, 20

CMR Analysis – volumetric assessment

CMR indices at baseline and follow-up are detailed Table 2. Although all volumetric indices were within the normal range at baseline and follow-up, there was an increase in RV end-systolic volume (ESV) from baseline to follow-up scan (63.1 ± 26.6 to 71.2 ± 21.7, p=0.04) that persisted after indexing for body surface area (p=0.050), as illustrated in Figure 1a. A trend towards reduction in RV ejection fraction (EF) over time was also observed (58.1 ± 7.0 to 54.6 ± 5.2, p=0.07, Figure 1b). Four patients had an absolute reduction in RV-EF by more than 10% and clinical characteristics of these patients are reported in Table 3. Mean RVOT volumes increased on follow-up scans, but the change was not statistically significant. Intra- and interobserver correlation coefficients for RVOT end diastolic volume (EDV) were 0.91 and 0.74, respectively. Baseline and follow-up CMR parameters were similar between patients with spontaneous type 1 ECG pattern and those with an inducible type 1 ECG pattern.
(Supplementary Tables 1 and 2). There were no significant differences in LV volumes
or LV-EF.

CMR Analysis – fibrosis assessment

No patients had evidence of LGE on the baseline scan. Four (22%) patients developed
LGE on follow-up CMR (Figure 2). The LGE was localised to the septum in all cases,
and specifically to the RV side of the basal septum in three patients. There was no
evidence of diffuse fibrosis on follow-up scans with parametric mapping indices in the
normal range (native T1 time 969.7 ± 36.7 ms and ECV 24.1 ± 5.4).

Patients exhibiting significant structural change during follow-up

The clinical and genetic features of patients with significant change in structural
phenotype (i.e. development of LGE and/or absolute reduction in RV-EF of ≥10%) are
described in Table 3. Amongst patients who developed LGE, three patients had a
spontaneous type one pattern, and the average Shanghai score was 4.1, compared
to 3.0 in the general cohort. Two of the four patients had a family history of BrS but all
were SCN5A negative. Amongst patients with a significant reduction in RV-EF, 3 of 4
had an inducible type 1 BrS ECG (mean Shanghai score 2.4). A disease-causing
SCN5A variant was present in patient TD3, part of a previously described family with
a SCN5A translocation associated with pleiotropic manifestations including BrS, SCD,
sick sinus syndrome and myocardial hypertrophy. Otherwise, all patients who
demonstrated significant structural changes during follow-up had no disease-causing
variants identified on comprehensive cardiac genetic testing, analysing genes
associated with cardiomyopathy and inherited arrhythmia syndromes.
DISCUSSION

Key findings

The key finding of this exploratory study is that structural abnormalities may evolve during follow-up of patients with BrS. We observed the development of focal replacement fibrosis evidenced by LGE in 22% of patients, as well as a reduction in RV-ESV and a trend towards reduction in RV-EF over time. However, diffuse interstitial fibrosis was not detected on parametric mapping techniques. To our knowledge, this is the first study to investigate whether the structural phenotype in BrS changes over time and also the first to report parametric mapping indices in a BrS cohort. Overall, these findings support the hypothesis that BrS has features of a cardiomyopathy with structural changes that may extend beyond the RVOT and, that these changes can progress over time, only becoming apparent with longitudinal assessment.

Histopathological substrate in BrS

Pathological studies of patients with BrS have reported a wide spectrum of abnormalities including interstitial fibrosis, inflammatory infiltrates and fibrofatty replacement. Indeed some findings have raised the possibility of overlap between the pathogenesis of BrS and other conditions such as arrhythmogenic cardiomyopathy and myocarditis. Epicardial and interstitial fibrosis, and reduced gap junction expression have been shown to co-locate with the abnormal electrical substrate in the RVOT. However, myocardial changes are subtle and may be difficult to detect in with current non-invasive imaging technology. Indeed, Miles et al identified increased collagen content throughout both the RV and LV (in the absence of overt histological abnormalities) on post-mortem examination of 28 BrS
decedents, confirming that even more subtle ultrastructural changes may be present on a global basis in BrS. These findings imply that BrS may actually be a generalised myocardial disease with the intrinsic properties of the RVOT predisposing this region to more overt fibrosis and electrical abnormalities.

Utility of CMR in BrS

As an extension of the pathological studies in BrS, CMR studies have also reported subtle changes in RV volumes and contractile function compared to healthy controls as well as the presence of septal and left ventricular LGE in some patients with BrS. The reported incidence of LGE is variable but is unequivocally lower than fibrosis in histological series, likely reflecting the lower sensitivity of CMR in detection of subtle fibrosis, as well as limitations of scar assessment in the thin-walled RV.

Development of Structural Changes during follow-up in BrS

The potential for progression in the structural phenotype of patients with BrS has not been systematically studied to date. Perhaps the most striking observation from the present study was the development of LGE in 4 of 18 patients that was not observed on their previous CMR imaging. The LGE was localised to the septum and confined to the mid-wall in all cases, thus not in a typically ischaemic distribution. Mid-wall LGE is a typical finding in non-ischaemic dilated cardiomyopathy and has been associated with increased arrhythmic events. Basal septal LGE has been reported in normal individuals and while a physiological LGE pattern has been proposed, this pattern was not seen in the individuals who developed LGE in the present study. The patients did not report any interval viral illness or chest pain syndrome to implicate myocarditis. Comprehensive cardiac genetic analysis excluded disease-causing genetic variants.
We also observed an increase in RV-ESV and a trend towards reduced RV-EF over time, suggesting that RV changes in BrS may also be a progressive process. This observation is in line with previous CMR studies which have demonstrated that RV-ESV is larger in patients with BrS compared to normal controls and associated with a reduction in RV-EF. However, we did not observe a significant change in RVOT volume in our small cohort. Perhaps, provocative assessment of the RV following Ajmaline infusion, or assessment of RV myocardial strain by CMR may further improve the sensitivity of detecting subclinical structural changes in the RV in BrS.

Potential Mechanisms for Structural Progression in BrS

Mechanistic explanations for the observed development of abnormal tissue architecture in BrS may be speculated. Firstly, we considered the interactions of age and SCN5A status. Patients with other inherited conditions such as HCM have been shown to have increased LGE with ageing. In BrS, the cardiac sodium channel encoded by the SCN5A gene is known to interact with proteins in both the desmosome and gap junctions, and variants may cause a primary disturbance of myocardial structure. Moreover, SCN5A knock-out mice have exhibited age-related development of fibrosis in ventricular myocardium and associated delay in epicardial activation. While age is associated with increased ventricular fibrosis in these settings, it does not appear to be an adequate explanation in our cohort. The average age at the follow-up scan of those who developed fibrosis was 46.7 years compared to 47.6 years for those who did not. The age of those who developed LGE was also
comparable to the mean age of patients without LGE in previous CMR studies of BrS (average mean age of 43.6 years with range of means from 38-48 years). 9, 10, 14, 24, 25, 31 SCN5A status did not appear to account for development of structural changes in our cohort either. None of the 4 patients who developed LGE, and only one of the 4 patients who developed significant reduction in RV-EF had a pathogenic SCN5A variant.

Another potential explanation may be sub-clinical inflammation. Acute inflammation has been postulated as a potential mechanism for disease progression, and so-called “hot phases” in arrhythmogenic cardiomyopathy. 32, 33 In BrS, lymphocytic infiltration has been identified at sites with progression of electro-anatomical substrate and in histological studies, appears to associate with fibrosis. 3, 21, 34 Elevated CRP and autoantibodies to cardiac proteins have been identified in BrS cohorts, and active myocardial inflammation detected by PET scan was implicated in two patients with BrS with recurrent VF, one of whom responded to immunosuppression rather than antiarrhythmic medications and catheter ablation. 35-37 Hence, myocardial inflammation may also have a role in pathogenesis, disease progression and arrhythmogenesis in BrS.

Parametric mapping in BrS

Although LGE is validated as a correlate of replacement myocardial fibrosis, it has limitations for the detection of diffuse interstitial fibrosis. Newer parametric techniques such as T1 mapping and ECV assessment have been used to detect diffuse interstitial fibrosis in HCM, DCM, and ACM 38, 39 but they have not been evaluated in patients with BrS to date.
Given the recent report of increased global collagen content in patients with BrS, we hypothesised that parametric mapping with CMR may allow in vivo detection of diffuse interstitial fibrosis in BrS. However, we did not detect any abnormal parametric mapping indices outside of the normal range. This may indicate that these techniques are insensitive to the detection of subtle increases in collagen deposition observed in histological evaluation of BrS. It is also possible that sampling the interventricular septum, one of the areas with relatively low distribution of collagen compared to the well described fibrosis of the RVOT, reduces the sensitivity for detecting subtle interstitial fibrosis in BrS. Unfortunately, the thin wall of the RV and particularly of the RVOT renders advanced fibrosis assessment on these areas difficult with current non-invasive techniques.

LIMITATIONS

The findings from this study should be considered exploratory and hypothesis-generating because the study cohort was small. Replication of the results in a larger, multicentre cohort will be important to confirm these early findings. It is possible that an alternative diagnosis such as cardiomyopathy may explain the CMR changes; however, only patients with a spontaneous or drug-induced type 1 pattern were included (mean Shanghai score of 3), no patients had clinical symptoms suggestive of myocarditis and there was no evidence of cardiomyopathy on the initial CMR scan or on comprehensive cardiac genetic testing. Baseline scans were performed at a number of sites with different protocols for image acquisition. Despite undertaking de novo analysis to standardise assessment, this real-world issue makes serial assessment more challenging. The time interval between CMR scans was not
standardized, and a longer interval between scans may have the potential to reveal an even higher burden of progressive structural changes. Patients with ICD were excluded from this study, it is possible that the degree of progressive structural change in BrS may be underestimated by our asymptomatic cohort.
IMPLICATIONS AND FUTURE DIRECTIONS

BrS appears to be a progressive substrate in some patients and changes may be detected on serial cardiac imaging. While Scheirlynck and colleagues have shown that patients with BrS and features of ACM have worse arrhythmic outcomes, the clinical significance of progressive structural changes such as the development of focal fibrosis in BrS requires further evaluation. It will be useful for future studies to compare patients with and without progressive structural changes, to understand demographic, genetic, and clinical differences and ultimately, outcomes. The mechanism for progressive changes should be explored as this may have implications for therapy. In particular, serial evaluation of PET-CT and/or inflammatory markers may shed light on the potential role of inflammation in disease progression. Although it remains to be seen whether disease progression is associated with poorer prognosis, it is plausible that it would have an impact on risk stratification, proposed therapies such as catheter ablation, and even immune modulation once the drivers of disease progression in these individuals are better understood.
CONCLUSION

Structural changes may emerge in a significant proportion of patients with BrS on longitudinal assessment. Subtle changes in RV-ESV and RV-EF and the development of septal LGE over time suggest there may be a degree of global myocardial dysfunction in BrS, beyond the RVOT. The clinical significance of these progressive structural changes remains unclear but, if shown to be associated with adverse clinical outcomes in follow-up studies, they may dictate a change in the approach to risk stratification and clinical management of BrS.
ACKNOWLEDGEMENTS

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REFERENCES:


### Table 1: Cohort characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (N=18)</th>
</tr>
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<tbody>
<tr>
<td>Male (N, %)</td>
<td>13 (72)</td>
</tr>
<tr>
<td>Age at baseline (years; mean ± SD)</td>
<td>42.4 ± 8.8</td>
</tr>
<tr>
<td>Age at follow-up (years; mean ± SD)</td>
<td>47.4 ± 8.9</td>
</tr>
<tr>
<td>Asymptomatic (N, %)</td>
<td>18 (100)</td>
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<tr>
<td>Spontaneous type 1 ECG (N, %)</td>
<td>9 (50)</td>
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<tr>
<td>Shanghai Score (mean ± SD)</td>
<td>3.0 ± 0.9</td>
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<tr>
<td>Family History of BrS (N, %)</td>
<td>3 (17)</td>
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<tr>
<td>Family History of SCD (N, %)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>SCN5A positive* (N, %)</td>
<td>3 (19)</td>
</tr>
<tr>
<td>Quinidine therapy (N, %)</td>
<td>4 (22)</td>
</tr>
<tr>
<td>Time between CMR imaging (years; mean ± SD)</td>
<td>5.0 ± 1.7</td>
</tr>
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</table>

*SCN5A status of 2 patients was unknown.
Table 2: CMR indices at baseline and follow-up

<table>
<thead>
<tr>
<th></th>
<th>Normal Range</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Body surface area</td>
<td></td>
<td>1.9 ± 0.2</td>
<td>1.9 ± 0.3</td>
<td>0.313</td>
</tr>
<tr>
<td>LV-EDV (ml)</td>
<td>77-195</td>
<td>129.7 ± 37.7</td>
<td>130.9 ± 32.6</td>
<td>0.765</td>
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<tr>
<td>LV-EDVi (ml/m²)</td>
<td>47-92</td>
<td>66.9 ± 15.4</td>
<td>66.8 ± 9.6</td>
<td>0.962</td>
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<td>LV-ESV (ml)</td>
<td>19-72</td>
<td>44.6 ± 16.9</td>
<td>46.9 ± 15.8</td>
<td>0.356</td>
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<tr>
<td>LV-ESVi (ml/m²)</td>
<td>13-30</td>
<td>22.9 ± 7.2</td>
<td>24.4 ± 5.1</td>
<td>0.305</td>
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<tr>
<td>LV-EF (%)</td>
<td>56-78</td>
<td>66.1 ± 6.4</td>
<td>64.6 ± 6.7</td>
<td>0.375</td>
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<tr>
<td>RV-EDV (ml)</td>
<td>88-227</td>
<td>147.4 ± 46.0</td>
<td>155.1 ± 40.3</td>
<td>0.126</td>
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<tr>
<td>RV-EDVi (ml/m²)</td>
<td>47-92</td>
<td>75.9 ± 18.4</td>
<td>78.8 ± 11.4</td>
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<tr>
<td>RV-ESV (ml)</td>
<td>23-103</td>
<td>63.1 ± 26.6</td>
<td>71.2 ± 21.7</td>
<td>0.041</td>
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<tr>
<td>RV-ESVi (ml/m²)</td>
<td>15-45</td>
<td>32.1 ± 11.6</td>
<td>36.2 ± 7.4</td>
<td>0.050</td>
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<tr>
<td>RV-EF (%)</td>
<td>47-74</td>
<td>58.1 ± 7.0</td>
<td>54.6 ± 5.2</td>
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<tr>
<td>RVOT-EDV (ml)</td>
<td>NA</td>
<td>10.3 ± 4.8</td>
<td>11.3 ± 3.7</td>
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<td>RVOT-EDVi (ml/m²)</td>
<td>NA</td>
<td>5.0 ± 2.5</td>
<td>5.8 ± 1.6</td>
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<td>RVOT as proportion of RV-EDV (%)</td>
<td>NA</td>
<td>6.8 ± 2.1</td>
<td>7.4 ± 1.8</td>
<td>0.214</td>
</tr>
</tbody>
</table>

Mean ± SD are reported.

End diastolic volume, EDV; end diastolic volume indexed to body surface area, EDVi; ejection fraction, EF; end systolic volume, ESV; end systolic volume indexed to body surface area, ESVi; left ventricle, LV; right ventricle, RV; right ventricular outflow tract, RVOT
<table>
<thead>
<tr>
<th>Patient Code</th>
<th>Structural Abnormality</th>
<th>Age at follow-up Scan (Years)</th>
<th>Time Between Scans (Years)</th>
<th>Ethnicity</th>
<th>Shanghai Score</th>
<th>BrS ECG</th>
<th>FHx of BrS</th>
<th>Genetic testing</th>
<th>SCN5A Status</th>
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<tr>
<td>BPU1</td>
<td>LGE</td>
<td>50.5</td>
<td>4.6</td>
<td>Southern and Central Asian</td>
<td>6.5</td>
<td>Spontaneous</td>
<td>Yes</td>
<td>Genome</td>
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<tr>
<td>BPS1</td>
<td>LGE</td>
<td>46.6</td>
<td>5.4</td>
<td>North African and Middle Eastern</td>
<td>3.5</td>
<td>Spontaneous</td>
<td>Yes</td>
<td>Exome</td>
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<td>ATT1</td>
<td>LGE</td>
<td>41.4</td>
<td>8.0</td>
<td>North-West European</td>
<td>3.5</td>
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<td>No</td>
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<td>BX11</td>
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<td>48.4</td>
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<td>North-West European</td>
<td>3</td>
<td>Fever Induced</td>
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<td>BTR1</td>
<td>RV-EF reduction of 12%</td>
<td>52.2</td>
<td>3.9</td>
<td>South-East Asian</td>
<td>2</td>
<td>Drug Induced</td>
<td>No</td>
<td>100 gene pan-cardiac panel</td>
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<td>TD3</td>
<td>RV-EF reduction of 13%</td>
<td>40.8</td>
<td>4.5</td>
<td>North-West European</td>
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<td>Drug Induced</td>
<td>No</td>
<td>Genome</td>
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<td>CBX1</td>
<td>RV-EF reduction of 14%</td>
<td>57.9</td>
<td>4.4</td>
<td>North-West European</td>
<td>3.5</td>
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<td>CGL1</td>
<td>RV-EF reduction of 17%</td>
<td>27.0</td>
<td>4.3</td>
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<td>2</td>
<td>Drug Induced</td>
<td>No</td>
<td>100 gene pan-cardiac panel</td>
<td>Negative</td>
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</table>

Family history, FHx; late gadolinium enhancement, LGE; right ventricular ejection fraction, RV-EF.
FIGURE LEGEND

**Figure 1:** Volumetric changes in BrS on longitudinal assessment

Panel A shows increased RV-ESVi over the follow up period. Panel B shows a trend towards reduction in RV-EF on serial CMR.

**Figure 2:** Late gadolinium enhancement on CMR during follow-up in BrS

Four patients developed LGE during the follow up period as demonstrated in these representative images (top row from baseline and bottom row from follow-up CMR). The most extensive LGE was seen in patient ATT1 with mid-wall enhancement in the septum. Patients BSP1, BPU1 and BXI1 developed LGE in similar distributions – on the RV side of the basal septum.
<table>
<thead>
<tr>
<th></th>
<th>Patient ATT1</th>
<th>Patient BPS1</th>
<th>Patient BPU1</th>
<th>Patient BXI1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td><img src="image1" alt="Image" /></td>
<td><img src="image2" alt="Image" /></td>
<td><img src="image3" alt="Image" /></td>
<td><img src="image4" alt="Image" /></td>
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<tr>
<td><strong>Follow-up</strong></td>
<td><img src="image5" alt="Image" /></td>
<td><img src="image6" alt="Image" /></td>
<td><img src="image7" alt="Image" /></td>
<td><img src="image8" alt="Image" /></td>
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</tbody>
</table>
KEY FINDINGS:

- Focal fibrosis evidenced by LGE on CMR and subtle increase in right ventricular volumes can develop during follow-up in BrS.
- Findings suggest a progressive myocardial pathology in some patients with BrS.
- Current parametric mapping techniques do not appear to detect diffuse fibrosis in patients with BrS.