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Safety, Utility, and Outcomes of Procainamide Challenge for the Diagnosis and Exclusion of Brugada Syndrome

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BACKGROUND: The safety, yield, and prognosis of a type 1 procainamide-induced Brugada pattern are incompletely understood and may differ from those of other sodium channel blockers with greater potencies.

METHODS: The safety of procainamide infusion and yield of a type 1 Brugada pattern were assessed according to indication in consecutive patients from the Canadian Hearts in Rhythm Organization registry. Outcomes were evaluated in patients with a standard or high-lead procainamide-induced Brugada pattern (without previous cardiac arrest) and compared with those with a spontaneous type 1 pattern.

RESULTS: In 947 consecutive patients undergoing procainamide infusion for the diagnosis or exclusion of Brugada syndrome, 2 patients (0.2%) experienced asymptomatic ventricular arrhythmias related to procainamide, which resolved upon discontinuation of the infusion. The yield of a type 1 pattern was 7.2% in 390 patients with unexplained cardiac arrest, 22.2% in 135 patients with a family history of Brugada syndrome, and 6.9% in 116 patients with a family history of unexplained cardiac arrest or sudden death. Test yield was 46.6% in 189 patients with a non-specific type 2 or 3 Brugada pattern and 92% in those with an intermittent spontaneous type 1 pattern (ie, implied sensitivity of 92%). Estimated specificity was very high. In 137 patients with a procainamide-induced type 1 Brugada pattern (with no previous cardiac arrest) followed for a mean of 5.9±4.5 years, no patients met the primary composite arrhythmic end point (0%). In 105 spontaneous type 1 patients, one patient (1%) met the primary end point after receiving appropriate shocks for ventricular fibrillation. Thirteen percent had a primary prevention implantable cardioverter defibrillator implanted at baseline (one appropriate shock), with an additional 7% undergoing implantable cardioverter defibrillator implantation during follow-up, predominantly for syncope with a suspected arrhythmic mechanism. No patient who underwent implantable cardioverter defibrillator implantation during follow-up subsequently received appropriate therapy.

CONCLUSIONS: Procainamide infusion is extremely safe for the diagnosis and exclusion of Brugada syndrome, with yield dependent on pretest probability and indication for testing. Estimated sensitivity and specificity appear to be high. Patients with an asymptomatic procainamide-induced type 1 Brugada pattern are at very low risk of malignant ventricular arrhythmias.

Key Words: Brugada syndrome ■ procainamide ■ prognosis ■ safety ■ sudden death

Sodium channel blockade (SCB) is routinely used for the diagnosis or exclusion of Brugada syndrome (BrS) in the absence of a spontaneous type 1 ECG pattern.[1,2] Clinical suspicion of BrS may arise after an unexplained cardiac arrest (UCA), for those with a significant family history (of BrS, UCA, or

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Clinical Perspective

What Is New?

- Procainamide challenge is extremely safe for the diagnosis and exclusion of Brugada syndrome, with yield dependent on indication and pretest probability.
- The estimated sensitivity of procainamide challenge for the diagnosis of Brugada syndrome appears to be high and the estimated specificity very high.
- Asymptomatic patients with a procainamide-induced type 1 Brugada pattern are at very low risk of malignant ventricular arrhythmias.

What Are the Clinical Implications?

- Clinicians in North America using procainamide challenge for the diagnosis of Brugada syndrome may use these data to counsel patients on the safety of procainamide challenge and probability of a positive result.
- Procainamide-induced type 1 Brugada patterns are very likely to represent a true positive (compared with a significant rate of false positives with ajmaline). Conversely, a small proportion of negative challenges may be false negatives.
- Lifestyle advice and reassurance are appropriate in asymptomatic patients with a procainamide-induced type 1 Brugada pattern.

Nonstandard Abbreviations and Acronyms

BrS	Brugada syndrome
HiRO	Hearts in Rhythm Organization
HLECG	high leads electrocardiogram
SCB	sodium channel blockade
SCD	sudden cardiac death
UCA	unexplained cardiac arrest
VA	ventricular arrhythmias

sudden cardiac death [SCD]), or for an individual with a suggestive but nondiagnostic ECG or arrhythmogenic syncope.[2,3] The relative yield of SCB is dependent on the pretest probability in each of these settings.[4–11] Typically, a drug-induced type 1 Brugada pattern requires the presence of another clinical factor to be considered BrS (hereafter, "drug-induced Brugada pattern" specifically refers to a type 1 pattern).[1] Outcomes of a drug-induced Brugada pattern, particularly in the absence of arrhythmogenic syncope or previous UCA, are favorable with a very low risk of future malignant ventricular arrhythmia (VA).[12–14] SCB carries a small risk of inducing a malignant VA, which may in itself be prognostic.[15,16]

The type of SCB available varies globally by region, and in the absence of a gold-standard test for BrS, diagnostic yield will depend on the relative potency of the SCB used. Ajmaline (and, to a lesser extent, flecainide and pilsicainide) is significantly more likely to provoke a type 1 pattern than procainamide, the primary SCB used in North America.[2,3,5,6,8] Limited literature exists describing the safety and yield of procainamide challenge for suspected BrS,[4,6] and indeed, the prognosis of a procainamide-induced Brugada pattern has never been studied. Given that procainamide is less sensitive but more specific than ajmaline, the safety, yield, and prognosis of a drug-induced Brugada pattern may differ between these agents. We therefore evaluated: (1) the safety and yield of procainamide infusion for the diagnosis and exclusion of BrS in the Canadian Hearts in Rhythm Organization (HiRO) registry, and (2) outcomes in patients with a procainamide-induced type 1 Brugada pattern compared with those with a spontaneous type 1 ECG.

METHODS

Registry Data and Ethics

Study participants were recruited from the HiRO registry. This registry enrolls patients with inherited arrhythmia syndromes and cardiomyopathies, as well as their first-degree relatives, from 25 inherited arrhythmia centers.[17] All patients referred to and reviewed in these 25 centers, as well as their first-degree relatives, are invited to participate and are eligible if willing to provide consent for health record information sharing. Eligible diagnoses for inclusion in the HiRO registry are listed in Table S1. Ethics approval was obtained from the University of British Columbia and Providence Health Care research boards. All participants provided written informed consent. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Patient Selection and Data Collection

The study cohort for part A comprised all consecutive patients in the HiRO registry from 2004 to 2024 who received procainamide infusion for the diagnosis or exclusion of BrS. A subset of 174 patients has been previously reported in the CASPER (Cardiac Arrest Survivors with Preserved Ejection Fraction Registry) study of procainamide infusion for the investigation of UCA.[4] The study cohort for part B comprised consecutive HiRO patients with either a procainamide-induced type 1 Brugada pattern at diagnosis or spontaneous type 1 ECG at diagnosis (comparator group), with at least 6 months follow-up, excluding those who presented with cardiac arrest. Patients with a fever-induced type 1 Brugada pattern were excluded from part B, as the primary aim was to assess prognosis in patients with a procainamide-induced Brugada pattern, and the prognosis of fever-induced Brugada patterns is less well established than for spontaneous type 1 patients (as a comparator group).[18]

The results of the baseline and high-lead ECG (HLECG) were classified as normal or type 1 or type 2/3 Brugada pattern. Standard definitions of Brugada ECG patterns were used.[1,19] All patients underwent clinical evaluation, including transthoracic echocardiography to exclude structural heart disease. Baseline data collection included demographics,

clinical history, family history, cardiac investigations, and SCN5A status. UCA was defined as cardiac arrest with sustained VA requiring defibrillation, with initial investigations nonrevealing (including ECG, echocardiography, and coronary imaging).[20]

Sodium Channel Blockade

All Canadian sites used a standard SCB challenge protocol.[4] Procainamide was infused through a peripheral intravenous line with continuous ECG monitoring at a dose of 15 mg/kg (maximum dose, 1000 mg) at 50 mg/min. In contrast to previous studies, which administered a dose of 10 mg/kg at 100 mg/min, the infusion protocol was adapted to comply with the product monograph in Canada. By doing so, a higher total dose was administered at a slower rate, thereby enhancing sensitivity.[4] Standard 12-lead ECG and HLECG were performed at baseline and at 10-minute intervals during infusion, then at 30-minute intervals for 1 hour after completion of the infusion. The results of the procainamide challenge were considered positive with the provocation of a type 1 Brugada ECG pattern in ≥1 lead in either the standard or HLECG positions.[1,19] The infusion was terminated if a type 1 Brugada ECG pattern was provoked, the QRS duration increased by ≥130%, premature ventricular contractions or VAs developed, or any significant side effects were noted. Isoproterenol reversal was administered at the discretion of the supervising clinician.

The primary indication for procainamide testing was classified by the supervising physician as known BrS (intermittent spontaneous type 1 ECG), UCA, family history of BrS, family history of UCA or sudden death, or nonspecific type 2 or 3 Brugada pattern ECG or symptoms (eg, suspected arrhythmogenic syncope). In those with a primary indication defined as a nonspecific type 2 or 3 Brugada pattern, no other indication was specified in the database (such as family history of BrS or SCD). The yield of a type 1 ECG was recorded for each indication. Significant side effects were recorded and categorized as cardiac (arrhythmic) or noncardiac.

Management of Patients With BrS Without a History of Cardiac Arrest

All patients with BrS (and those with a type 1 drug-induced Brugada pattern) received lifestyle advice, including avoiding drugs with SCB properties, treating fever aggressively, avoiding heavy alcohol intake, and avoiding heavy carbohydrate meals before bed. Patients with asymptomatic spontaneous type 1 BrS were generally followed at closer intervals than patients with a procainamide-induced Brugada pattern (eg, yearly compared with alternating years). Primary prevention implantable cardioverter defibrillators (ICDs; alternatively, implantable loop recorders) were considered in a minority of patients at the discretion of the treating clinician, particularly in the setting of suspected arrhythmogenic syncope or rarely in the context of other risk factors.[1,19] Electrophysiology study was not routine and was seldom performed in intermediate-risk patients as a tiebreaker at the physician's discretion. ICD programming at the time of implantation changed over time, with the ventricular fibrillation detection rate increasing from 180 bpm to >200 bpm as well as longer detection intervals, in accordance with guidelines.[21]

Follow-Up and Outcomes

Patients with a procainamide-induced Brugada pattern at diagnosis and no previous cardiac arrest were entered into part B of the study and compared with patients with a spontaneous type 1 ECG at diagnosis. The primary outcome in part B of the study was a composite arrhythmic outcome, including SCD, UCA, appropriate ICD therapy (shocks or antitachycardia pacing), and sustained VA. The secondary outcome was all-cause death. Patients with ICDs were generally seen every 6 months (or yearly with remote monitoring), whereas those without a device were generally seen every 1 to 2 years in the clinic. Follow-up included clinical assessment, ECG, HLECG, Holter monitor, and device interrogation if applicable.

Sensitivity and Specificity Calculations

The sensitivity of procainamide challenge for the diagnosis of BrS was calculated using the gold standard of an intermittent spontaneous type 1 ECG pattern.[22,23] A precise calculation for specificity was not possible in the absence of a true gold standard, but an estimate for specificity was generated by considering specific clinical scenarios whereby a "false positive" was either proven or deemed likely (assuming that all negative procainamide challenges who were not found to have a spontaneous type 1 ECG during follow-up were true negatives). These clinical scenarios included: (1) inducible type 1 pattern in an individual with a family history of SCD or UCA in which the proband was found to have an alternative diagnosis to BrS, (2) an inducible type 1 pattern in a patient with UCA who was later found to have an alternative explanatory diagnosis to BrS, and (3) an inducible type 1 pattern in an individual with a family history of BrS in which other family members carried a pathogenic SCN5A variant, but the inducible individual did not carry this variant.

Statistical Analysis

Statistical analysis was performed using SPSS version 29.0.2.0. Continuous variables are presented as mean±SD and categorical variables as frequency with percentage. Comparisons between groups were performed using either the chi-square or *t* test. $P<0.05$ was considered statistically significant. Kaplan-Meier survival curves were constructed for freedom from the primary outcome, with significance between groups assessed via log-rank test.

RESULTS

Yield of Procainamide Infusion

A total of 947 HiRO patients underwent procainamide infusion for the diagnosis or exclusion of BrS. The mean age at procainamide infusion was 42.0±15.2 years, with 65% of patients being men. Ethnicity was reported as White in 59.2%, Asian in 20.2%, and other/unknown in 20.6% (see Appendix). A pathogenic SCN5A variant was identified in 41 patients. Genetic testing was performed in 154 of 215 patients with an inducible type 1 Brugada pattern, with 19% (30 of 154) found to have a pathogenic SCN5A variant. An additional 11 patients

with negative procainamide challenges were found to have pathogenic SCN5A variants (of 334 who underwent genetic testing, either family specific, targeted, or comprehensive, depending on the indication). Specific SCN5A pathogenic variants identified are listed in Table S2.

The indications for procainamide challenge and results are listed in Table 1. Of the 390 patients with UCA referred for procainamide challenge, 28 developed a type 1 ECG (7.2%). Of the 116 patients referred for a family history of UCA or SCD, 8 developed a type 1 ECG (6.9%); the diagnosis of the affected relative was confirmed to be BrS in one patient but could not be confirmed in the other 7 patients. There was no difference in type 1 inducibility between patients with a type 2 or 3 Brugada pattern, for which this was listed as the primary indication for testing (P=0.09).

The yield across all patients with a pathogenic SCN5A variant for a type 1 ECG was 73% (30 of 41). Of the 135 patients referred with a family history of BrS, 16 patients were SCN5A positive, and 12 of 16 demonstrated a type 1 pattern (8 probands proven to be SCN5A positive). Of 119 patients with a family history of BrS who did not have a pathogenic SCN5A variant themselves, 18 were inducible for a type 1 Brugada pattern (15%). Of these 18 patients with an inducible type 1 pattern, one family member proband was known to have a pathogenic SCN5A variant (despite the patient themselves not carrying this variant).

Eleven of the 13 patients with a known intermittent spontaneous type 1 pattern before procainamide challenge were inducible for a type 1 pattern. The indication for testing was: (1) not specified, (2) to confirm inducibility with standard leads after a spontaneous type 1 pattern was observed in HLECG, or (3) attributable to a "borderline type 1 pattern" that was subsequently deemed diagnostic on review. An additional 12 patients with a procainamide-induced type 1 Brugada pattern were documented to have an intermittent spontaneous type 1 pattern during follow-up so that the sensitivity of procainamide challenge in those with an intermittent spontaneous type 1 pattern was 92% (23 of 25 positive). No patient with a negative procainamide challenge was documented to have a spontaneous type 1 pattern during follow-up. With respect to follow-up of procainamide-negative patients, 96% of all patients with previous UCA were followed for ≥6 months (mean, 8.3±5.2 years; seen every 6 months), whereas 72% of those with no previous UCA were followed for ≥6 months (mean, 6.0±4.4 years; seen every 2 to 3 years).

An example of a procainamide-induced type 1 ECG is displayed in Figure 1.

Safety of Procainamide Infusion

Asymptomatic VAs requiring intervention occurred in 2 patients (0.2%). In the first patient, a long run of polymorphic ventricular tachycardia (VT) occurred in a 69-year-old woman with UCA and a type 2 Brugada pattern ECG. The test was positive for a type 1 pattern, and the patient was later found to have a pathogenic SCN5A variant. The infusion was stopped, and the arrhythmia resolved without active intervention. In the second patient, repetitive nonsustained monomorphic VT was observed in a 66-year-old man with UCA, requiring termination of the infusion. The test was negative for a type 1 pattern, and the diagnosis remained UCA. Neither patient required defibrillation during the procainamide challenge, and during follow-up, neither patient received appropriate ICD therapy. Significant noncardiac adverse effects requiring termination of the infusion were observed in 4 patients (0.4%). These included severe nausea, blurred vision and chest pressure, nausea with emesis and paresthesia, and finally nausea with presyncope and hypotension.

Outcomes in Patients With Procainamide-Induced and Spontaneous BrS

A total of 137 patients with a procainamide-induced Brugada pattern and 105 patients with a spontaneous type 1 pattern with no previous history of cardiac arrest were

Table 1. Yield of Inducible Type 1 Brugada Pattern ECG According to Primary Indication for Procainamide Challenge

Indication for test	Number	Negative	Positive
Known BrS (type 1 ECG)	13	2 (15.4%)	11 (84.6%)
UCA	390	362 (92.8%)	28 (7.2%)
Family history of BrS	135	105 (77.8%)	30 (22.2%)
Family history of UCA or SCD	116	108 (93.1%)	8 (6.9%)
Type 2 or 3 Brugada ECG	189	101 (53.4%)	88 (46.6%)
Symptoms*	88	41 (46.6%)	47 (53.4%)
Other	16	13 (81.3%)	3 (18.8%)

BrS indicates Brugada syndrome; SCD, sudden cardiac death; and UCA, unexplained cardiac arrest.
*Including syncope, presyncope, or palpitations with clinical suspicion of BrS.

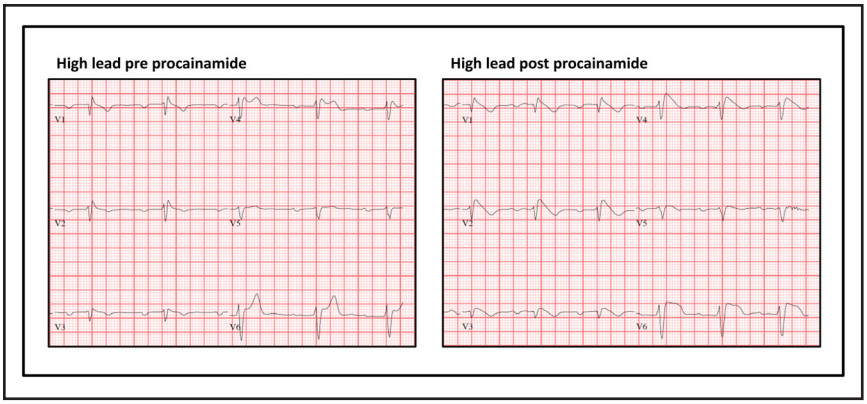

Figure 1. Procainamide-induced type 1 Brugada pattern.
High-lead ECG positioning before and after infusion is depicted.

included for analysis. Baseline characteristics are listed in Table 2; there were no significant differences between groups, except for slightly more men in the spontaneous group (*P*=0.04). ICDs were implanted at baseline in 15 procainamide-induced and 16 spontaneous patients (10.9% versus 15.2%, *P*=0.32), predominantly because of a history of syncope with suspected arrhythmic mechanism (see Table S3 for ICD indications). An electrophysiology study was performed in 10 patients with a procainamide-induced Brugada pattern (3 inducible) and 7 patients with a spontaneous type 1 pattern (2 inducible).

Over a mean follow-up of 5.9±4.5 years after diagnosis, 0 patients (0%) in the procainamide-induced Brugada pattern group and one patient (1%) in the spontaneous type 1 group met the primary composite arrhythmic outcome. The procainamide-induced and spontaneous type 1 Brugada pattern groups contributed 771 and 639 patient-years, respectively, to follow-up. Kaplan-Meier curves depicting survival free of the primary outcome are shown in Figure 2. The mean age at last follow-up was 55.8±15.5 years.

The primary outcome event in the spontaneous group occurred in a 28-year-old woman who presented with severe presyncope and a spontaneous type 1 ECG pattern, with a pathogenic SCN5A variant. An ICD was implanted, and she received appropriate shocks for ventricular fibrillation 6 months later, managed with quinidine. Two other spontaneous type 1 patients presented with wide-complex tachycardias during follow up, deemed unrelated to BrS. The first patient was a 63-year-old man with idiopathic posteromedial papillary muscle VT, which was ablated. The second patient received antitachycardia pacing from his single chamber primary prevention ICD at 51 years of age (10 years after BrS diagnosis), deemed most likely supraventricular in origin, but refused an electrophysiology study.

ICDs were implanted in 10 patients in the procainamide-induced group and 6 patients in the spontaneous group during follow-up (7.3% versus 5.7%, *P*=0.62), primarily because of syncope with suspected arrhythmic mechanism (Table S3). No patient who received an ICD during follow-up subsequently received appropriate therapy.

Table 2. Baseline Characteristics of Study Populations

Characteristic	Procainamide-induced (n=137)	Spontaneous (n=105)	*P* value
Age at diagnosis	47.5±14.2	48.9±16.0	0.47
Sex (male)	98 (71.5%)	87 (82.9%)	0.04
Race and ethnicity			
Caucasian	58 (42.3%)	50 (47.6%)	0.67
Asian	50 (36.5%)	33 (31.4%)	0.68
Other/unknown*	29 (21.2%)	22 (21.0%)	…
Genotyping	112 (81.8%)	93 (88.6%)	0.14
SCN5A variant (P/LP)	26 (19.0%)	15 (14.3%)	0.33
History of syncope	22 (16.1%)	19 (18.1%)	0.68
Family history			
BrS	19 (13.9%)	8 (7.6%)	0.13
SCD <40 years of age	9 (6.6%)	4 (3.8%)	0.35
ICD at baseline	15 (10.9%)	16 (15.2%)	0.32
ILR	13 (9.5%)	12 (11.4%)	0.62

BrS indicates Brugada syndrome; ICD, implantable cardioverter defibrillator; ILR, implantable loop recorder; P/LP, pathogenic/likely pathogenic; and SCD, sudden cardiac death.
*Other indicates Black, Latin American, or unknown.

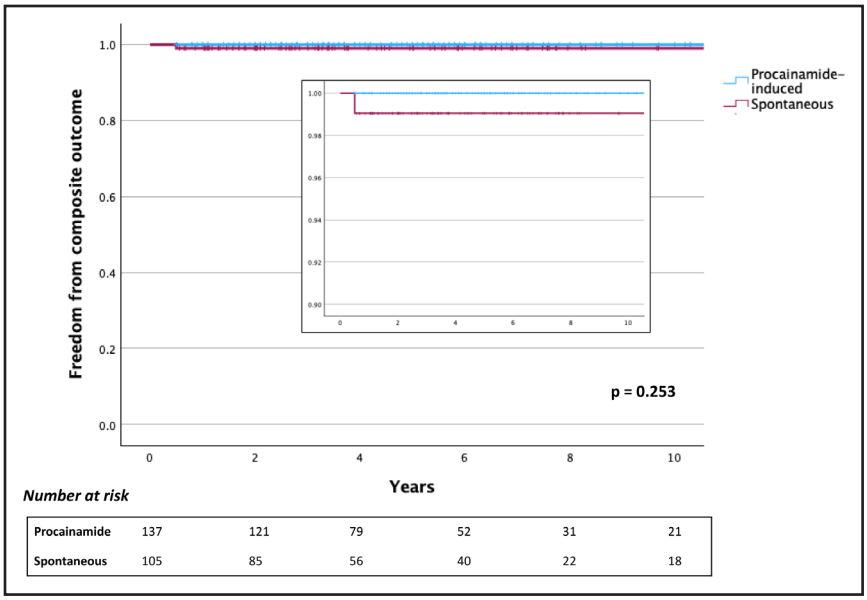

Figure 2. Kaplan-Meier survival curves for patients with a procainamide-induced Brugada pattern and spontaneous type 1 pattern.
Survival free from composite arrhythmic outcome is displayed (sudden cardiac death, cardiac arrest, appropriate implantable cardioverter defibrillator therapy, and sustained ventricular arrhythmia). The inset depicts the same survival curves with abbreviated *y* axis range (0.9–1.0).

Recurrent syncope occurred in 2 of 33 patients with ICDs implanted for syncope, with no logged arrhythmias. Syncope occurred in 6 of 25 patients with an implantable loop recorder, also with no logged arrhythmias.

Of the 370 procainamide-negative patients with no previous UCA, 72% were followed ≥6 months, with 2 patients meeting the composite arrhythmic outcome (first-degree relative of a patient with SCD who had UCA and a patient with syncope later diagnosed with arrhythmogenic right ventricular cardiomyopathy who received appropriate shocks). Of the 362 procainamide-negative patients who had previous UCA, 346 were followed ≥6 months, with 21% meeting the composite arrhythmic outcome. This was not significantly different from patients with an inducible type 1 Brugada pattern and previous cardiac arrest (29% met the composite arrhythmic outcome, *P*=0.32 versus procainamide-negative patients with UCA).

Deaths

No deaths occurred in the spontaneous BrS group during the follow-up period. Two deaths occurred in the procainamide-induced group, deemed unrelated to BrS (Appendix). No deaths were documented in the procainamide-negative group with no previous UCA. Five deaths occurred in the procainamide-negative group with previous UCA, and 2 deaths in the procainamide-positive group with previous cardiac arrest.

DISCUSSION

This study reports the safety and utility of procainamide infusion for the diagnosis and exclusion of BrS (Figure 3). Procainamide is the predominant sodium channel blocker used in North America, and with significant differences in potency, extrapolation of results from other sodium channel blockers should not be assumed. The main findings were as follows.

(1) Procainamide infusion for the diagnosis and exclusion of BrS is extremely safe.
(2) Yield is dependent on indication and pretest probability.
(3) Estimated sensitivity of procainamide challenge for the diagnosis of BrS is high and estimated specificity very high.
(4) Patients with a procainamide-induced type 1 Brugada pattern are at very low risk of malignant VA.
(5) Relatively conservative use of ICDs without systematic electrophysiology study risk stratification resulted in no SCDs or cardiac arrests.

Yield of Procainamide Infusion With Respect to Indication

Our study expands upon the 174 UCA patients previously reported from the CASPER registry[4] and supports the use of SCB in this context, with a 7.2% yield of a type 1 pattern. The diagnosis of BrS in an UCA survivor has important implications for individualized therapy and familial screening. A type 1 yield of 10% to 20% has been reported with other SCBs (predominantly ajmaline) in UCA and likely includes a significant false positive rate; however, these diagnoses are rarely questioned.[3,5,9] Tadros et al found that positive ajmaline results were confounding in up to 8% of families investigated for UCA or sudden death, for which an alternative diagnosis was deemed more probable.[9]

BrS demonstrates a complex and often polygenic inheritance pattern that is Mendelian in only ≈20%.[24] Our yield in family members of those with definite BrS

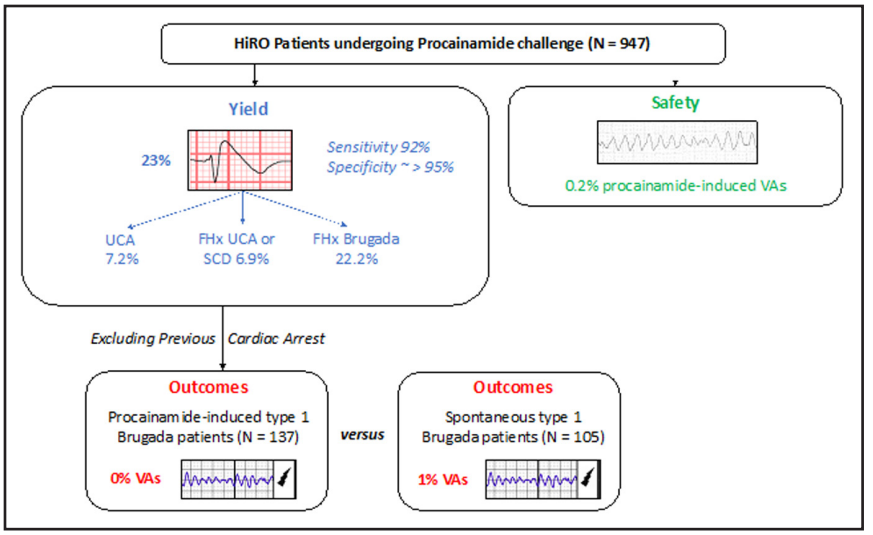

Figure 3. Safety, yield, and outcomes of procainamide challenge for the diagnosis and exclusion of Brugada syndrome.
FHx indicates family history; HiRO, Canadian Hearts in Rhythm Organization; SCD, sudden cardiac death; UCA, unexplained cardiac arrest; and VAs, ventricular arrhythmias.

was 22%. Up to 50% of BrS family members were found to be positive with ajmaline, probably reflecting both SCB potency and penetrant phenotypes, with at least 2 family members required to be affected in this study.[8] Unsurprisingly, a baseline type 2/3 Brugada ECG pattern increases the pretest probability of a positive result in family members.[8] In those with a pathogenic SCN5A variant, a type 1 pattern was induced in 80% with ajmaline[11] and 73% with procainamide in our study; this may reflect penetrance rather than sensitivity.

SCB to investigate a nonspecific type 2/3 Brugada pattern in the absence of symptoms or other factors (such as family history of UCA or sudden death) is a questionable indication.[2,3] Testing this population is likely to result in increased false positives with minimal change in management and potential psychosocial consequences of a BrS diagnosis. Our conversion rate to type 1 was surprisingly high in this group, 46.6%, which is comparable to a study by Evain et al reporting a 59% type 1 rate with a combination of flecainide and ajmaline.[10] In that study, a family history of BrS or sudden death was present in 30% of cases for each factor. It is possible that other clinical factors raising suspicion of BrS were not captured in the HiRO registry for this population. We would recommend procainamide testing in those with a type 2/3 pattern and the presence of other factors (eg, family history of BrS, UCA, or sudden death), considering HLECG only in those with a nondiagnostic pattern and no other features suggestive of BrS. This aligns with the principles of the Shanghai criteria.[1]

Sensitivity and Specificity?

In the absence of a gold-standard test for BrS, it is difficult to determine the relative sensitivity and specificity of SCB agents. A known intermittent spontaneous type 1 ECG has been proposed as the gold standard, and in this setting, the reported sensitivity of ajmaline is 100% and that of flecainide 80%.[22,23,25] Extrapolating to procainamide, sensitivity was 92% in a small subset of our cohort. Follow-up was less stringent for procainamide-negative patients with no previous UCA; thus, sensitivity may have been overestimated if subsequent spontaneous type 1 ECGs were missed. Reassuringly, in the procainamide-negative group with previous UCA, nearly all patients were followed long term at 6-month intervals with no spontaneous type 1 ECGs documented. Sensitivity calculated from a gold standard of carriership of a pathogenic SCN5A variant is likely to be underestimated because of incomplete penetrance of BrS[11,22,26] and indeed was 73% in our study. An interesting alternative approach proposed by Therasse et al is to assess sensitivity of SCB in obligate transmitters (ie, a person connecting 2 affected relatives in a pedigree).[26] We were not able to identify sufficient eligible individuals to reproduce this approach with procainamide.

Arguably, false positives (and therefore specificity) could be determined by inducible type 1 patterns in patients with a family history of UCA or sudden death in which the proband was found to have a non-BrS diagnosis. Our study did not allow for a specificity calculation via this method, as 7 of 8 family member probands with UCA or SCD remained unexplained, with only one proven to have definite BrS. No procainamide-positive patient who presented with UCA was subsequently found to have an alternative diagnosis to BrS. One patient was referred with a family history of BrS and pathogenic SCN5A variant in the proband; this patient was inducible for a type 1 Brugada pattern but did not carry the familial SCN5A variant. This may represent a false positive or may simply reflect the polygenic architecture of BrS.[27] The identification of only a single (possible) false positive suggests that the specificity of procainamide for BrS is very high (> 95%), although this is an imperfect estimate.

Safety of Procainamide Infusion

Procainamide infusion for the diagnosis and exclusion of BrS appears to be extremely safe, with a VA rate of 0.2% in our study. Both cases resolved with termination of infusion. With procainamide's reduced potency compared with other SCBs, this is probably unsurprising. Nevertheless, this is a valuable message to convey in consultations with patients referred for procainamide challenge, who, in our experience, often ask this question. In a meta-analysis of VAs attributable to SCB by Dobbels et al, the weighted average of VAs (including ventricular ectopy) was 2.4%, with 0.3% nonsustained VT, 0.6% VT, and no fatalities.[16] Again, most included studies reported ajmaline and a minority flecainide and pilsicainide, with procainamide only represented in the CASPER study of UCA. Notably, there have been case reports of rare refractory VF attributable to ajmaline requiring intervention, such as extracorporeal membrane oxygenation.[15,28] This study supports the safety of procainamide challenge in higher-risk groups such as those with a pathogenic SCN5A variant (or known BrS).[15,16] The most malignant event (nonsustained polymorphic VT) did, however, occur in a patient with UCA and a pathogenic SCN5A variant.

Outcomes in Procainamide-Induced and Spontaneous BrS Patients

Over medium-term follow-up averaging 5.9 years, we found that patients with a procainamide-induced Brugada pattern (symptomatic or asymptomatic) were at extremely low risk of malignant VAs, with 0 patients meeting the primary composite arrhythmic outcome in 771 patient-years. Despite the average follow-up duration, it is worth noting that the average age at last review was 56 years. Given that most events occur in BrS patients <60 years of age,[29] this in itself provides further reassurance. It is also reassuring that no procainamide-negative patient was subsequently found to have a spontaneous type 1 ECG or an arrhythmic event. The benign prognosis of asymptomatic drug-induced patients with a Brugada pattern has been well described with ajmaline (0.03% to 0.35% per annum risk),[12–14] but given that procainamide is proposed to be more specific for BrS, these findings should not be extrapolated without supporting data. This study was underpowered with respect to risk in drug-induced patients with true arrhythmogenic syncope, and therefore we would still recommend consideration of an ICD in these patients, considering other risk factors and patient preferences.

In the comparator group with a spontaneous type 1 ECG, we found a low but not negligible risk of malignant VA (1 patient, 1%). Indeed, a generational trend has been reported toward lower risk in newly diagnosed BrS patients because of improved screening and identification of low-risk individuals with the syndrome.[30] The risk of malignant VAs in a study by Gaita et al of asymptomatic spontaneous type 1 patients was very low at 0.4% per annum.[12] We observed a referral bias towards lower-risk patients in our Canadian population, which may be a more general population referral group, with the majority managed with lifestyle advice only.

With respect to management, this study supports relatively conservative use of ICDs and rare use of electrophysiology study risk stratification with good outcomes. Thirteen percent of patients had an ICD implanted at baseline referral, with only 7% implanted during follow-up; no cases of SCD were observed. Indeed, in 8 patients with syncope during follow-up and an implantable device (6 with an implantable loop recorder and 2 with an ICD), no arrhythmias were logged, perhaps suggesting that implantable loop recorders could safely be considered over ICDs, for which the clinical history is not convincing for an arrhythmogenic mechanism. The sole patient who received appropriate ICD shocks, we would argue, was well suited to noninvasive risk stratification, with a spontaneous type 1 pattern, SCN5A pathogenic variant, and arrhythmogenic severe presyncope at presentation. We would suggest that extended novel risk factors, multiparametric risk scores, and artificial intelligence–modulated risk stratification will supplant the need for invasive risk stratification in the vast majority of cases.[13,31]

Limitations

This is a retrospective analysis of a prospectively enrolled cohort study subject to the limitations of this type of study design. The cohort size is relatively small, as is the nature of rare conditions; therefore, power to accurately estimate risk of clinical outcomes is attenuated. Nevertheless, we believe that it adds important data to an understudied drug in this field. Average duration of follow-up was not sufficiently long to comment on long-term risk of malignant arrhythmias, although reassurance can be drawn from the average age at last follow-up. Although the HLECG was standard protocol in our procainamide challenges, the relative rates of inducible type 1 patterns between standard ECG and HLECG positions were not routinely recorded in the database, particularly before 2012.

Conclusions

Procainamide infusion is extremely safe for the diagnosis and exclusion of BrS. Yield is dependent on indication and pretest probability, with estimated sensitivity and specificity appearing to be high. Asymptomatic patients with a procainamide-induced type 1 Brugada pattern are at very low risk of malignant VAs.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S3
Supplemental Appendix

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