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Altered two-dimensional strain measures of the right ventricle in patients with Brugada syndrome and arrhythmogenic right ventricular dysplasia/cardiomyopathy

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Aims Brugada syndrome (BrS) is an inherited channelopathy that can be characterized by mild right ventricular (RV) abnormalities that are not detectable with conventional echocardiography. The aim of this study was to evaluate the presence of RV abnormalities in BrS patients when compared with controls and a group of patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) using two-dimensional (2D) strain analysis.

Methods and results We enrolled 25 BrS, 15 ARVD/C patients, and 25 controls. Right and left ventricular dimension and systo-diastolic function were evaluated by conventional echocardiography. Longitudinal systolic strain (sS) peak, systolic and early diastolic strain rate of lateral RV segments were evaluated by 2D speckle tracking analysis. Left ventricle global and segmental strain measures were also evaluated. A reduced basal or mid-RV lateral sS were the parameters mostly associated with both BrS and ARVD/C. In BrS patients the minimum sS observed in these segments was significantly lower than that of controls ($-28.9 \pm 3.2\%$ vs. $-32.3 \pm 3.2\%$, P: 0.002) but significantly greater than that evaluated in ARVD/C patients ($-24.6 \pm 6.7\%$, $P < 0.001$ both vs. BrS and controls). No differences were found between the BrS and the control group when left ventricular strain measures were analysed.

Conclusion By 2D strain technique it is possible to observe mild abnormalities in RV systolic and diastolic function of BrS patients that are less pronounced than those observed in ARVD/C patients. These results help to better define the phenotypic characteristics of BrS patients and represent the basis for future studies aimed at testing their clinical usefulness in BrS patients.

Keywords Echocardiography • Two-dimensional speckle tracking • Right ventricule • Brugada syndrome • Arrhythmogenic right ventricular dysplasia/cardiomyiopathy

Introduction

Brugada syndrome (BrS) is an inherited channellopathy that is characterized by typical spontaneous or drug induced electrocardiogram (ECG) findings (i.e. right bundle branch block, ST-segment elevation, and inverted T-wave in the right precordial leads) and by an increased risk of sudden death.[1–3]

Even if BrS is not associated with right and left ventricular structural abnormalities, cardiac computed tomography, magnetic resonance, and endomyocardial biopsies[4–7] have found/identified mild right ventricular (RV) abnormalities.

Abnormalities in conventional echocardiographic parameters used to explore RV function have not been reported but, to the best of our knowledge, there are no data available on the

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characteristics of BrS heart function evaluated by new echocardiographic techniques based on the analysis of myocardial deformation.[8] The information obtained by these techniques has already demonstrated their potential clinical usefulness in patients affected by arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C).[9,10] In these patients, strain measures were characterized by a greater association with the disease when compared with most of the conventional echocardiographic and Doppler parameters.

The aim of this study was to better characterize the phenotypic expression of BrS patients by comparing two-dimensional (2D) RV strain measures obtained in these patients with those of ARVD/C patients and controls.

Methods

A group of patients with BrS or ARVD/C who had been referred to our Unit for Cardiomyopathies and a group of controls, free from cardiovascular and systemic disease, were enrolled in the study. According to the criteria of the Heart Rhythm Society and the European Heart Rhythm Society, BrS[11,12] was defined as the presence of a spontaneous or drug induced Type 1 Brugada pattern at ECG associated to one of the following conditions: documented ventricular fibrillation or polymorphic tachycardia, family history of sudden cardiac death, a type 1 ECG in family members, inducibility of ventricular tachycardia, syncope, nocturnal agonal respiration. In all BrS patients structural disease was excluded by cardiac magnetic resonance.

ARVD/C was diagnosed on the basis of the Task Force criteria of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology.[13] The control group consisted in subjects with a normal ECG (sinus rhythm and no apparent conduction abnormalities), no history of heart disease and no family history of sudden cardiac death.

All patients gave their informed consent. The study protocol was conformed with the Declaration of Helsinki and was approved by the local ethics committee.

Electrocardiogram analysis

The 12-lead ECGs were acquired by a flat scanner (HP 3970, Hewlett-Packard Company, Palo Alto, CA, USA), with a resolution of 600 dots per inch (equivalent to <1 ms per dot), and then displayed on a monitor. The QRS duration, QT interval, and the preceding RR interval were measured using specific software written in Visual Basic 6.0 language for PC-compatible computers that works with all Windows operating systems[14] and provided the use of semiautomatic calculation. Despite the difficulty in obtaining an accurate estimate in precordial leads of BrS patients, QRS duration was calculated in standard leads from the start to the end of the QRS complex and the longest QRS was considered.[15] The QT interval corrected for heart rate (QTc, Bazett's formula) was calculated in V_1 V_2 and V_5 V_6.[16]

Echocardiographic examination

In all subjects, standard parasternal long- and short-axis and apical four-chamber, two-chamber, and long-axis views were acquired (frame rate 50–70/s) by Vivid 7 (GE Vingmed Ultrasound, General Electric, Milwaukee, WI, USA). A right ventricle focused apical four-chamber view was also acquired in order to analyse RV strain (*Figure 1*).[17] At least three consecutive sinus rhythm cycles were recorded for each view at end expiration and then digitally stored. The interventricular septum (IVS) was evaluated in the long-axis view. Left ventricular (LV) volumes and systolic function were

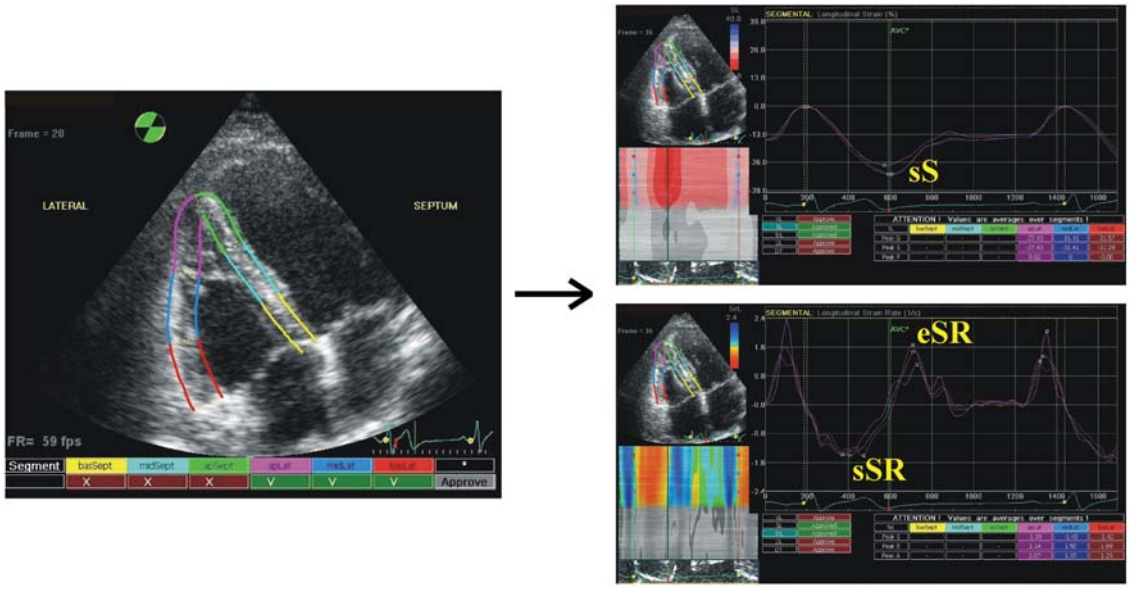

Figure 1 A right ventricular focused four-chamber view of a Brugada syndrome patient. Two-dimensional speckle tracking analysis was performed in order to obtain strain measures of the basal, mid, and apical lateral wall. As shown, after tracking the region of interest (left part of the figure), the systolic strain and systolic and diastolic strain rate measures were obtained by the automatic software analysis (right part of the figure). They were then verified and stored after approval. sS, peak systolic strain; sSR, peak systolic strain rate; eSR, peak early diastolic strain rate.

evaluated by calculating left ventricular end-diastolic volume (LVEDV), end-systolic volumes, and left ventricular ejection fraction (LVEF) by Simpson's rule, following the current guidelines.[18]

Proximal and distal RV outflow (RVOT) were evaluated from the short-axis parasternal view. RV dimensions (RVD) were also obtained by calculating basal RVD and RV area (RVA) at the end of diastole and systole from the right focused four-chamber view.[17] Based on these values, RV two-dimensional, fractional area change (FAC) was calculated.[17]

The systolic and diastolic function of both RV and LV were obtained by pulsed Doppler and pulsed tissue Doppler measures. Tricuspid and mitral pulsed Doppler inflow profiles were obtained at the level of the tip of the tricuspid and mitral leaflets. Peak E-wave (*E*) and *A*-wave velocity were evaluated.[19] Pulsed tissue Doppler profiles were obtained at the level of the lateral tricuspid annulus and of the septal and lateral mitral annulus from the apical four-chamber view using a 1 mm sample, with care being to reach the best alignment of the Doppler beam. Systolic (*S′*) and early diastolic (*E′*) peak velocity were defined as the mean of three beats. Moreover, *S′* and *E′* of the mitral annulus were calculated as the mean values of septal and lateral measurements. Finally, the *E*/*E′* ratio for the tricuspid and mitral annulus was calculated.

In order to obtain strain measures, a RV focused four-chamber view was analysed off-line by a single experienced observer blinded to disease. By means of two-dimensional speckle tracking analysis (EchoPAC PC version, GE Vingmed Ultrasound, General Electric, Milwaukee, WI, USA) of the basal, mid, and apical segments of the right lateral ventricular wall, longitudinal systolic strain (sS) and strain rate (sSR) and longitudinal early diastolic strain rate (eSR) were obtained as the mean of three cycles. The systolic measures were determined before aortic valve closure. In 20 patients intraobserver reproducibility was evaluated by the two separate analyses of the same images. Interobserver reproducibility was also tested in 20 patients by a second observer.

Finally, the global and segmental sS, sSR, eSR of LV were also calculated using the standard apical views.

In this paper the terms 'reduced systolic strain' and 'strain rate' indicate less negative values.

Statistical analysis

The continuous variables are expressed as mean values ± Standard Deviation (SD) and the categorical variables are given as frequencies and percentages. The between-group comparisons were made by variance analysis (ANOVA) followed by the Newman–Keuls test for multiple comparisons. The odds ratios (OR) and 95% confidence intervals (CI) were also computed to estimate the association between echocardiographic parameters (two-dimensional strain analysis of the right lateral ventricular wall or global and segmental two-dimensional strain analysis of the left ventricle) and BrS or ARVD/C, considering controls as a reference category. The OR and 95%CI for each analysed variable refers to 1-SD change. Frequencies were compared using the χ^2 or Fisher's exact test as appropriate. Receiver operating characteristic (ROC) curves, area under the curve (AUC) of the ROC, sensitivity and specificity were calculated to determine the values of studied variables that best differentiate patients from control subjects. Intraobserver data reproducibility was evaluated by means of the intraclass correlation coefficient (ICC), which measures the strength of the association between the two baseline recordings.[20] The data were considered reproducible if the ICC was >0.60; in particular, reproducibility was considered almost perfect if it was between 0.81 and 1.00.[21] $P < 0.05$ was considered statistically significant. Statistica 6.1 software (StatSoft Inc., Tulsa, OK, USA) and R (R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria) were used for analyses.

Results

Twenty-five of 28 patients with BrS and 15 of 17 patients with ARVD/C were enrolled in the study. The remaining 5 (11%) patients were excluded due to poor-quality imaging. Eleven (73%) of the ARVD/C patients and 17 (68%) of the BrS patients enrolled had an implantable cardioverter defibrillator, but none of the patients showed ventricular pacing at ECG. Moreover, 14 (93%) ARVD/C patients were on beta-blocker therapy. The clinical and electrocardiographic characteristics of the three groups are shown in *Table 1*. No differences were found in terms of age, gender distribution, body mass index, and QTc intervals among the groups. Patients with BrS showed a longer QRS duration at the level of the peripheral leads.

Two-dimensional and Doppler measurement comparisons

When LV and RV two-dimensional and Doppler measurements were compared in the three groups, no differences were found between BrS patients and the control group, as shown in *Table 2*. Patients with ARVD/C showed a significantly greater LVEDV, as well as distal and proximal RVOT, basal RVD, end-diastolic and end-systolic RVA when compared with BrS patients and controls (*Table 2*). Moreover, they showed a greater tricuspid *E*, a lower tricuspid *E′* and a greater *E*/*E′* (*Table 2*). No differences were found between the remaining parameters.

Reproducibility, comparisons and diagnostic accuracy of right ventricular strain measures

The ICC values of the RV strain measurements showed an intraobserver reproducibility >0.80 for sS of the basal, mid,

Table 1 Clinical and electrocardiographic characteristics of controls, Brugada syndrome, and arrhythmogenic right ventricular dysplasia/cardiomyopathy patients

	Controls	BrS	ARVD/C	*P*-value
Number	**25**	**25**	**15**	
Age (years)	45 ± 10	45 ± 9	44 ± 15	0.93
Males (%)	84	84	93	0.66
BMI (kg/m^2)	24.2 ± 2.3	25.6 ± 3.9	25.7 ± 4.7	0.27
Heart rate (*b*/*m′*)	67 ± 8	67 ± 11	66 ± 10	0.94
QRS duration (ms)	92 ± 11	106 ± 16*	95 ± 13†	**0.001**
QTc V1 (msec)	387 ± 26	403 ± 38	404 ± 26	0.22
QTc V2 (msec)	396 ± 23	413 ± 40	410 ± 21	0.16
QTc V5 (msec)	403 ± 20	406 ± 28	406 ± 24	0.87
QTc V6 (msec)	402 ± 20	404 ± 30	407 ± 20	0.84

BrS, Brugada syndrome patients; ARVD/C, arrhythmogenic right ventricular dysplasia/cardiomyopathy.
P refers to ANOVA analysis.
The bold values indicate the statistical significance.
*$P < 0.05$ vs. controls at *post hoc* analysis.
†$P < 0.05$ vs. Brugada syndrome patients at *post hoc* analysis.

Table 2 Right and left ventricular two-dimensional and Doppler measurements in controls, Brugada syndrome, and arrhythmogenic right ventricular dysplasia/cardiomyopathy patients

	Controls	BrS	ARVD/C	*P*-value
Left ventricle				
IVS (mm)	10.4 ± 1	10.4 ± 1.22	10.6 ± 1.64	0.86
LVEDV (mL)	83 ± 15	79 ± 20	98 ± 14*,†	**0.005**
LVEF (%)	63 ± 5	63 ± 4	60 ± 5	0.12
E mitral (cm/s)	82 ± 18	81 ± 17	76 ± 12	0.62
E/A mitral	1.36 ± 0.37	1.29 ± 0.26	1.29 ± 0.39	0.74
E′ mitral (cm/s)	13.5 ± 2.1	12.7 ± 2.8	12.9 ± 4.1	0.59
E/E′ mitral	6.08 ± 1.38	6.74 ± 2.66	6.43 ± 2.09	0.55
S′ mitral (cm/s)	10.8 ± 1.7	10.8 ± 2.3	10.0 ± 1.9	0.37
Right ventricle				
RVOT proximal (mm)	26.0 ± 3.2	25.8 ± 3.8	30.9 ± 2.9*,†	**<0.001**
RVOT distal (mm)	19.5 ± 2.9	18.7 ± 2.4	21.5 ± 2.7*,†	**0.018**
Basal RVD (mm)	27.2 ± 4.1	28.3 ± 2.7	31.0 ± 3.7*,†	**0.005**
End-diastolic RVA (cm^2)	16.5 ± 4.2	15.9 ± 3.3	19.2 ± 3.8*,†	**0.026**
End-systolic RVA (cm^2)	8.99 ± 2.90	8.86 ± 2.13	11.03 ± 2.33*,†	**0.021**
FAC (%)	46 ± 6	44 ± 8	42 ± 7	0.22
E tricuspid (cm/s)	62 ± 13	62 ± 10	72 ± 17*,†	**0.033**
E/A tricuspid	1.38 ± 0.39	1.45 ± 0.27	1.33 ± 0.36	0.55
E′ tricuspid (cm/s)	14.7 ± 2.7	13.1 ± 3.5	11.8 ± 3.0*	**0.017**
E/E′ tricuspid	4.33 ± 1.15	5.07 ± 1.57	6.56 ± 2.28*,†	**<0.001**
S′ tricuspid (cm/s)	14.4 ± 2.7	14.2 ± 2.3	13.0 ± 2.1	0.18

ARVD/C, arrhythmogenic right ventricular dysplasia/cardiomyopathy; BrS, Brugada syndrome patients; *E*, peak velocity of early diastolic pulsed Doppler wave; *A*, peak velocity of the diastolic pulsed Doppler wave due to atrial contraction; *E′*, peak velocity of early diastolic pulsed tissue Doppler wave; FAC, fractional area change; IVS, interventricular septum; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; RVA, right ventricular area; RVD, right ventricular dimension; RVOT, right ventricular outflow tract.
P refers to ANOVA analysis.
The bold values indicate the statistical significance.
*$P < 0.05$ vs. controls at *post hoc* analysis.
†$P < 0.05$ vs. Brugada syndrome patients at *post hoc* analysis.

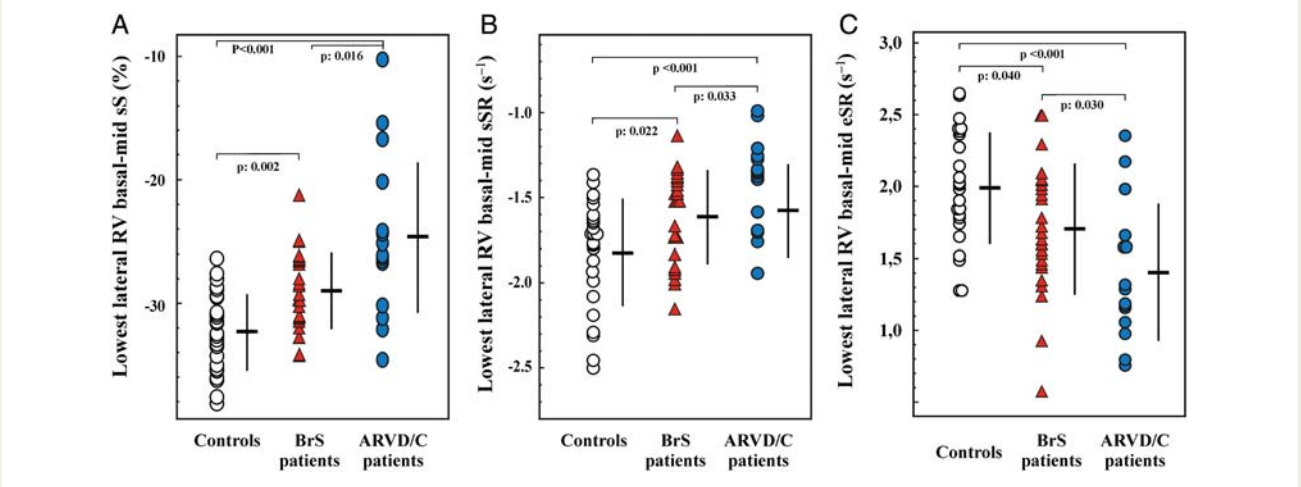

Figure 2 Distribution and comparison of the lowest systolic strain peak (*A*), systolic strain rate peak (*B*), and early diastolic strain rate peak (*C*) measure observed in the basal or mid-right ventricular lateral wall in controls (white circles), Brugada syndrome patients (red triangles), and arrhythmogenic right ventricular dysplasia/cardiomyopathy (blue circles). BrS, Brugada syndrome; ARVD/C, arrhythmogenic right ventricular dysplasia/cardiomyopathy; RV, right ventricle; sS, peak systolic strain; sSR, peak systolic strain rate; eSR, peak early diastolic strain rate.

Table 3 Two-dimensional strain analysis of the lateral right ventricular wall in controls, Brugada syndrome and arrhythmogenic right ventricular dysplasia/cardiomyopathy patients

	Controls	BrS	ARVD/C	*P*-value
RV basal lateral				
sS	−32.7 ± 3.3	−29.5 ± 3.5*	−25.1 ± 7.0*†	**<0.001**
sSR	−2.02 ± 0.42	−1.86 ± 0.46	−1.51 ± 0.30*†	**0.002**
eSR	2.28 ± 0.52	2.08 ± 0.60	1.87 ± 0.76	0.13
RV mid-lateral				
sS	−34.0 ± 3.8	−30.4 ± 3.0*	−27.5 ± 5.2*†	**<0.001**
sSR	−1.98 ± 0.38	−1.73 ± 0.26*	−1.58 ± 0.27*	**<0.001**
eSR	2.12 ± 0.48	1.78 ± 0.44*	1.50 ± 0.40*	**<0.001**
RV apical lateral				
sS	−27.3 ± 5.3	−25.7 ± 5.1	−24.1 ± 6.9	0.23
sSR	−1.53 ± 0.80	−1.54 ± 0.30	−1.46 ± 0.45	0.90
eSR	1.89 ± 0.56	1.78 ± 0.59	1.66 ± 0.50	0.45
Mean of RV lateral segments				
sS	−31.4 ± 3.5	−28.5 ± 2.3*	−25.6 ± 5.1*†	**<0.001**
sSR	−1.84 ± 0.41	−1.71 ± 0.26	−1.52 ± 0.21*	**0.011**
eSR	2.10 ± 0.39	1.88 ± 0.41	1.68 ± 0.39*	**0.007**

ARVD/C, arrhythmogenic right ventricular dysplasia/cardiomyopathy; BrS, Brugada syndrome patients; sS, systolic strain; sSR, systolic strain rate; eSR, early diastolic strain rate.
P refers to ANOVA analysis.
The bold values indicate the statistical significance.
*$P < 0.05$ vs. controls at *post hoc* analysis.
†$P < 0.05$ vs. Brugada syndrome patients at *post hoc* analysis.

and apical segments, for sSR of the mid and apical segments and for eSR of the mid and apical segments. Reproducibility for basal sSR and eSR was >0.7. The interobserver reproducibility values were >0.80 for sS of the mid and apical segments and for sSR and eSR of the apical segment. ICC was >0.7 for sSR and eSR of the mid-segment and >0.6 for sSR and eSR of the basal segment.

Patients with BrS had a significantly lower basal and mid-sS of the lateral RV when compared with controls, but which was greater than that of ARVD/C patients. At the level of the mid-lateral RV segment, sSR and eSR were also lower than for controls, but not significantly different from ARVD/C patients. ARVD/C patients also showed a lower sSR of the basal segment than controls or BrS patients. *Figure 2* shows the distribution of the lowest observed segment strain measures between basal and mid-lateral RV segments of the three groups and the relative comparisons. Finally, as shown in *Table 3*, the mean RV lateral sS in BrS patients was significantly lower than in controls but greater than ARVD/C patients, whereas the mean RV lateral sSR and eSR were lower than in controls but not different from the values observed in ARVD/C.

In BrS patients no relations were found between QRS duration, QTc intervals, and RV strain measures and no differences in strain measures were found when patients with type 1 and those with type 2–3 ECG at the time of echocardiographic examination were compared (data not shown).

At ROC analysis for diagnosis of ARVD/C the lowest basal and mid-sS value observed for each patient showed a greater AUC for both ARVD/C (0.87, $P < 0.001$) and BrS (0.76, $P < 0.001$). The detection of a sS greater than −29% in the basal or mid-lateral RV was characterized by a 73% sensitivity for ARVD/C and 48% sensitivity for BrS, with an 80% specificity. When the lowest sSR between basal and lateral RV sSR was considered, the AUC were 0.85 ($P < 0.001$) for ARVD/C and 0.69 (*P*: 0.014) for BrS. When the lowest eSR between the basal and mid-lateral segment was evaluated, AUC were 0.83 ($P < 0.001$) for ARVD/C and 0.68 (*P*: 0.021) for BrS.

Comparison of left ventricular strain measures

As shown in *Table 4*, no differences were found between LV global and segmental strain measures in BrS patients and controls. Patients with ARVD/C showed significantly lower values of LV global sSR and eSR, lower basal and mid-inferoseptal sS and sSR as well as lower mid-anteroseptal sSR.

Figure 3 shows the association between the lowest RV basal–mid-lateral sS, sSR, eSR, mean RV lateral sS, sSR, eSR and global LV sS, sSR and eSR in BrS and ARVD/C, considering controls a as reference category. Most of the RV strain parameters were significantly associated both to BrS and ARVD/C, whereas global LV strain measures were associated only to ARVD/C.

Discussion

The main finding of this study is that two-dimensional speckle tracking analysis permits a better definition of phenotype expression in BrS patients by detecting mild systolic and diastolic function

Table 4 Global and segmental two-dimensional strain analysis of the left ventricle in controls, Brugada syndrome, and arrhythmogenic right ventricular dysplasia/cardiomyopathy patients

Left ventricle analysis	Controls	BrS	ARVD/C	*P*-value
Global sS	−20.4 ± 2.2	−20.3 ± 2.9	−18.6 ± 2.4	0.06
Global sSR	−1.07 ± 0.13	−1.04 ± 0.17	−0.91 ± 0.10*†	**0.003**
Global eSR	1.33 ± 0.27	1.23 ± 0.29	1.06 ± 0.36*	**0.030**
Basal anterior				
sS	−20.2 ± 3.6	−19.9 ± 4.5	−18.0 ± 2.5	0.27
sSR	−1.20 ± 0.32	−1.18 ± 0.36	−0.99 ± 0.29	0.20
eSR	1.54 ± 0.40	1.53 ± 0.32	1.24 ± 0.51	0.09
Mid-anterior				
sS	−21.6 ± 2.9	−20.7 ± 3.3	−20.7 ± 3.5	0.58
sSR	−1.16 ± 0.23	−1.08 ± 0.19	−1.03 ± 0.14	0.18
eSR	1.43 ± 0.26	1.37 ± 0.29	1.28 ± 0.46	0.42
Apical anterior				
sS	−22.9 ± 4.7	−23.1 ± 6.8	−19.9 ± 4.8	0.21
sSR	−1.38 ± 0.32	−1.40 ± 0.46	−1.21 ± 0.30	0.33
eSR	1.93 ± 0.53	1.84 ± 0.67	1.58 ± 0.56	0.24
Basal inferoseptal				
sS	−17.8 ± 3.3	−16.7 ± 3.8	−13.4 ± 2.2*†	**<0.001**
sSR	−1.08 ± 0.35	−0.96 ± 0.27	−0.82 ± 0.25*	**0.041**
eSR	1.21 ± 0.37	1.25 ± 0.44	1.13 ± 0.41	0.70
Mid-inferoseptal				
sS	−20.6 ± 2.5	−19.7 ± 2.9	−17.7 ± 2.3*†	**0.004**
sSR	−1.10 ± 0.13	−1.07 ± 0.21	−0.91 ± 0.15*†	**0.005**
eSR	1.37 ± 0.37	1.24 ± 0.33	1.10 ± 0.44	0.09
Basal anteroseptal				
sS	−19.4 ± 2.7	−18.6 ± 3.1	−18.7 ± 2.5	0.62
sSR	−1.20 ± 0.26	−1.13 ± 0.24	−0.97 ± 0.24*	**0.049**
eSR	1.40 ± 0.46	1.22 ± 0.40	1.22 ± 0.37	0.32
Mid-anteroseptal				
sS	−20.4 ± 4.6	−20.8 ± 3.7	−19.5 ± 3.3	0.64
sSR	−1.15 ± 0.13	−1.17 ± 0.29	−0.98 ± 0.12*†	**0.040**
eSR	1.56 ± 0.46	1.55 ± 0.30	1.26 ± 0.32	0.06
Apical septal				
sS	−23.4 ± 4.0	−22.1 ± 4.0	−21.0 ± 5.1	0.24
sSR	−1.33 ± 0.29	−1.31 ± 0.29	−1.17 ± 0.25	0.20
eSR	2.26 ± 0.69	2.03 ± 0.54	1.94 ± 0.67	0.26
Basal inferior				
sS	−20.3 ± 3.3	−20.7 ± 4.4	−18.7 ± 3.7	0.30
sSR	−1.27 ± 0.30	−1.35 ± 0.42	−1.15 ± 0.32	0.28
eSR	1.76 ± 0.46	1.60 ± 0.49	1.68 ± 0.59	0.57
Mid-inferior				
sS	−20.1 ± 4.1	−21.6 ± 3.1	−19.2 ± 2.8	0.12
sSR	−1.13 ± 0.26	−1.23 ± 0.22	−1.03 ± 0.15†	**0.038**
eSR	1.29 ± 0.43	1.33 ± 0.36	1.20 ± 0.47	0.67
Apical inferior				
sS	−23.2 ± 5.4	−24.6 ± 6.5	−20.9 ± 3.9	0.16
sSR	−1.40 ± 0.30	−1.45 ± 0.41	−1.21 ± 0.27	0.13
eSR	2.01 ± 0.76	1.89 ± 0.65	1.56 ± 0.77	0.22
Basal anterolateral				
sS	−20.9 ± 4.2	−21.9 ± 4.9	−18.3 ± 4.6	0.06
sSR	−1.45 ± 0.35	−1.49 ± 0.40	−1.20 ± 0.34	0.05

Continued

Table 4 *Continued*

Left ventricle analysis	Controls	BrS	ARVD/C	*P*-value
eSR	1.75 ± 0.50	1.76 ± 0.53	1.57 ± 0.46	0.47
Mid-anterolateral				
sS	−20.6 ± 4.3	−20.4 ± 4.0	−18.7 ± 2.9	0.29
sSR	−1.14 ± 0.25	−1.12 ± 0.24	−0.99 ± 0.19	0.13
eSR	1.43 ± 0.34	1.40 ± 0.37	1.26 ± 0.30	0.30
Basal posterolateral				
sS	−20.5 ± 4.9	−20.6 ± 5.2	−18.6 ± 5.8	0.58
sSR	−1.43 ± 0.45	−1.55 ± 0.46	−1.25 ± 0.27	0.19
eSR	1.76 ± 0.60	1.84 ± 0.62	1.39 ± 0.51	0.14
Mid-posterolateral				
sS	−19.8 ± 5.9	−19.6 ± 3.4	−17.6 ± 3.2	0.38
sSR	−1.11 ± 0.26	−1.08 ± 0.21	−0.96 ± 0.22	0.21
eSR	1.55 ± 0.48	1.49 ± 0.27	1.22 ± 0.43	0.08
Apical lateral				
sS	−20.6 ± 5.1	−19.8 ± 4.3	−18.6 ± 5.3	0.46
sSR	−1.21 ± 0.30	−1.15 ± 0.27	−1.06 ± 0.24	0.23
eSR	1.96 ± 0.62	1.76 ± 0.47	1.64 ± 0.48	0.17

sS, systolic strain; sSR, systolic strain rate; eSR, early diastolic strain rate. BrS, Brugada syndrome patients; ARVD/C, arrhythmogenic right ventricular dysplasia/cardiomyopathy.
P refers to ANOVA analysis.
The bold values indicate the statistical significance.
*$P < 0.05$ vs. controls at *post hoc* analysis.
†$P < 0.05$ vs. Brugada syndrome patients at *post hoc* analysis.

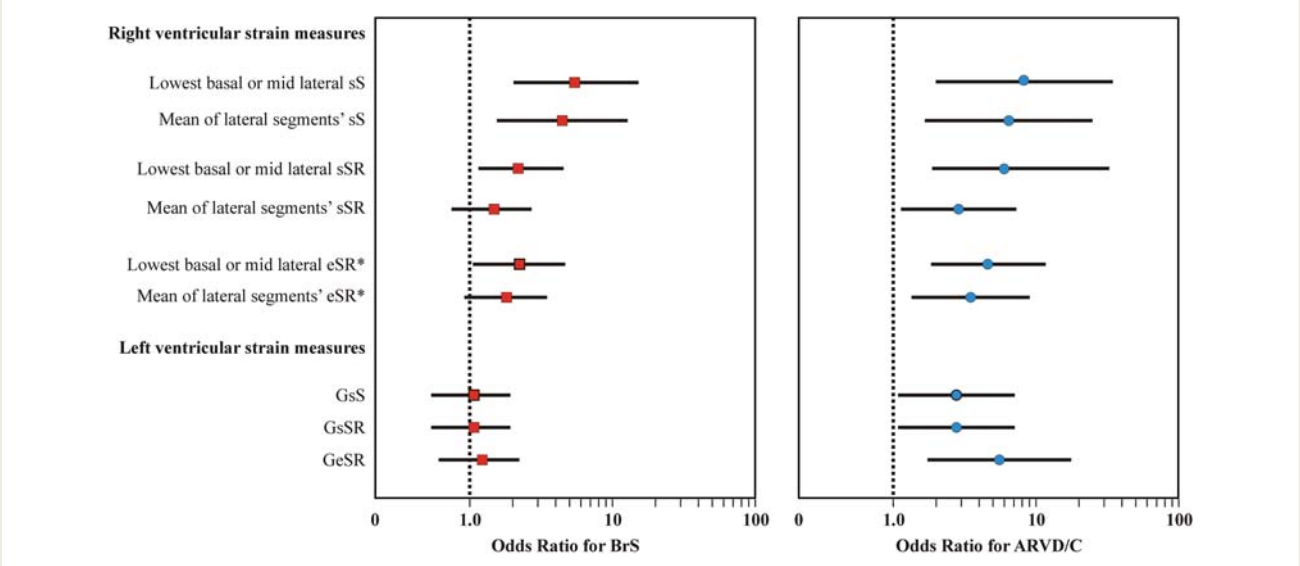

Figure 3 Odds ratios with a 95% confidence interval for Brugada syndrome (red squares, left panel) and arrhythmogenic right ventricular dysplasia/cardiomyopathy (blue circles, right panel) patients, considering controls as a reference category. The values were reported on logarithmic scale (base 10). Odds ratios were calculated for 1-standard deviation increase for sS and sSR, whereas for eSR they were computed for 1-standard deviation decrease. BrS, Brugada syndrome patients; ARVD/C, arrhythmogenic right ventricular dysplasia/cardiomyopathy; sS, systolic strain; sSR, systolic strain rate; eSR, early diastolic strain rate; GsS, global left ventricular sS; GsSR, left ventricular global sSR; GeSR, global left ventricular eSR.

abnormalities in RV basal and mid-lateral segments. When compared with a control group matched for age and gender, these abnormalities were less pronounced than those observed in ARVD/C patients.

These findings suggest that the new techniques may prove useful for evaluating myocardial deformation in BrS patients, permitting global and regional cardiac function to be quantified more

accurately and objectively.[8,22] To date, two methods for strain analysis are widely available, one derives from tissue Doppler analysis, the other from two-dimensional speckle tracking analysis of greyscale B-mode images. The latter method has been validated by sonomicrometry and tagged magnetic resonance imaging[23] and has already been used to detect ventricular function abnormalities both in left and RV cardiomyopathies.[8,9] Compared with the tissue Doppler derived approach, the 2D strain is characterized by less criticisms such as angle dependency, noise interference and intra- and interobserver variability.[24] On this basis, we used 2D strain to evaluate longitudinal RV strain and obtained a good reproducibility, also in the segmental analysis of the RV lateral wall.

By using 2D systolic strain analysis we were able to detect differences in RV function between BrS patients and controls that could not be observed by conventional echocardiographic and Doppler parameters. RVD, pulsed Doppler and pulsed tissue Doppler measurements in BrS patients were similar to those of the control group, whereas significantly lower values in RV basal and mid-lateral sS peak, as well as in systolic and early diastolic mid-lateral SR, were observed. The detection of these differences is in line with previous studies which have demonstrated mild RV structural and functional abnormalities in BrS patients by using alternative imaging techniques.[4,6] Takagi *et al.*[6] using electrobeam computed tomography have uncovered morphological RV abnormalities in 81% of BrS patients and only in 9% of controls. Similarly, by using cardiac magnetic resonance, Catalano *et al.*[4] demonstrated that, when compared with controls, BrS patients showed a higher frequency of mild abnormalities in radial fractional shortening in the anterior apical segment, the outflow tract and the inferior mid-ventricular segment in the inflow tract. Our study adds new data by demonstrating that BrS patients are also characterized by a mild reduction in the longitudinal strain of the basal and mid-lateral RV wall.

Our study did not aim to evaluate the pathophysiological background of the mild abnormalities we found, however, some hypotheses may be made. The lack of any relationship between strain measures and the electrocardiographic features of BrS patients (QRS duration, QT interval and type 1 ECG at echocardiographic examination) makes the hypothesis that the strain abnormalities observed in our series could be related to ion channel dysfunction per se unlikely. Consequently, they could be related to the mild structural abnormalities that have been observed at endomyocardial biopsy. In a group of patients with normal cardiac magnetic resonance, Frustaci *et al.*[5] have shown that RV endomyocardial biopsies of BrS patients revealed histological abnormalities such as myocarditis, cardiomyopathic changes and also fatty infiltration. However, the involvement of ion channel mutations in determining mild RV function abnormalities cannot be excluded. It has been shown that some ion channel mutations are related both to BrS phenotype and to a wide spectrum of disease pnenotypes including dilated cardiomyopathy.[11] Moreover, some Na+ channel mutations have been found to be associated with fibrosis by mechanisms which have not yet been clearly defined, but which are probably linked to the interaction with membrane proteins.[25]

The association between ARVD/C and lower systolic strain measures confirms the potential clinical usefulness of these parameters in diagnosing this type of cardiomyopathy, as already suggested by previous studies.[9,10] However, in our data a broad overlap in values of all RV strain parameters was observed, thus limiting clinical usefulness of a strain measures' cut-off for discriminating the presence of BrS as well as of ARVD/C.

In our study the mean values and the cut-off for RV systolic strain measures in ARVD/C and controls was slightly different when compared with previous studies.[9,10] These differences could be related to a number of causes, such as the different severity of RV dysfunction in ARVD/C patients, the use 2D strain instead of TDI technique,[9,10] the wide reported variability in the strain and strain rate mean values of the lateral RV segments.[17] Finally, we cannot exclude that the analysis of 2D strain on a RV focused four-chamber view could have influenced the values we found.

It is worth noting that, in our study, ARVD/C patients showed differences not only in RV but also in LV strain measures when compared with controls. The comparison of strain measures at different LV segments revealed more marked differences in the septal segments considered, but there was a tendency in all other segments. Consequently all three strain measures of LV systo-diastolic function were associated to ARVD/C at regression analysis, as shown in *Figure 3*. These differences are even more relevant considering that of the ARVD/C patients we enrolled, only one showed a LVEF of between 50 and 55%, and no differences were found when mean LVEF values were compared with controls. On the basis of these considerations it is possible to suggest that 2D strain analysis may be useful to better characterize not only RV, but also LV function, in ARVD/C patients.

Like in previous studies,[9,10] a possible limitation of our results is the use at the time of the enrolment of beta-blocker therapy in ARVD/C patients. However, it is worth noting that in subgroups analysis of Prasaka *et al.*[10] no influence on strain measures was observed according to the presence of beta-blocker therapy.

Future studies ought to focus on demonstrating the clinical relevance of mild strain abnormalities in BrS and ARVD/C patients, e.g. in predicting malignant ventricular arrhythmia occurrence or the progression of RV disease. In such cases 2D strain could prove to be a useful tool in detecting and monitoring RV abnormalities as it is feasible and safe in most patients, whereas nuclear magnetic resonance imaging cannot be serially performed in patients with a cardioverter defibrillator and computed tomography is limited by radiation exposure and the limited information obtained on myocardial function. Finally, the use of 3D derived strain measures could offer the possibility of a more complete analysis of the RV which is not limited to the lateral free wall, as in our study.

In conclusion, in patients with BrS it is possible to observe mild abnormalities in RV systolic and diastolic function evaluated by 2D strain. The values observed in these patients were mid-way between those for healthy subjects without cardiac disease and those for ARVD/C patients with known structural RV disease. These results help to better define the phenotypic characteristics of BrS patients and represent the basis for future studies aimed at testing the clinical usefulness of echocardiographic evaluation in these patients.

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References

1. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. *J Am Coll Cardiol* 1992;**20**:1391–6.
2. Brugada R, Brugada J, Antzelevitch C, Kirsch GE, Potenza D, Towbin JA *et al.* Sodium channel blockers identify risk for sudden death in patients with ST-segment elevation and right bundle branch block but structurally normal hearts. *Circulation* 2000;**101**:510–5.
3. Antzelevitch C, Nof E. Brugada syndrome: recent advances and controversies. *Curr Cardiol Rep* 2008;**10**:376–83.
4. Catalano O, Antonaci S, Moro G, Mussida M, Frascaroli M, Baldi M *et al.* Magnetic resonance investigations in Brugada syndrome reveal unexpectedly high rate of structural abnormalities. *Eur Heart J* 2009;**30**:2241–8.
5. Frustaci A, Priori SG, Pieroni M, Chimenti C, Napolitano C, Rivolta I *et al.* Cardiac histological substrate in patients with clinical phenotype of Brugada syndrome. *Circulation* 2005;**112**:3680–7.
6. Takagi M, Aihara N, Kuribayashi S, Taguchi A, Shimizu W, Kurita T *et al.* Localized right ventricular morphological abnormalities detected by electron-beam computed tomography represent arrhythmogenic substrates in patients with Brugada syndrome. *Eur Heart J* 2001;**22**:1032–41.
7. Corrado D, Nava A, Buja G, Martini B, Fasoli G, Oselladore L *et al.* Familial cardiomyopathy underlies syndrome of right bundle branch block, ST segment elevation and sudden death. *J Am Coll Cardiol* 1996;**27**:443–8.
8. Geyer H, Caracciolo G, Abe H, Wilansky S, Carerj S, Gentile F *et al.* Assessment of myocardial mechanics using speckle tracking echocardiography: fundamentals and clinical applications. *J Am Soc Echocardiogr* 2010;**23**:351–69.
9. Teske AJ, Cox MG, De Boeck BW, Doevendans PA, Hauer RN, Cramer MJ. Echocardiographic tissue deformation imaging quantifies abnormal regional right ventricular function in arrhythmogenic right ventricular dysplasia/cardiomyopathy. *J Am Soc Echocardiogr* 2009;**22**:920–7.
10. Prakasa KR, Wang J, Tandri H, Dalal D, Bomma C, Chojnowski R *et al.* Utility of tissue Doppler and strain echocardiography in arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Am J Cardiol* 2007;**10**:507–12.
11. Lehnart SE, Ackerman MJ, Benson DW Jr, Brugada R, Clancy CE, Donahue JK *et al.* Inherited arrhythmias: a National Heart, Lung, and Blood Institute and Office of Rare Diseases workshop consensus report about the diagnosis, phenotyping, molecular mechanisms, and therapeutic approaches for primary cardiomyopathies of gene mutations affecting ion channel function. *Circulation* 2007; **116**:2325–45.
12. Antzelevitch C, Brugada P, Borggrefe M, Brugada J, Brugada R, Corrado D *et al.* Consensus Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. *Circulation* 2005;**111**:659–70.
13. McKenna WJ, Thiene G, Nava A, Fontaliran F, Blomstrom-Lundqvist C, Fontaine G *et al.* Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Task Force of the Working Group Myocardial and Pericardial Disease of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology. *Br Heart J* 1994;**71**:215–8.
14. Pitzalis MV, Anaclerio M, Iacoviello M, Forleo C, Guida P, Troccoli R *et al.* QT-interval prolongation in right precordial leads: an additional electrocardiographic hallmark of Brugada syndrome. *J Am Coll Cardiol* 2003;**42**:1632–7.
15. Bayés de Luna A. Normal QRS complex. In: *Clinical Electrocardiography: A Textbook*. Mount Kisco, New York: Futura Publishing Company, Inc.; 1993. p78–93.
16. Surawicz B. Long QT interval, torsade de pointes, and early afterdepolarizations. In: *Electrophysiologic Basis of ECG and Cardiac Arrhythmias*. Malvern, USA: Williams & Wilkins; 1995. p191–229.
17. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K *et al.* Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 2010;**23**:685–713.
18. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA *et al.* Recommendations for chamber quantification. *Eur J Echocardography* 2006;**7**:79–108.
19. Quiñones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA. Recommendations for quantification of Doppler echocardiography: a report from the Doppler quantification task force of the nomenclature and standards committee of the American Society of Echocardiography. *J Am Soc Echocardiogr* 2002;**15**: 167–84.
20. Fleiss JL. Reliability of measurements. In: *The Design and Analysis of Clinical Experiments*. New York: Wyley; 1986. p1–32.
21. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;**33**:159–74.
22. Teske AJ, De Boeck BW, Melman PG, Sieswerda GT, Doevendans PA, Cramer MJ. Echocardiographic quantification of myocardial function using tissue deformation imaging, a guide to image acquisition and analysis using tissue Doppler and speckle tracking. *Cardiovasc Ultrasound* 2007;**30**:5–27.
23. Korinek J, Kjaergaard J, Sengupta PP, Yoshifuku S, McMahon EM, Cha SS *et al.* High spatial resolution speckle tracking improves accuracy of 2-dimensional strain measurements: an update on a new method in functional echocardiography. *J Am Soc Echocardiogr* 2007;**20**:165–70.
24. Becker M, Bilke E, Kühl H, Katoh M, Kramann R, Franke A *et al.* Analysis of myocardial deformation based on pixel tracking in two dimensional echocardiographic images enables quantitative assessment of regional left ventricular function. *Heart* 2006;**92**:1102–8.
25. Gavillet B, Rougier JS, Domenighetti AA, Behar R, Boixel C, Ruchat P *et al.* Cardiac sodium channel Nav1.5 is regulated by a multiprotein complex composed of syntrophins and dystrophin. *Circ Res* 2006;**99**:407–14.