The clinical utility of procainamide-induced late potentials on the signal averaged ECG

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Title: The Clinical Utility of Procainamide-induced Late Potentials on the Signal Averaged ECG

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Abstract

Background:

Late potentials (LPs) identified on the signal averaged electrocardiogram (SAECG) are a marker for an increased risk of arrhythmias in Brugada syndrome (BrS). Procainamide is a sodium channel blocker used to diagnose BrS. The effects of Procainamide on the SAECG in those with BrS and the significance of Procainamide-induced LPs are unknown.

Methods:

Procainamide provocation was performed for suspected BrS with 12-lead and SAECG pre- and post-infusion. Filtered QRS duration (fQRSd), duration of low amplitude signals <40μV (LAS40) and root-mean-square voltage in the terminal 40 ms (RMS40) were determined.

Results:

Data from 150 patients were included in the analysis (mean age 44.5 years, 109 males). Procainamide increased fQRSd (Pre 118.8±10.5ms, post 121.2±10.2ms, p<0.001) and LAS40 (Pre 38.7±9.8ms, post 40.2±10.5ms, p=0.005) and decreased RMS40 (Pre 24.6±12ms, post 22.8±12ms, p=0.002). LPs were present in 68/150 (45%) at baseline. Fifteen patients with negative baseline SAECGs had LPs unmasked by Procainamide, but six patients had LPs at baseline that were no longer present following Procainamide. Comparing those with normal hearts (n=48) to those with a final diagnosis of BrS (n=38), Procainamide prolonged fQRSd to a greater extent in those with BrS. Comparing those with Procainamide-induced LPs to those with no LPs at any time did not highlight any aspect of phenotype and did not correlate with a history of ventricular arrhythmias.

Conclusions:

Procainamide influences the SAECG, provoking LPs in a small proportion of patients. However, there is no evidence that Procainamide-induced LPs provide additional diagnostic information or aid risk stratification.

Keywords: Brugada, Procainamide, SAECG, late potentials

Abbreviations

ECG	Electrocardiogram
SAECG	Signal-averaged electrocardiogram
LP	Late potential
BrS	Brugada syndrome
MRI	Magnetic resonance imaging
ICS	Intercostal space
fQRSd	Filtered QRS duration
RMS40	Root mean square of the terminal 40ms of the filtered QRS complex
LAS40	Duration of low amplitude signals < 40 μV
ICS	Intercostal space

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Introduction

Brugada syndrome (BrS) is a rare inherited arrhythmia syndrome associated with a characteristic ECG abnormality of coved ST-segment elevation and T-wave inversion in the precordial leads[1]. BrS is frequently associated with variants in *SCN5A*, the gene encoding the cardiac sodium current I_{Na} , though the underlying genetic variant or variants remain elusive in many affected individuals [2]. These variants typically decrease I_{Na}, although the extent of sodium current loss is only weakly correlated with phenotype[3]. Pharmacological suppression of I_{Na} can be used for diagnosis using sodium channel blockers such as Procainamide, Flecainide or Ajmaline to unmask a BrS ECG pattern that is hidden at baseline[4].

Although BrS is associated with a risk of ventricular arrhythmias and sudden death, these potentially catastrophic events occur in only a minority of those with the condition[5]. Identifying those at higher risk is of vital importance. Those with a history of prior arrhythmias or syncope are widely acknowledged to have a higher risk of future events, but risk stratification in those at intermediate or low risk remains suboptimal[4].

In an attempt to improve risk stratification, many diagnostic tests including the signal averaged ECG (SAECG) have been evaluated.[6] Late potentials (LP) on SAECG – abnormal low amplitude signals present in the terminal portion of the QRS complex – are more commonly seen in BrS patients with a history of ventricular arrhythmias than those without, although the positive predictive value remains low[7]. While the mechanism underlying late potentials in BrS remains controversial, it is likely that sodium channel dysfunction plays a key role[8,9].

Conceivably, the sodium current blocking effects of Procainamide might reveal late potentials in those with BrS that were otherwise latent. In a group of patients referred for provocation testing for suspected BrS, we hypothesised that (1) Procainamide would reveal late potentials in a proportion of those tested, (2) late potentials would be revealed more frequently in those with BrS than those without.

Methods

Patient population

This study was approved by the UBC-Providence Health Care Research Ethics Board. Patients undergoing Procainamide provocation for evaluation of suspected BrS at Saint Paul's Hospital, Vancouver, between December 2016 and July 2021 were eligible for inclusion[10]. Patients were excluded if QRS duration was >120ms on baseline ECG, as a high rate of false positives has been reported in this group[11]. Records were reviewed retrospectively by JW and CMP. Twelve lead and signal averaged ECGs were stored as high-resolution digital files. Baseline SAECG and 12-lead ECG recordings were compared with those generated 10 minutes post-infusion. Variant pathogenicity was assessed using American College of Medical Genetics criteria[12].

Procainamide provocation

Informed consent was obtained from all patients. Pre-existing medications were cross-referenced with www.brugadadrugs.org to ensure they had no effect on test outcome. Provocation was conducted as previously described[13]. Procainamide was infused through a peripheral intravenous line with continuous ECG monitoring at a dose of 15 mg/kg over 20 minutes at a maximum rate and dose of 50 mg/min and 1g respectively. SAECG recordings were conducted at baseline and 10 minutes post-infusion. Standard ECG recordings were conducted at baseline, at 10 and 20 minutes during the infusion, and post-infusion at 10 minutes, 30 minutes and 60 minutes. High lead ECG recordings were conducted at baseline, at 10 and 20 minutes during the infusion, and post-infusion at 10 minutes. High lead ECG monitoring consisted of V_1 and V_2 elevated to the 2^{nd} and 3^{rd} intercostal space (ICS) respectively[14].

The infusion was terminated if the QRS complex prolonged by ≥130% of baseline value, if frequent premature ventricular complexes or ventricular arrhythmias were seen, if systolic blood pressure (SBP) < 90 mmHg or symptoms of hypotension and SBP < 100 mmHg occurred, or if any other significant side effects secondary to the infusion were experienced. Isoproterenol was available at the bedside and infused at 2 mcg/min for 30 minutes with continuous ECG monitoring if ventricular arrhythmias were observed.

Provocation was defined as positive if V_1 or V_2 within the 2^{nd}, 3^{rd} or 4^{th} ICS demonstrated a Type 1 BrS ECG characterized by J-point elevation ≥2mm and a coved ST segment[15]. A type 2 BrS ECG pattern (T2ECG) was recorded if J-point elevation ≥2mm was followed by ≥0.5mm saddle-back ST segment[15].

Signal averaged ECG acquisition

SAECGs were recorded via the MAC VU resting ECG analysis system (GE Health Care, Chicago, Illinois) in sinus rhythm using Frank X, Y, Z corrected orthogonal leads. A minimum of 250 beats were averaged for each recording with a noise level < 0.7 μV and bandpass filter frequency of 40-250Hz. The following parameters were analysed: filtered QRS duration (fQRSd), root mean square of the terminal 40ms of the filtered QRS complex (RMS40), and duration of low amplitude signals <40 μV duration (LAS40). LPs were deemed positive if 2 of the following 3 criteria were met: fQRSd >114 ms, RMS40 < 20 μV or LAS40 > 38 ms [16].

Statistical analysis

Statistical analysis was performed using Microsoft Excel and IBM SPSS Statistics for Windows, version 26.0 (IBM Corporation, Armonk, NY). Data are presented as mean ± standard deviation or n(%) unless otherwise indicated. Comparisons within groups were made via the paired t-test or Wilcoxon signed rank test as appropriate. For comparisons across groups, continuous variables were evaluated via student's t-test or Welch's t-test if normally distributed, and via the Mann-Whitney U test if not normally distributed. Categorical variables were compared using the Chi-squared test for unpaired data and McNemar's test for paired data. $P < 0.05$ was considered significant.

Results

172 consecutive patients underwent Procainamide provocation testing. 22 patients were excluded (missing pre-or post SAECG n=10, noise>0.7 μV n=1, infusion terminated early n=1, baseline QRS >120ms n=10). 150 patients were therefore included in this analysis (Table 1). Indications for Procainamide testing were an ECG suspicious for BrS without type 1 pattern (n=83), unexplained cardiac arrest (n=26), family history of unexplained cardiac arrest (n=22), family history of BrS (n=16), or investigation of an incidentally found *SCN5A* variant (n=3). Genetic testing was performed in 53 patients, identifying *SCN5A* variants in seven patients (Supplemental Table 1).

Procainamide provocation induced a type 1 BrS ECG pattern in 36/114 (24%) cases. Ten cases had spontaneous Type 1 ECGs during follow up including two with negative Procainamide provocation. In total 38 patients received a diagnosis of Brugada syndrome. 75 patients had a normal Procainamide challenge and no history of arrhythmias or any other cardiac diagnosis. Of these, 48 had undergone cardiac imaging with echocardiography and/or cardiac MRI that demonstrated structurally normal hearts. This group of 48 patients served as a control cohort of normal hearts for subsequent analyses.

Effects of Procainamide on signal averaged and 12 lead ECG

Prior to infusion of Procainamide, 68/150 (45%) participants had SAECGs that met criteria for positive late potentials (Figure 1). Infusion of Procainamide increased the filtered QRS duration (fQRSd) in 122/150 (81%) patients. Overall, mean fQRSd increased by 2.4±5.6 ms (2.1%). LAS40 increased in 91/150 (61%) patients with a mean increase of 1.6±6.8 ms (5.7%). RMS40 decreased in 94/150 (63%) patients with a mean reduction of 1.9±7.2 ms (5.2%) (Table 2).

After Procainamide, 15 of the 72 patients with negative baseline SAECGs developed late potentials (21%), but interestingly 6 patients with late potentials on baseline SAECG had a negative SAECG post-Procainamide. On analysis of 12 lead ECGs, Procainamide increased heart rate, PR interval, QRS duration, and the absolute and corrected QT intervals (Table 2).

Differential effects of Procainamide in BrS vs. Control

We next asked whether those with BrS exhibited a more pronounced effect of Procainamide on SAECG. Stratifying electrocardiographic findings by clinical cohorts, 38 patients with a final diagnosis of BrS were compared with a control group of 48 patients with normal hearts. At baseline, patients with BrS had longer QRS durations on 12-lead but similar SAECG parameters. Procainamide prolonged fQRSd and the

QT interval to a greater extent in those with BrS (Figure 2). Other parameters were similar between groups. (Table 3).

We then asked whether identifying late potentials pre- or post- Procainamide identified any aspect of phenotype (Table 4). Compared to those who did not exhibit late potentials at any time, those with late potentials at baseline or after Procainamide were more likely to be male. No other aspect of phenotype, including persence of structural heart disease or history of prior cardiac arrest was associated with late potentials before or after Procainamide.

We finally asked whether an exaggerated response to Procainamide was associated with any patient characteristics. Participants showing an absolute change in fQRSd greater than the 90th centile (>7 ms) had similar characteristics to the population as a whole, as were those with an absolute change in LAS40 over the 90th percentile (>10 ms), and those with a change in RMS40 more negative than the 10th percentile (<-9μV) (Supplemental Table 2).

Sensitivity analyses

To explore whether more pronounced changes might be seen in those with a more severe phenotype, we reanalysed the data including only the ten patients with BrS who manifested a spontaneous Type 1 ECG (ST1) during follow up. Those with a ST1 had longer fQRSd on SAECG and PR and QRSd on 12 lead ECG than control. The SAECG response to Procainamide was numerically greater than that seen in the primary analysis but did not reach statistical significance (Supplemental Table 3).

As it has been suggested that the accuracy of the SAECG for identifying late potentials may be impaired at higher noise levels, we repeated the analysis including only patients whose SAECG had a noise level <0.3mcV (normal heart n=38, BrS n=29). Results were similar to those seen in the primary analysis.

Discussion

We examined the effects of a procainamide challenge on SAECG findings in patients suspected to have Brugada syndrome. The main findings were: (1) Procainamide increases fQRSd and LAS40 and decreases RMS40 thereby meeting the criteria for late potentials in a subset of the patients. (2) Procainamide has a greater effect on fQRSd and QT interval in those with BrS. (3) Procainamide-induced late potentials do not seem to identify any specific subgroup of patients.

In BrS the mechanisms underlying the late potentials are likely to differ from those causing late potentials in patients with gross structural heart disease. In early reports post myocardial infarction, late potentials were thought to represent delayed activation of regions of scarred myocardium[17]. Whilst right ventricular outflow tract (RVOT) fibrosis has been described in BrS [18], many patients with BrS have no identifiable structural abnormalities. In the present study, late potentials were no more likely to be seen in those with myocardial scarring as evidenced by late gadolinium enhancement on cMRI.

Instead, potential mechanisms for late potentials in BrS include delayed activation of the RVOT caused by sodium current loss (the depolarisation hypothesis)[19,20], or a second depolarisation generated by the accentuated action potential dome found in the epicardial RVOT facilitated by an increased transient outward potassium current (the repolarisation hypothesis)[21]. These competing hypotheses are similar to those underlying arrhythmogenesis and the characteristic ECG pattern seen in BrS, as reviewed by Behr et al[9]. A common feature of both these mechanisms is a change in the balance of inward to outward currents which might both slow conduction and exaggerate the action potential notch.

In the present study, Procainamide prolonged fQRSd and LAS40 and attenuated RMS40, consistent with previous work in humans[22] and dogs[23] post myocardial infarction. This may have occurred secondary to the depolarisation or repolarisation mechanisms described above. The effects of Procainamide were variable and a small minority of participants experienced a paradoxical shortening of fQRSd and LAS40, with the range of effects approximating a normal distribution.

We hypothesised that the late potential-amplifying effects of Procainamide would occur less frequently in those without BrS, analogous to the minor effects of Procainamide on the surface ECG in those with structurally normal hearts, compared to the unmasking of a Type 1 ECG pattern in those with BrS. However, in the present study, those with BrS were no more likely to show Procainamide-induced late potentials than those with apparently normal hearts. Only 5 patients were identified with a pathogenic *SCN5A* variant making it impossible to draw firm conclusions about this small subset.

One possible explanation for this finding is that Procainamide might cause a similar relative decrease in sodium current in those with normal or impaired baseline sodium channel function. Secondly, some cases of BrS may be unrelated to a sodium channelopathy but instead be due to calcium or potassium handling defects. Thirdly, as Procainamide also inhibits potassium channels, a complex effect on the still disputed mechanism of late potentials is possible.

Signal-averaged ECG has been suggested to enhance risk-stratification in BrS. In 2001, Ikeda et. al reported that 74% of a cohort of 33 patients with BrS had late potentials compared to 3% of age and sex matched controls [24]. Furthermore, those with late potentials were more likely to experience arrhythmias during follow up. These findings have been repeated in subsequent larger series, also associating late potentials with symptoms, inducible arrhythmias, and appropriate ICD discharges[7,25,26]. In our cohort as a whole comprising patients with multiple pathologies, similar proportions of patients with prior cardiac arrest were seen in those with late potentials pre- or post- Procainamide compared to those with no late potentials at any time. Whilst it would be useful to explore whether Procainamide-induced late potentials improve risk stratification in a pure BrS cohort, only a single patient with BrS in this study had a history of ventricular arrhythmias. It is therefore not possible to draw any solid conclusions regarding the prognostic value of Procainamide-induced late potentials in BrS.

Limitations

The majority of patients with BrS included in this study had a mild phenotype, potentially underestimating the differential effects of Procainamide that might have been seen had a cohort with a more severe phenotype been studied. However, similar results to the primary analysis were seen in the sensitivity analysis including patients with spontaneous Type 1 BrS ECG pattern during follow up, supporting the validity of our findings.

The cutoffs used to define late potentials are arguably arbitrary. The values are based on the distribution seen in healthy cohorts, values which vary according to the population studied and the recording equipment used[27]. The meaning of a small shift in value from one side of a binary cutoff to another could be questioned. However, the values we have used follow consensus definitions[16].

Other agents used for provocative testing such as Ajmaline and Flecainide have been shown to be more sensitive than Procainamide for identifying BrS and therefore may have led to better separation of groups and potentially had a greater effect on the SAECG[14]. However, a higher rate of false positives has been described with these agents, negating the benefits of greater sensitivity[9].

The cohort of patients used as controls, although having no apparent cardiac according to the investigations perfromed, included patients with a family history of arrhythmias. These patients could have had concealed forms of channelopathies, potentially masking a true difference between groups. Finally, this study had an adequate number of patients to detect large differences between those with BrS and those without, but small differences may have been missed due to a lack of statistical power.

Conclusions

Procainamide influences the signal-averaged ECG, increasing the fQRSd and LAS40, decreasing RMS40, and in a subset of patients shifting these values sufficiently to meet commonly accepted criteria for late potentials. Those with BrS exhibit a greater degree of Procainamide-induced fQRSd prolongation but wer no more likely to have Procainamide-induced late potentials. In a mixed cohort including patients with a mild phenotype of Brugada syndrome, identification of Procainamide-induced late potentials does not appear helpful as a marker for specific patient groups.

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Disclosures

The authors have no conflicts of interest to disclose.

Figures

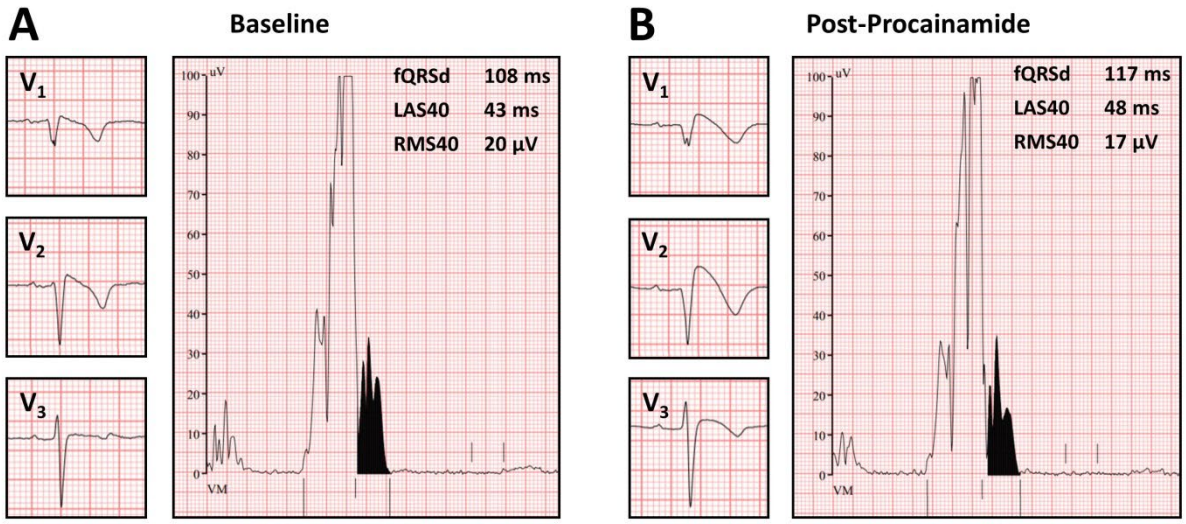

Figure 1 - Recordings from a 63 year-old South East Asian female with a positive Procainamide provocation test. 12-lead and signal averaged electrocardiogram recordings at (A) baseline and (B) following Procainamide infusion showing drug-induced Type 1 Brugada pattern and late potentials.

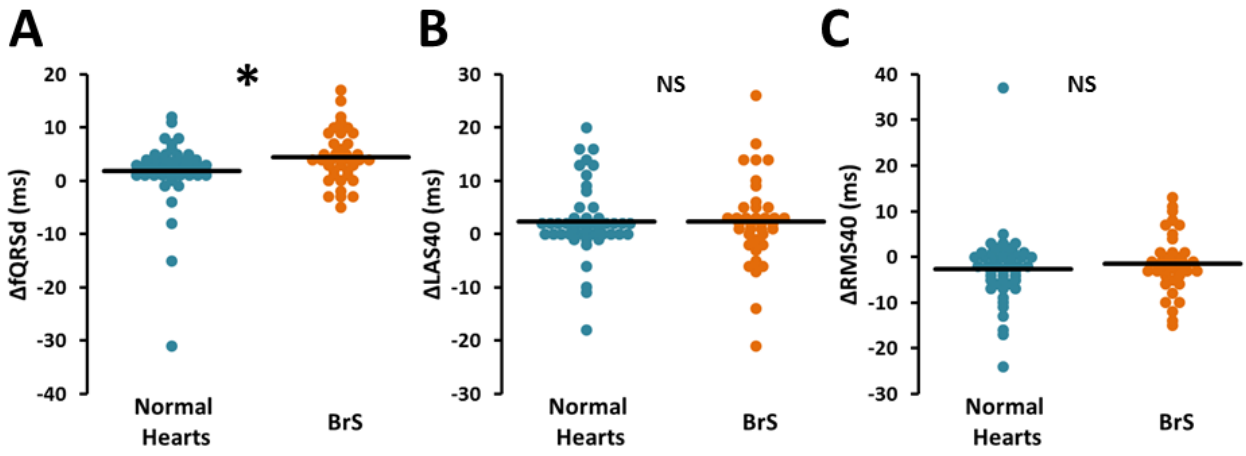

Figure 2 – Beeswarm plots showing effects of Procainamide on SAECG indices comparing those with normal hearts and Brugada syndrome. A – fQRSD, B LAS40, C – RMS40. * - $p<0.05$, NS - not significant, BrS – Brugada syndrome

Tables

Age (years)	44.5 ± 14.7
Male (n, %)	109/150 (72.7%)
Southeast asian (n, %)	32/150 (21.3%)
FHx of BrS (n, %)	16/150 (10.7%)
FHx of sudden death (n, %)	31/150 (20.7%)
Smoker (n, %)	22/128 (17.2%)
Coronary artery disease (n, %)	7/150 (4.7%)
Diabetes (n, %)	6/150 (4%)
Hypertension (n, %)	23/150 (15.3%)
Paroxysmal atrial fibrillation (n, %)	6/150 (4%)
LV ejection fraction (%)	60.5 ± 5.2
LGE on cMRI (n, %)	5/35 (14.3%)
BMI ($kg.m^{-2}$)	25 ± 4.2
Pacemaker (n, %)	1/150 (0.7%)
ICD (n, %)	25/150 (16.7%)
Palpitations (n, %)	28/150 (18.7%)
Pre-syncope (n, %)	22/150 (14.7%)
Syncope (n, %)	48/150 (32%)
Cardiac arrest (n, %)	25/150 (16.7%)
Genetic testing performed (n, %)	53/150 (35.3%)
***SCN5A* variant identified (n, %)**	7/53 (13.2%)
Path/LPath *SCN5A* variant identified (n, %)	5/53 (9.4%)
Non-SCN5A variant (n, %)	14/53 (26.4%)

Table 1 - Demographics of study participants. FHx – family history, BrS – Brugada syndrome, LV – left ventricle, BMI – body mass index, LGE – late gadolinium enhancement, cMRI – cardiac magnetic resonance imaging, ICD – implantable cardioverter defibrillator, Path/LPath – American College of Medical Geneticists grade pathogenic or likely pathogenic.

	Baseline	Post-Procainamide	p
SAECG			
Filtered QRS duration (ms)	118.8 ± 10.5	121.2 ± 10.2	**<0.001**
LAS40 (ms)	38.7 ± 9.8	40.2 ± 10.5	**0.005**
RMS40 (μV)	24.6 ± 12	22.8 ± 12	**0.002**
Abnormal parameters (n)	1.5 ± 1.2	1.7 ± 1.2	**<0.001**
2+ Abnormal parameters (n)	68/150 (45.3%)	77/150 (51.3%)	0.08
12 lead ECG			
Heart rate (min^{-1})	62.4 ± 9.8	70.3 ± 10.6	**<0.001**
PR interval (ms)	166.6 ± 24.4	177.8 ± 21.8	**<0.001**
QRS duration (ms)	97 ± 9.7	104.8 ± 12.8	**<0.001**
QT interval (ms)	405.6 ± 28.4	433.5 ± 33	**<0.001**
QTc (ms)	410.6 ± 26	465.6 ± 27.9	**<0.001**

290 **Table 2** – Effects of Procainamide on signal averaged and 12 lead ECGs.

	Normal heart (n=48)	BrS (n=38)	
	Mean ± SD	Mean ± SD	p
Signal Averaged ECG			
Baseline			
fQRSd (ms)	120.3 ± 10.4	123.8 ± 9	0.11
LAS40 (ms)	40.5 ± 9.2	41.9 ± 11.7	0.54
RMS40 (μV)	23.8 ± 12.1	20.3 ± 9.9	0.16
fQRSd >114ms (n)	32/48 (66.7%)	34/38 (89.5%)	**0.01**
LAS40 >38ms (n)	24/48 (50%)	21/38 (55.3%)	0.63
RMS40 <20μV (n)	21/48 (43.8%)	21/38 (55.3%)	0.29
LPs at baseline	21/48 (43.8%)	21/38 (55.3%)	0.28
Post-Procainamide			
fQRSd (ms)	120.3 ± 10.4	123.8 ± 9	0.11
LAS40 (ms)	40.5 ± 9.2	41.9 ± 11.7	0.54
RMS40 (mcV)	23.8 ± 12.1	20.3 ± 9.9	0.16
fQRSd >114ms (n)	32/48 (66.7%)	34/38 (89.5%)	**0.01**
LAS40 >38ms (n)	24/48 (50%)	21/38 (55.3%)	0.63
RMS40 <20mcV (n)	21/48 (43.8%)	21/38 (55.3%)	0.29
LPs post procainamide	24/48 (50%)	21/38 (55.3%)	0.54
Difference			
ΔfQRSd (ms)	1.8 ± 6.4	4.4 ± 5	**0.04**
ΔLAS40 (ms)	2.4 ± 6.8	2.4 ± 8.2	0.99
ΔRMS40 (mcV)	-2.6 ± 8.1	-1.4 ± 6.5	0.49
Induced LPs	4/27 (14.8%)	3/17 (17.6%)	0.80
12 Lead ECG			
Baseline			
Heart rate (min^{-1})	61.9 ± 10.3	64.2 ± 10.5	0.32
PR (ms)	166.5 ± 21.8	169.3 ± 22.9	0.57
QRS (ms)	94.9 ± 9.3	99.8 ± 9.8	**0.02**
QT (ms)	404.5 ± 28.1	401.6 ± 28.5	0.64
QTc (ms)	407.5 ± 26.4	411.7 ± 23.3	0.45

Post-Procainamide			
Heart rate (min^{-1})	68.9 ± 9.6	72.5 ± 12.9	0.14
PR (ms)	176.2 ± 23.5	179.8 ± 20.4	0.45
QRS (ms)	102.1 ± 9.2	109.4 ± 15.6	**0.01**
QT (ms)	429 ± 30.4	438.1 ± 40.7	0.24
QTc (ms)	456.5 ± 27.2	476.1 ± 27.2	**<0.01**
Difference			
ΔHR (min^{-1})	7 ± 7.2	8.3 ± 6.8	0.39
ΔPR (ms)	9.6 ± 13.1	10.5 ± 13.5	0.75
ΔQRS (ms)	7.3 ± 5.5	9.5 ± 12.5	0.26
ΔQT (ms)	24.5 ± 23.3	36.5 ± 19.8	**0.01**
ΔQTc (ms)	49 ± 21.9	64.4 ± 22.9	**<0.01**

Table 3– Changes in signal averaged and 12 lead ECGs stratified by patient group. LPs – late potentials.

	No LPs	LPs at baseline		LPs post Procainamide		Induced LPs	
		Mean ± SD or n	p	Mean ± SD or n	p	Mean ± SD or n	p
Age (years)	43 ± 15.3	45.4 ± 13.4	0.33	46.1 ± 14.4	0.21	46.8 ± 17.5	0.4
Male (n)	42/67 (62.7%)	56/68 (82.4%)	**0.01**	61/77 (79.2%)	**0.03**	11/15 (73.3%)	0.44
Coronary artery disease (n)	2/67 (3%)	4/68 (5.9%)	0.41	5/77 (6.5%)	0.33	1/15 (6.7%)	0.49
Brugada syndrome (n)	14/67 (20.9%)	21/68 (30.9%)	0.16	21/77 (27.2%)	0.34	3/15 (20%)	0.95
Cardiac arrest (n)	14/67 (20.9%)	8/68 (11.8%)	0.15	10/77 (13%)	0.2	3/15 (20%)	0.94
EF (%)	60 ± 4.9	61.2 ± 4.4	0.19	60.8 ± 5.5	0.39	60 ± 8.5	0.98
EF <55% (n)	5/55 (9.1%)	2/46 (4.3%)	0.35	4/55 (7.3%)	0.73	2/12 (16.7%)	0.44
LGE on cMRI (n)	4/17 (23.5%)	1/15 (6.7%)	0.19	1/18 (5.6%)	0.13	0/3 (0%)	0.35
Any *SCN5A* variant (n)	3/23 (13%)	2/24 (8.3%)	0.6	3/27 (11.1%)	0.83	2/6 (33.3%)	0.24
Path or LPath *SCN5A* variant (n)	3/23 (13%)	1/24 (4.2%)	0.28	1/27 (3.7%)	0.23	1/6 (16.7%)	0.82
Non-SCN5A variant (n)	7/23 (30.4%)	6/24 (25%)	0.68	6/27 (22.2%)	0.51	1/6 (16.7%)	0.5

295 **Table 3** – Patient characteristics stratified by presence of late potentials. LGE – late gadolinium enhancement, cMRI – cardiac magnetic resonance imaging, LPs – late potentials, Path – pathogenic, LPath – likely pathogenic.

References

1. Brugada J, Campuzano O, Arbelo E, Sarquella-Brugada G, Brugada R. Present Status of Brugada Syndrome: JACC State-of-the-Art Review. *Journal of the American College of Cardiology.* 2018;72(9):1046-1059.
2. Cerrone M, Remme CA, Tadros R, Bezzina CR, Delmar M. Beyond the One Gene-One Disease Paradigm: Complex Genetics and Pleiotropy in Inheritable Cardiac Disorders. *Circulation.* 2019;140(7):595-610.
3. Pearman CM, Denham NC, Mills RW, Ding WY, Modi SS, Hall MCS, Todd DM, Mahida S. Relationship between sodium channel function and clinical phenotype in SCN5A variants associated with Brugada syndrome. *Human mutation.* 2020;41(12):2195-2204.
4. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck KH, Hernandez-Madrid A, Nikolaou N, Norekval TM, Spaulding C, Van Veldhuisen DJ. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *European heart journal.* 2015;36(41):2793-2867.
5. Priori SG, Napolitano C, Gasparini M, Pappone C, Della Bella P, Giordano U, Bloise R, Giustetto C, De Nardis R, Grillo M, Ronchetti E, Faggiano G, Nastoli J. Natural history of Brugada syndrome: insights for risk stratification and management. *Circulation.* 2002;105(11):1342-1347.
6. Adler A, Rosso R, Chorin E, Havakuk O, Antzelevitch C, Viskin S. Risk stratification in Brugada syndrome: Clinical characteristics, electrocardiographic parameters, and auxiliary testing. *Heart rhythm : the official journal of the Heart Rhythm Society.* 2016;13(1):299-310.
7. Huang Z, Patel C, Li W, Xie Q, Wu R, Zhang L, Tang R, Wan X, Ma Y, Zhen W, Gao L, Yan GX. Role of signal-averaged electrocardiograms in arrhythmic risk stratification of patients with Brugada syndrome: a prospective study. *Heart rhythm : the official journal of the Heart Rhythm Society.* 2009;6(8):1156-1162.
8. Antzelevitch C, Patocskai B. Brugada Syndrome: Clinical, Genetic, Molecular, Cellular, and Ionic Aspects. *Current problems in cardiology.* 2016;41(1):7-57.
9. Behr ER, Ben-Haim Y, Ackerman MJ, Krahn AD, Wilde AAM. Brugada syndrome and reduced right ventricular outflow tract conduction reserve: a final common pathway? *European heart journal.* 2021.
10. Krahn AD, Healey JS, Chauhan V, Birnie DH, Simpson CS, Champagne J, Gardner M, Sanatani S, Exner DV, Klein GJ, Yee R, Skanes AC, Gula LJ, Gollob MH. Systematic assessment of patients with unexplained cardiac arrest: Cardiac Arrest Survivors With Preserved Ejection Fraction Registry (CASPER). *Circulation.* 2009;120(4):278-285.
11. Gatzoulis KA, Carlson MD, Biblo LA, Rizos I, Gialafos J, Toutouzas P, Waldo AL. Time domain analysis of the signal averaged electrocardiogram in patients with a conduction defect or a bundle branch block. *European heart journal.* 1995;16(12):1912-1919.
12. Denham NC, Pearman CM, Ding WY, Waktare J, Gupta D, Snowdon R, Hall M, Cooper R, Modi S, Todd D, Mahida S. Systematic re-evaluation of SCN5A variants associated with Brugada syndrome. *Journal of cardiovascular electrophysiology.* 2018.
13. Somani R, Krahn AD, Healey JS, Chauhan VS, Birnie DH, Champagne J, Sanatani S, Angaran P, Gow RM, Chakrabarti S, Gerull B, Yee R, Skanes AC, Gula LJ, Leong-Sit P, Klein GJ, Gollob MH, Talajic M, Gardner M, Simpson CS. Procainamide infusion in the evaluation of unexplained

cardiac arrest: from the Cardiac Arrest Survivors with Preserved Ejection Fraction Registry (CASPER). *Heart rhythm : the official journal of the Heart Rhythm Society.* 2014;11(6):1047-1054.

14. Cheung CC, Mellor G, Deyell MW, Ensam B, Batchvarov V, Papadakis M, Roberts JD, Leather R, Sanatani S, Healey JS, Chauhan VS, Birnie DH, Champagne J, Angaran P, Klein GJ, Yee R, Simpson CS, Talajic M, Gardner M, Yeung-Lai-Wah JA, Chakrabarti S, Laksman ZW, Sharma S, Behr ER, Krahn AD. Comparison of Ajmaline and Procainamide Provocation Tests in the Diagnosis of Brugada Syndrome. *JACC Clinical electrophysiology.* 2019;5(4):504-512.
15. Antzelevitch C, Yan GX, Ackerman MJ, Borggrefe M, Corrado D, Guo J, Gussak I, Hasdemir C, Horie M, Huikuri H, Ma C, Morita H, Nam GB, Sacher F, Shimizu W, Viskin S, Wilde AA. J-Wave syndromes expert consensus conference report: Emerging concepts and gaps in knowledge. *Heart rhythm : the official journal of the Heart Rhythm Society.* 2016;13(10):e295-324.
16. Breithardt G, Cain ME, el-Sherif N, Flowers N, Hombach V, Janse M, Simson MB, Steinbeck G. Standards for analysis of ventricular late potentials using high resolution or signal-averaged electrocardiography. A statement by a Task Force Committee between the European Society of Cardiology, the American Heart Association and the American College of Cardiology. *European heart journal.* 1991;12(4):473-480.
17. el-Sherif N, Gomes JA, Restivo M, Mehra R. Late potentials and arrhythmogenesis. *Pacing and clinical electrophysiology : PACE.* 1985;8(3 Pt 1):440-462.
18. Catalano O, Antonaci S, Moro G, Mussida M, Frascaroli M, Baldi M, Cobelli F, Baiardi P, Nastoli J, Bloise R, Monteforte N, Napolitano C, Priori SG. Magnetic resonance investigations in Brugada syndrome reveal unexpectedly high rate of structural abnormalities. *European heart journal.* 2009;30(18):2241-2248.
19. Nagase S, Kusano KF, Morita H, Fujimoto Y, Kakishita M, Nakamura K, Emori T, Matsubara H, Ohe T. Epicardial electrogram of the right ventricular outflow tract in patients with the Brugada syndrome: using the epicardial lead. *Journal of the American College of Cardiology.* 2002;39(12):1992-1995.
20. Nademanee K, Veerakul G, Chandanamattha P, Chaothawee L, Ariyachaipanich A, Jirasirirojanakorn K, Likittanasombat K, Bhuripanyo K, Ngarmukos T. Prevention of ventricular fibrillation episodes in Brugada syndrome by catheter ablation over the anterior right ventricular outflow tract epicardium. *Circulation.* 2011;123(12):1270-1279.
21. Szél T, Antzelevitch C. Abnormal repolarization as the basis for late potentials and fractionated electrograms recorded from epicardium in experimental models of Brugada syndrome. *Journal of the American College of Cardiology.* 2014;63(19):2037-2045.
22. Kulakowski P, Bashir Y, Heald S, Paul V, Anderson MH, Gibson S, Malik M, Camm AJ. Prediction of antiarrhythmic efficacy of class I and III agents in patients with ventricular tachycardia by signal-averaged ECG analysis. *Pacing and clinical electrophysiology : PACE.* 1992;15(11 Pt 2):2116-2121.
23. de Langen CD, Hanich RF, Michelson EL, Kadish AH, Levine JH, Balke CW, Spear JF, Moore EN. Differential effects of procainamide, lidocaine and acetylstrophanthidin on body surface potentials and epicardial conduction in dogs with chronic myocardial infarction. *Journal of the American College of Cardiology.* 1988;11(2):403-413.
24. Ikeda T, Sakurada H, Sakabe K, Sakata T, Takami M, Tezuka N, Nakae T, Noro M, Enjoji Y, Tejima T, Sugi K, Yamaguchi T. Assessment of noninvasive markers in identifying patients at risk in the Brugada syndrome: insight into risk stratification. *Journal of the American College of Cardiology.* 2001;37(6):1628-1634.
25. Ciconte G, Santinelli V, Vicedomini G, Borrelli V, Monasky MM, Micaglio E, Giannelli L, Negro G, Giordano F, Mecarocci V, Mazza BC, Locati E, Anastasia L, Calovic Z, Pappone C. Non-invasive assessment of the arrhythmogenic substrate in Brugada syndrome using signal-averaged

electrocardiogram: clinical implications from a prospective clinical trial. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology.* 2019;21(12):1900-1910.

26. Ajiro Y, Hagiwara N, Kasanuki H. Assessment of markers for identifying patients at risk for life-threatening arrhythmic events in Brugada syndrome. *Journal of cardiovascular electrophysiology.* 2005;16(1):45-51.

27. Marcus FI, Zareba W, Sherrill D. Evaluation of the normal values for signal-averaged electrocardiogram. *Journal of cardiovascular electrophysiology.* 2007;18(2):231-233.