Spontaneous type 1 electrocardiographic pattern is associated with cardiovascular magnetic resonance imaging changes in Brugada syndrome

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BACKGROUND Patients with Brugada syndrome (BrS) and a spontaneous type 1 ECG are considered to be at greater increased risk for sudden cardiac death than are patients with an abnormal ECG only after administration of sodium channel blockers and therefore represent a more severe phenotype. Thus, it can be hypothesized that in the presence of a more severe electrical phenotype, structural and functional changes are more likely expected because electrical changes can play a causal role in producing structural changes.

OBJECTIVE The purpose of this study was to investigate whether the different ECG manifestations in patients with BrS are associated with structural changes detected by cardiovascular magnetic resonance imaging.

METHODS Cardiovascular magnetic resonance imaging was performed on 69 consecutive patients with proven BrS and 30 healthy controls. Twenty-six patients had a spontaneous diagnostic type 1 BrS ECG; the remainder had a type 1 response to ajmaline provocation. Left and right ventricular volumes and dimensions were assessed and compared with respect to ECG pattern.

RESULTS The right ventricular outflow tract area was significantly enlarged in patients with a spontaneous type 1 ECG compared to patients with a nondiagnostic resting ECG or controls (11 cm^2, 9 cm^2, and 9 cm^2, respectively, $P < .05$). Patients with a spontaneous type 1 BrS ECG revealed significantly lower left ventricular ejection fraction than did patients with a nondiagnostic resting ECG and controls (56 $\pm$ 5 vs 59 $\pm$ 5 vs 60 $\pm$ 4, respectively, $P < .05$) and significantly lower right ventricular ejection fraction (54 $\pm$ 5 vs 59 $\pm$ 5, $P = .001$) as well as end-systolic volumes compared to controls (34 $\pm$ 9 mL/m^2 vs 28 $\pm$ 79 mL/m^2, $P = .02$).

CONCLUSION Patients with a spontaneous type 1 BrS ECG reveal significantly functional and morphological alterations in both the left and right ventricles compared to patients with basal nondiagnostic ECG or controls.

KEYWORDS Brugada syndrome; Cardiovascular magnetic resonance imaging; Spontaneous type 1 electrocardiogram

ABBREVIATIONS **ARVC** = arrhythmogenic right ventricular cardiomyopathy; **BrS** = Brugada syndrome; **CMR** = cardiovascular magnetic resonance imaging; **ECG** = electrocardiogram; **FISP** = fast imaging with steady-state precession; **LV** = left ventricular; **RV** = right ventricular; **RVOT** = right ventricular outflow tract

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Introduction

Brugada syndrome (BrS) is characterized by coved-type ST-segment elevations in the right precordial leads (V_1–V_3) complicated by ventricular tachycardia/ventricular fibrillation, sudden cardiac death, or syncope.[1–4] The syndrome has been found to occur in patients without apparent structural abnormalities.[1] To date it has been linked to mutations leading to a loss of function in the sodium channel, either through the SCN5A[1,5] or GPD-1L gene.[6] Furthermore, loss-of-function mutations in genes encoding the cardiac L-type calcium channel (CACNA1c and its β-subunit CACNB2b) also can be responsible for an overlap syndrome with both a short QT interval and a BrS syndrome ECG.[7]

Currently, risk stratification is based on the basal ECG, history of syncope or sudden cardiac death, gender, and inducibility of ventricular tachyarrhythmias during programmed ventricular stimulation. The presence of a spontaneous type 1 ECG (i.e., coved-type ECG pattern with an ST-segment elevation >0.2 mV in at least two right precordial leads) has been described as strong predictor for the occurrence of spontaneous ventricular tachyarrhythmias.[2,4] A nondiagnostic baseline

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ECG seems to be associated with a lower risk of ventricular tachyarrhythmias during follow-up.[2,4,8]

Cardiovascular magnetic resonance imaging (CMR) has been shown to be an accurate and reproducible tool for estimation of both left ventricular (LV) and right ventricular (RV) volumes and mass and is now considered the gold standard for such measurements.[9,10] In addition, it is useful for imaging the RV, and particularly the right ventricular outflow tract (RVOT), which has been identified as a potential source of ECG abnormalities and site of origin of ventricular tachyarrhythmias in patients with BrS.[11] The RVOT usually is more difficult to image using echocardiography, radionuclide ventriculography, or cine angiography.[12]

Patients with a spontaneous diagnostic BrS type 1 ECG are considered to be at higher risk for sudden cardiac death than are patients with an abnormal ECG after administration of a sodium channel blocker and therefore represent a more severe electrical phenotype. Thus, it can be hypothesized that in presence of a more severe electrical phenotype, structural and functional changes are more likely expected because electrical changes may result in structural changes of the myocardium. The aim of the present study was to investigate whether the different ECG manifestations in patients with BrS are associated with structural changes assessed with CMR. For this purpose, we prospectively evaluated CMR findings in 69 consecutive patients with BrS and compared them to matched healthy controls.

Methods

Study population

Sixty-nine consecutive patients (47 males and 22 females; mean age 44 ± 12 years) with proven BrS were selected between March 2002 and November 2009. The population included 20 patients from a previous report.[13] Diagnosis of BrS was based on the criteria of the BrS consensus report.[14] Diagnostic workup included baseline ECG (n = 69), echocardiography (n = 69), coronary angiography, left and right ventriculography, programmed electrical stimulation (n = 69), and CMR (n = 69). Genetic screening for SCN5A and CACNB2b mutation was completed in 57 patients, is still ongoing in 5 patients, and was not performed in the remaining 7 patients. Arrhythmogenic right ventricular cardiomyopathy (ARVC) was carefully excluded in accordance with the task force criteria for the diagnosis of ARVC in all patients.[15]

CMR images were analyzed both qualitatively and quantitatively, and the results were compared to results from a control population. The control population was sex and age matched to the whole collective as well as to two smaller Brugada subgroups. After institutional review board approval was obtained, 30 healthy volunteers (20 men and 10 women; mean age 47 ± 7 years) were recruited from our hospital stuff. All volunteers showed no contraindications for magnetic resonance imaging and satisfied the following criteria: normal physical examination, normal blood pressure (<120 mm Hg and <80 mm Hg), normal ECG findings, no history of chest pain or dyspnea, no diabetes, and normal two-dimensional echocardiography. None of the subjects was taking any medication. Exclusion criteria were the presence of signs or symptoms of cardiac diseases, hypertension, diabetes, smoking, or participation in competitive sports. All control subjects underwent CMR examination using the same protocol. Informed consent for the CMR protocol was obtained from all subjects.

Image acquisition

All studies were performed using a 1.5-T whole-body imaging system (Magnetom Sonata, Siemens Medical Systems, Erlangen, Germany). A dedicated four-element, phased-array cardiac coil was used. Images were acquired during repeated end-expiratory breath-holds. Scout images (coronal, sagittal, and axial planes) were obtained for planning of the final double-oblique long-axis and short-axis views. To evaluate functional parameters, ECG-gated cine images were acquired using a segmented steady-state free precession sequence [(TrueFISP); TE/TR 1.2/3.2 ms, temporal resolution 35 ms, in-plane spatial resolution 1.4 × 1.8 mm^2, slice thickness 5 mm, interslice gap 5 mm]. From 7 to 12 short-axis views covering the whole LV and RV were obtained.

For evaluation of RV anatomy and morphology, a dark blood prepared T1-weighted multislice turbo spin-echo pulse sequence was used to obtain axial images from the diaphragm to the level of the right coronary artery (i.e., to include the pulmonary outflow tract). Imaging parameters were as follows: TR 800 ms, TE 24 ms, slice thickness 4 mm, interslice gap 2 mm, field of view 24 to 28 cm.

Image analysis and determination of ventricular parameters

All image analyses were performed by experienced observers (TP, TG) blinded to all clinical patient details. Each study was examined for abnormalities in RV and LV morphology using the spin-echo images. Global and regional function was assessed on the cine images.

Ventricular function, end-diastolic volumes, end-systolic volumes, and myocardial mass were assessed offline from the serial short-axis true FISP cine loops using dedicated software (ARGUS, Siemens). In addition to volumetric measurements, one-dimensional measurements of LV end-diastolic diameter, posterior wall thickness, and anterior interventricular septum thickness were measured from an end-diastolic short-axis slice immediately basal to the tips of the papillary muscles. Chamber size dimensions of the RV included RV end-diastolic diameter, RV end-systolic diameter, and right atrial diameter. RV systolic and diastolic diameters were measured on four-chamber cine images by a line drawn from the interventricular septum to the RV free wall 1 cm below and parallel to the tricuspid valve. Right atrial diameter was measured on end-systolic four-chamber cine images by a line drawn from the interatrial septum to the right atrial wall in the mid-right atrium parallel to the tricuspid valve. RVOT area was measured by tracing the circumference of the outflow tract at the level of the aortic

valve on the axial dark blood spin-echo images. RVOT diameter was measured on an additional short-axis cine image, about 1 cm below the AV valvular plane. The largest anteroposterior diameter was acquired perpendicular to the long axis of the RVOT during end-diastole.

ECG analysis

All patients included in the study had a type 1 coved-type ECG diagnostic of BrS according to the criteria of the BrS consensus conference 2002 and 2005.[14,16] A coved-type ECG pattern (type 1) with ≥ 2 mm ST-segment elevation in at least two right precordial leads was defined as diagnostic for BrS. Patients with type II or III or with unspecified changes were excluded from the study. A median of eight ECGs was recorded per patient. There were no significant differences in the number of ECGs recorded between patients with and those without a spontaneous type 1 ECG pattern.

Programmed ventricular stimulation

Programmed ventricular stimulation was performed applying a maximum of three basic cycle lengths (500, 430, and 370 ms) with up to three extrastimuli until refractoriness at two RV sites (RV apex and RVOT).

Statistical analysis

All data are presented as mean ± SD. Continuous variables between two groups were analyzed using the unpaired, two-tailed Student's t-test. The Chi-square test was used for categorical variables. To assess interobserver reproducibility of RVOT diameter and area measurements, a second independent and blinded observer (CD) repeated measurements on 15 randomly selected subjects with BrS using the same conventions (5 patients with spontaneous diagnostic type 1 BrS ECG and 10 patients with type 1 response to ajmaline provocation). The observer was blinded to patient details and to the findings of the first observer. Interobserver agreement was assessed using correlation coefficient and Bland-Altmann analysis. The SPSS 10.0 software package (SPSS, Inc., Chicago, IL, USA) was used for analysis. $P < .05$ was considered significant.

Results

The clinical, electrophysiologic, and genetic characteristics of the BrS study subjects are listed in Table 1. Sixty-nine patients with BrS were studied. Twenty-six patients had a spontaneous resting type 1 BrS ECG; the remainder had a type 1 response to ajmaline provocation. There were significantly more men in the group of patients with a spontaneous type 1 BrS ECG than in those without. In addition, patients with a spontaneous type 1 BrS ECG revealed a significantly higher inducibility of ventricular arrhythmias compared to patients with a type 1 response to ajmaline provocation.

Table 2 lists the values for LV parameters measured by CMR for patients with a spontaneous type 1 BrS ECG (group A), patients with a type 1 BrS ECG during ajmaline challenge (group B), and controls. Table 2 also lists values for LV end-diastolic volume, LV end-systolic volume, and cardiac output as well as LV mass normalized to body surface area. Patients with a spontaneous type 1 BrS ECG revealed a significantly lower LV ejection fraction (56 ± 5 vs 59 ± 5, $P = .02$), thicker posterior wall thickness (9 ± 2 mm vs 8 ± 2 mm, $P = .005$), and larger LV mass (132 ± 23 g vs 113 ± 33 g, $P = .02$) than did patients with a nondiagnostic baseline ECG.

Table 1 Clinical characteristics of patients with Brugada syndrome

	Patients with spontaneous type 1 Brugada syndrome ECG	Patients with type 1 response to ajmaline provocation	*P* value
Total	26	43	
Age (years)	45 ± 14	41 ± 12	.14
Male gender	22	25	.03
Syncope	5	18	.07
Presyncope	0	1	.43
SCA	1	2	1
Family history of sudden cardiac death	1	5	.4
Inducibility of ventricular tachycardia/ventricular fibrillation	19	19	.03
Palpitations	1	3	.59
Supraventricular tachycardia	2	2	.6
Paroxysmal atrial fibrillation	1	1	.71
AV nodal reentrant tachycardia	1	1	.71
SCN5A positive	4/18	4/39	.25

SCA=Sudden cardiac arrest.

CMR results for RV parameters for patients with a spontaneous type 1 BrS ECG (group A), patients with a type 1 BrS ECG during ajmaline challenge (group B), and controls are listed in Table 3. Table 3 also lists values for RV end-diastolic volume, RV end-systolic volume, and cardiac output as well as RVOT area normalized to body surface area. RVOT area was significantly wider in patients with a spontaneous type 1 BrS ECG (group A) compared to patients without (group B) and controls (11 vs 9 cm^2, $P = .006$ and $P = .001$, respectively; Figures 1 and 2)). The difference between RVOT measurements remained significant after indexation to body surface area ($P = .001$ and $P = .005$ respectively). RVOT diameter was also significantly increased in patients with a spontaneous type 1 BrS ECG (group A) compared to patients without (group B) and controls (28 ± 4 mm vs 23 ± 3 mm vs 24 ± 3 mm, $P = .01$ and $P = .03$, respectively). Patients with a spontaneous diagnostic BrS ECG revealed a significantly lower RV ejection fraction than did controls (54 ± 5 vs 59 ± 5, $P = .001$). End-systolic volume (68 ± 20 mL/m^2 vs 54 ± 16 mL/m^2, $P = .01$) and end-systolic volume/body surface area (34 ± 9 mL/m^2 vs 28 ± 7 mL/m^2, $P = .02$) were also significantly larger in patients with a spontaneous diagnostic BrS ECG than in controls. Also, patients without a spontaneous diagnostic type 1 ECG (group B) revealed a significantly lower RV ejection fraction than did controls (55 ± 6 vs 59 ± 5, $P = .03$.

There was excellent correlation between observers in reporting the measurements of RVOT area and diameters, as

Table 2 Left ventricular parameters of patients with Brugada syndrome and spontaneous type 1 ECG (group A) or type 1 response to ajmaline provocation (group B) and controls determined by cardiovascular magnetic resonance imaging

	Patients with Brugada syndrome			*P* value		
	Group A (n = 26)	Group B (n = 43)	Controls (n = 30)	Group A vs group B	Group A vs controls	Group B vs controls
LVEDD (mm)	53 ± 7	50 ± 8	51 ± 4	NS	NS	NS
SWT (mm)	10 ± 2	10 ± 6	10 ± 2	NS	NS	NS
PWT (mm)	9 ± 2	8 ± 2	8 ± 2	.005	.03	NS
LV mass (g)	132 ± 23	113 ± 33	125 ± 37	.02	NS	NS
LV mass/BSA (g)	69 ± 10	61 ± 16	64 ± 15	.07	NS	NS
EF (%)	56 ± 5	59 ± 5	60 ± 4	.02	.009	NS
EDV (mL)	148 ± 29	139 ± 31	145 ± 36	NS	NS	NS
EDV/BSA (mL/m^2)	75 ± 16	74 ± 14	74 ± 11	NS	NS	NS
ESV (mL)	65 ± 16	57 ± 16	60 ± 15	NS	NS	NS
ESV/BSA (mL/m^2)	33 ± 9	31 ± 8	31 ± 6	NS	NS	NS
CO (L/min)	5 ± 1	6 ± 1	6 ± 1	NS	NS	NS
CO/BSA [(L/min)/m^2]	3 ± 0	3 ± 1	3 ± 1	NS	NS	NS

Data are presented as mean ± SD.

BSA = body surface area; CO = cardiac output; EDV = end-diastolic volume; ESV = end-systolic volume; EF = ejection fraction; LV = left ventricular; LVEDD = left ventricular end-diastolic diameter; PWT = posterior wall thickness; SWT = septal wall thickness.

reflected by correlation coefficients of 0.91 and 0.98 for RVOT area and RVOT diameter, respectively ($P < .001$ for all). In addition, Bland-Altmann analysis showed excellent agreement between the two observers for RVOT area and RVOT diameter, with a bias (mean difference ± SD) of 0.08 ± 0.45 cm^2 and 0.40 ± 0.20 mm, respectively.

Discussion

The main findings of the present study are as follows. (1) Patients with BrS and spontaneous diagnostic type 1 ECG show significant dilation of the RVOT as seen using state-of-the-art CMR compared to patients with a nondiagnostic ECG at rest and controls. (2) Patients with BrS, irrespective of the ECG, showed lower RV ejection fraction compared to controls. (3) Patients with a spontaneous diagnostic ECG displayed a lower LV ejection fraction and thicker posterior wall thickness compared to patients without and controls. (4) Besides a lower RV ejection fraction, there were no significant differences in CMR measurements between patients with BrS and a nondiagnostic ECG at rest and controls.

BrS is defined as a primary electrical cardiac disease.[1] Although cardiac function may appear normal on echocardiography, more sophisticated tools, such as CMR, positron emission tomography, and pathologic evaluation of biopsies, have identified anatomic abnormalities in patients diagnosed with BrS. RV interstitial derangements (myocarditis, cardiomyocyte vacuolization, fibrofatty infiltration) have been found in endomyocardial biopsies of BrS patients.[17] Accordingly, Coronel at al[18] found RV fibrosis, fatty infiltration, conduction slowing, and reentrant arrhythmias in the explanted heart of a BrS patient carrying an SCN5a mutation. In contrast, Remme et al[19] found no evidence of structural disease in the vast majority of a large

Table 3 Right ventricular parameters of patients with Brugada syndrome and spontaneous type 1 ECG (group A) or type 1 response to ajmaline provocation (group B) and controls determined by cardiovascular magnetic resonance imaging

	Patients with Brugada syndrome			*P* value		
	Group A (n = 26)	Group B (n = 43)	Controls (n = 30)	Group A vs group B	Group A vs controls	Group B vs controls
RVEDD (mm)	43 ± 5	42 ± 7	42 ± 5	NS	NS	NS
RVESD (mm)	32 ± 5	30 ± 5	31 ± 5	NS	NS	NS
RAD (mm)	46 ± 7	44 ± 6	44 ± 5	NS	NS	NS
RVOT (cm^2)	11 ± 2	9 ± 1	9 ± 2	.004	.001	NS
RVOT/BSA (cm^2/m^2)	6 ± 1	5 ± 1	5 ± 1	.01	.001	NS
RVOT diameter (mm)	28 ± 4	23 ± 3	24 ± 3	.01	.03	NS
EF (%)	54 ± 5	55 ± 6	59 ± 5	NS	.001	.03
EDV (mL)	147 ± 34	134 ± 33	137 ± 33	NS	NS	NS
EDV/BSA (mL/m^2)	74 ± 14	71 ± 14	68 ± 13	NS	NS	NS
ESV (mL)	68 ± 20	59 ± 19	54 ± 16	NS	.01	NS
ESV/BSA (mL/m^2)	34 ± 9	32 ± 9	28 ± 7	NS	.02	NS
CO (L/min)	5 ± 1	5 ± 1	6 ± 3	NS	NS	NS
CO/BSA [(L/min)/m^2]	3 ± 0.5	3 ± 0.5	4 ± 3	NS	NS	NS

Data are presented as mean ± SD.

BSA = body surface area; CO =cardiac output; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; RAD = right atrial diameter; RVEDD = right ventricular end-diastolic diameter; RVESD = right ventricular end-systolic diameter; RVOT = right ventricular outflow tract.

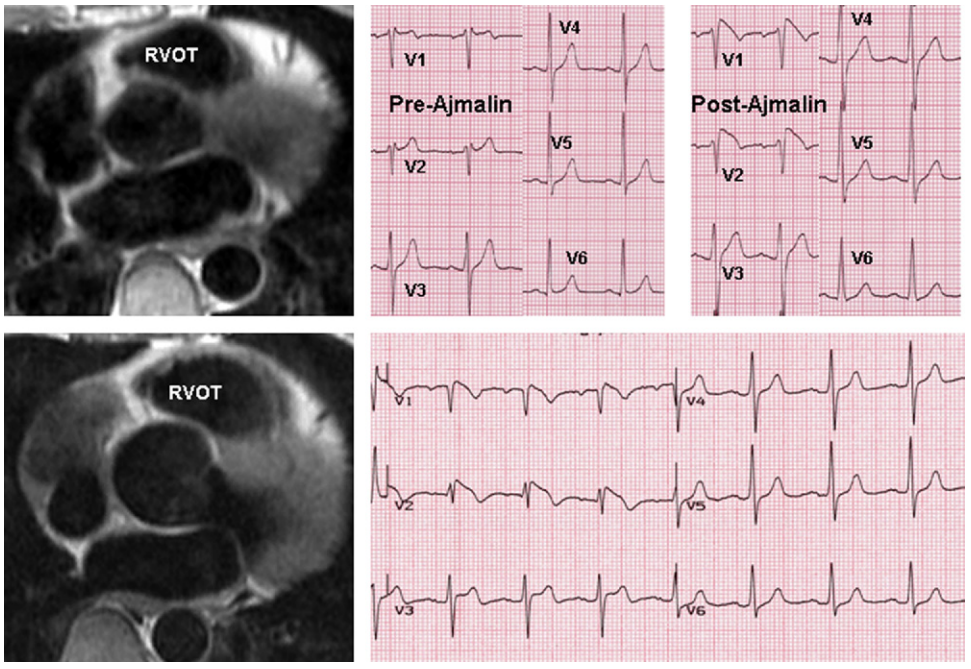

Figure 1 Axial T1-weighted black blood spin-echo images showing a normal right ventricular outflow tract (RVOT) in a patient with type 1 ECG after intravenous ajmaline challenge **(A)** and enlargement of the RVOT in a patient with Brugada syndrome and a spontaneous diagnostic type 1 ECG **(B)**.

group of Brugada patients using echocardiography, cine angiography, radionuclide ventriculography, and endomyocardial biopsies. Subsequent follow-up revealed ARVC in two patients.[20] Using electron beam computed tomography, Takagi et al[21] demonstrated wall-motion abnormalities in the RVOT (n = 17) and the inferior wall of the RV (n = 4) in 21 of 26 Brugada patients. Similar to the study by Takagi et al,[21] Catalano et al[22] reported data suggesting the presence of RV contractility abnormalities in a clinically relevant percentage (50%) of 30 consecutive patients with BrS. Although such contractile abnormalities are commonly considered indicative of structural problems, some studies[23,24] suggest that contractile dysfunction can result from loss of the action potential dome in regions of the RV epicardium and, thus, does not necessarily indicate diseased myocardium.[25] Loss of the action potential dome leads to contractile dysfunction because calcium entry into the cells is greatly diminished and sarcoplasmic reticulum calcium stores are depleted.

Meanwhile, the RVOT has been identified as the source of ECG abnormalities and the site of origin of ventricular tachyarrhythmias in patients with BrS.[11] These manifestations have been attributed to the greater I_{to}-mediated phase 1 and epicardial action potential notch.[26] In this context, a previous study by our group using CMR found that patients

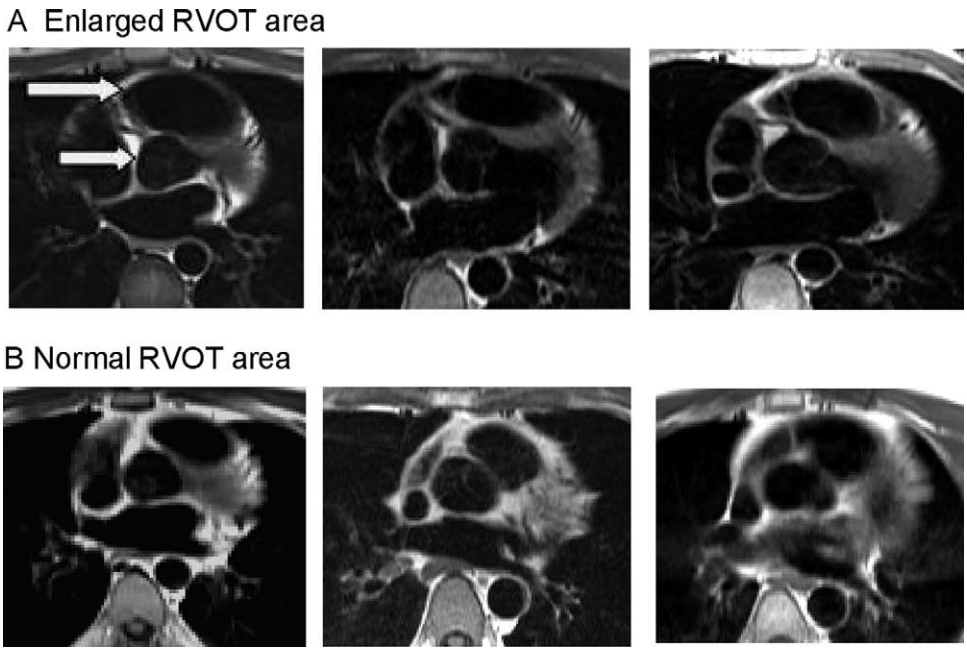

Figure 2 **A:** Axial T1-weighted black blood spin-echo images from patients with Brugada syndrome and a spontaneous type 1 ECG showing enlargement of the RVOT (*large arrow*). Note diameter of RVOT is greater than that of the adjacent aorta (*small arrow*). **B:** Axial T1-weighted black blood spin-echo images from healthy controls showing normal RVOTs, which are comparable to the size of the aorta. RVOT = right ventricular outflow tract.

with BrS revealed significant dilation of the RVOT area compared to healthy controls, reflecting the presence of an electrophysiologic abnormality in this area.[13]

The present study shows, for the first time, significant differences in static and functional measurements of the RV and LV cavities between patients with BrS and a spontaneous diagnostic type 1 ECG compared to patients without and controls as obtained by CMR. Patients with a spontaneous diagnostic type 1 ECG showed significant enlargement of the RVOT, lower LV ejection fraction, and thicker posterior wall thickness compared to patients with a nondiagnostic ECG at rest and controls. In addition, patients with BrS, irrespective of the ECG, showed lower RV ejection fraction compared to controls. However, we would like to emphasize that, although significantly different between patients and controls, the majority of these differences (LV ejection fraction, RV ejection fraction and posterior wall thickness) still were within normal limits. In contrast, the RVOT values of the Brugada patients with a spontaneous diagnostic type 1 ECG were comparable to those assessed by CMR in patients with arrhythmogenic RV dysplasia in previous studies.[27] In the present study, fat could be visualized in 15% of patients. However, in previous studies, subjective assessment of fatty infiltration of the myocardium by CMR proved problematic.[28,29] In addition, significant fatty involvement without concomitant fibrosis of the RV is commonplace in normal hearts.[30] Thus, to date, the identification of fat within the myocardium is of limited value.[31]

Catalano et al[22] performed quantification of several CMR parameters in a cohort of 30 consecutive patients with BrS and 30 normal volunteers. They found comparable RVOT dimensions, RV end-diastolic volume, LV parameters, and atrial areas compared to normal subjects. However, in that study, pooled data of all BrS patients (i.e., patients with and without a spontaneous type 1 ECG) were analyzed. Different from that study, in our series of BrS patients, we performed an analysis of the ECG pattern from 69 consecutive BrS patients. Of interest, in the present study when patients with and without a spontaneous type 1 ECG were pooled together, their mean RVOT diameter was almost identical to the value reported in the study by Catalano et al[22] (25.5 ± 4 mm in our patients vs 25 ± 4 mm in the study by Catalano et al). However, analysis of our patients with respect to the ECG pattern clearly demonstrated that patients with a spontaneous type 1 ECG have significantly larger RVOT diameters compared to patients without a spontaneous Brugada pattern and controls. Regarding the LV parameters, although indexed LV mass was not significantly different between BrS patients and controls, there was an obvious trend toward a higher LV mass in BrS patients in both studies. In addition, Catalano et al found slight but significant interventricular septum thickening in BrS patients (9.5 ± 1.1 vs 9.0 ± 1.1, $P = .030$).

Although the baseline ECG correlates with the CMR results, the clinical parameters, except for inducibility of ventricular tachycardia/ventricular fibrillation, are not significantly different between both groups. Whether significant differences become potentially visible by increasing the size of the study population is not known.

Patients with a spontaneous diagnostic type 1 ECG are generally considered to be at higher risk for sudden cardiac death and therefore represent a more severe clinical phenotype of BrS.[2,4] The current findings show a close correlation of the presence of a spontaneous diagnostic ECG and structural changes as detected by CMR. Thus, in the presence of a more severe clinical phenotype, structural and functional changes are more likely expected because electrical changes can play a causal role in producing structural changes. Whether the alterations in RV measurements are caused by fibrosis or structural remodeling of the ventricular tissue or represent just functional alteration caused by a loss of calcium influx mediated by a loss of function in sodium currents remains to be determined.

Clinical implications

The current findings show a close correlation of spontaneous diagnostic type 1 ECG and structural changes as detected by CMR. However, the incidence of fluctuation between spontaneous diagnostic and nondiagnostic ECGs of patients with BrS is high. Possible fluctuations between diagnostic and nondiagnostic ECGs have major implications for correct phenotyping and for risk stratification of patients diagnosed with BrS. Thus, in case of nondiagnostic index ECGs and coexisting CMR findings, multiple ECG recordings should be performed due to potential considerable changes of risk stratification of the individual patient.

Study limitations

Late enhancement on CMR could show fibrotic replacement of the LV and/or RV myocardium.[32] However, characterizing the RV myocardium may be difficult because of the very thin RV wall and possible confusion with fat.[32] In the present study, we did not perform late gadolinium imaging due to difficult and often misleading interpretation of RV late enhancement. Thus, we focused on functional criteria to exclude ARVC by CMR as proposed by the task force committee for diagnosis of ARVC.[15]

BrS affects predominantly men. In accordance with results reported by Benito et al,[33] our population also consists of 68% men and 32% women. The study by Benito et al also showed that men have higher rates of spontaneous type 1 ECG than women, which is also reflected in our population (group A with spontaneous type 1 ECG consists of 80% men). Thus, between the smaller Brugada subgroups there is a significant difference in gender, which we cannot actually influence due to the nature of the disease. These gender differences might account for small differences in CMR measurements. However, according to previously published data, factors related to LV function are independent of gender, whereas parameters concerning cardiac masses and the RV are gender dependent.[34–36] Between the two Brugada groups, there were significant differences in measurements of LV ejection fraction (%), absolute LV mass, and posterior wall thickness. The indexed LV mass, which is the

most accurate value, was not significantly different. Except for the measurements of RVOT area, there were no significant differences in RV measurements. In order to clarify the impact of gender on our findings, we randomly matched both subgroups with regard to gender, but this did not change the results.

Regarding the statistical analysis, we did not implement an alpha-error adjustment, as only three group-wise comparisons were performed using a two-sample t-test, and the resulting *P* values were considered rather exploratory. Using a family-wise error correction such as Bonferroni would have yielded higher stringency on the individual test level at 0.016 (= 5% ÷ 3). Such an adjustment seems recommendable each and every time when multiple significance outcomes are collapsed into one single content-wise global conclusion. If results can be interpreted separately, adjustment procedures might be omitted. We preferred to use the 5% threshold; otherwise, significance results would not have adequately reflected the clinical patterns as shown in the descriptive statistics. However, the reader might feel free to use the stricter perception. Notwithstanding, this does not profoundly change the main findings from a qualitative viewpoint.

Conclusion

Patients with BrS who exhibit spontaneous electrical abnormalities on the surface ECG in the form of coved-type ST-segment elevation reveal significant functional and morphologic alterations in both LV and RV compared to patients with basal nondiagnostic ECG or controls. These findings support the notion that BrS may represent a cardiomyopathy with RV and LV abnormalities.

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