Cardiac arrest occurs most commonly in the context of underlying structural heart disease. Unexplained cardiac arrest (UCA) is less common with a broad differential diagnosis, including subclinical cardiomyopathy, long-QT syndrome (LQTS), Brugada syndrome, catecholamine-sensitive polymorphic ventricular tachycardia (CPVT), and idiopathic ventricular fibrillation. Growing recognition of uncommon genetic conditions that lead to cardiac arrest has reduced the number of cases that remain unexplained after extensive clinical testing.

Cardiac ion channel disorders, termed primary electrical disease, may be difficult to diagnose unless overt ECG abnormalities are present. Subclinical or intermittent QT prolongation, ST-segment shifts, or ventricular arrhythmias may be difficult to unmask. Although an implantable cardioverter-defibrillator (ICD) is indicated in patients who have experienced a cardiac arrest without a correctable cause, optimal management to reduce recurrence requires a diagnosis. In addition, diagnosis and therapy of family members are often dependent on genetic testing, which is not widely available, or recognition of a phenotype that allows case finding and prophylactic intervention. We describe the yield of progressive noninvasive and invasive challenges to provoke abnormalities in index cases of UCA survivors and their family members.

**Methods**

Patients were divided into 2 groups: UCA survivors and family members. UCA survivors had experienced a documented cardiovascular collapse with ventricular tachycardia or fibrillation requiring DC cardioversion or defibrillation to restore sinus rhythm. Patients were also included if they had experienced syncope with documented polymorphic ventricular tachycardia thought to be responsible for the index event. Follow-up testing demonstrated normal left ventricular function (left ventricular ejection fraction ≥50%) and normal coronary arteries. Patients were excluded when males had a resting corrected QT (QTc) >460 ms and females with a QTc >480 ms or when a reversible cause of cardiac arrest, such as marked hypokalemia or drug overdose, was present. No patient or family member had a QTc <350 ms. Patients with hemodynamically stable, sustained, monomorphic ventricular tachycardia with a QRS mor-
phology consistent with recognized forms of idiopathic ventricular tachycardia (outflow tract or apical septal) were excluded. The second group, comprising family members, included all first-degree relatives of UCA patients who were offered noninvasive testing as indicated later. Because of the uncertain penetrance of potential genetically mediated repolarization abnormalities, testing was offered to all second-degree relatives when evidence suggested that >1 family member was affected. All patients provided written, informed consent. Family members were further subdivided into those who were symptomatic (palpitations or syncope) or asymptomatic. The protocol was approved by the Health Sciences Research Ethics Board of the University of Western Ontario.

Testing

Patients with cardiac arrest underwent standard testing to rule out underlying heart disease (Figure 1). This included continuous ECG telemetry for at least 72 hours, transthoracic echocardiography, and coronary angiography. Those meeting inclusion criteria underwent additional testing, including signal-averaged ECG, exercise testing, cardiac magnetic resonance imaging (MRI), and adrenaline and procainamide challenge. Electrophysiological testing was used on a discretionary basis but was not applied routinely because of its limited utility in primary electrical disease.26–28 Electrophysiological testing was performed with a standard technique by using up to 3 ventricular extrastimuli at 2 drive cycle lengths for induction of ventricular arrhythmias.28 Family members underwent screening clinical assessment, a resting ECG, echocardiography, and exercise testing. Based on the findings of invasive testing in the proband, additional testing was offered to first-degree relatives to unmask the potential phenotype.

Symptom-limited exercise testing used a modified Bruce protocol. The signal-averaged ECG was considered positive when it met published criteria.29 Cardiac MRI findings were reviewed with an MRI radiologist to assess any evidence for arrhythmogenic right ventricular dysplasia. Arrhythmogenic right ventricular dysplasia was diagnosed when findings met McKenna criteria, based on the results of the MRI scans, in conjunction with other imaging modalities, monitoring, electrophysiological testing, and family history.30

Adrenaline and procainamide challenges were performed through a peripheral intravenous line with continuous ECG monitoring in the electrophysiology laboratory or the coronary care unit. Adrenaline was administered starting at 0.05 \(\mu g\)·kg\(^{-1}\)·min\(^{-1}\) and was increased to 0.10, 0.20, 0.30, and 0.40 \(\mu g\)·kg\(^{-1}\)·min\(^{-1}\) at 5-minute intervals.31 Twelve-lead ECGs were performed at baseline and just before each dose increment. The infusion was discontinued when systolic blood pressure fell below 80 mm Hg or exceeded 200 mm Hg; when monitoring detected nonsustained ventricular tachycardia or polymorphic ventricular tachycardia, >10 premature ventricular contractions (PVCs) per minute, or previously absent T-wave alternans; or when patient intolerance occurred due to headache and/or nausea.32 If symptoms persisted after discontinuation, metoprolol 2.5 to 5 mg IV was administered over 1 minute. The QT interval and heart rate were measured at the end of each 5-minute period, and the QTc was calculated according to Bazett’s formula.33 The end of the T wave was defined as the intersection of the maximum downslope of the ST segment with the isoelectric line of the T-P segment. In keeping with the series by Ackerman et al, Shimizu et al, and Shimizu, a QTc prolongation ≥65 ms was considered above the mean control response to adrenaline.

After a 30-minute washout period, 15 mg/kg procainamide to a maximum of 1 g was infused over 30 minutes to assess the development of new or increased ST-segment elevations in the anterior precordial leads, consistent with Brugada syndrome.15,33,36 ECGs were recorded every 15 minutes for 1 hour during procainamide infusion in standard precordial lead positions. ST-segment elevation was categorized as saddle back or coved according to established criteria, and the test was categorized as negative, positive, or indeterminate on the basis of published standards.15,36 A test was considered positive when there was an increase in ST\(_{20}\) elevation >1 mm or >1 mm of new ST\(_{20}\)-segment elevation in response to procainamide.15

In patients with ≥1-mm ST-segment elevation in response to procainamide, isoproterenol was infused at 2 \(\mu g\)/min for 30 minutes to assess the response of ST-segment changes.12,36 ECGs were recorded every 15 minutes during the isoproterenol infusion. ST segments were analyzed as for procainamide.

Treatment and Follow-Up

All probands with resuscitated cardiac arrest received an ICD. Patients with a clinical phenotype suggestive of CPVT also received beta-blockers in the form of atenolol 25 to 100 mg OD, nadolol 20 to 80 mg OD, or bisoprolol 2.5 to 10 mg OD. The dose of beta-blocker
was titrated on the basis of ICD interrogation and repeated exercise testing. Family members with phenotype testing results suggesting that they were affected by CPVT were offered β-blocker therapy as indicated previously if they were asymptomatic. A discussion was held with all affected family members about the risks and benefits of ICD implantation, based on the limited published natural history of the disease.

Follow-up was performed by 3 methods. Probands and affected family members with ICDs were followed up in the arrhythmia device clinic every 6 months to assess device function, symptoms, and detected asymptomatic ventricular arrhythmias. Affected family members who did not receive an ICD were offered annual reassessment, including exercise testing in the case of CPVT. Unaffected family members were contacted by telephone to verify health status. New symptoms in previously asymptomatic family members were assessed promptly with repeated testing, as indicated earlier.

Analysis

Differences in baseline variables between UCA patients, asymptomatic family members, and symptomatic family members were compared by ANOVA for continuous variables and by the χ² or Fisher’s exact test for categorical variables. The distribution of continuous variables was examined for normality (Shapiro-Wilk test). Age was not normally distributed (P=0.002); thus, it was compared with a Kruskal-Wallis test. The QTc interval before and after adrenaline testing was compared with a paired t test. Statistical analysis was performed with JMP statistical software version 5.1 (SAS Institute, Inc). A probability value <0.05 was considered significant.

Results

Eighteen survivors of cardiac arrest met the inclusion criteria for UCA and underwent further testing, including adrenaline and procainamide infusions. Four of these patients had syncope with documented polymorphic ventricular tachycardia and a family history of sudden death and did not require resuscitation. Fifty-five family members of UCA patients underwent noninvasive testing according to the outline in Figure 1. Of these patients, 50 were family members of UCA patients, 5 were first-degree relatives of unexplained sudden death cases with negative autopsy findings, 47 were entirely asymptomatic, and 8 were symptomatic. This included syncope in 6 and palpitations in 4 (2 had both). Baseline characteristics of the 3 groups are shown in Table 1. Cardiac arrest survivors were older than family members (P=0.002). There was no difference in sex or baseline QTc intervals.

Noninvasive testing in the UCA patients showed no evidence of structural heart disease by imaging or signal-averaged ECG. Exercise testing showed occasional polymorphic ventricular ectopy in 7 patients, without nonsustained, sustained, or symptomatic tachycardia. Adrenaline infusion demonstrated a positive response with polymorphic ventricular ectopy or nonsustained ventricular tachycardia in 7 patients and frequent ventricular ectopy, including bigeminy and couplets, in 2 patients. One patient developed sustained ventricular tachycardia that resulted in an ICD shock. The tachycardia recurred after the successful shock but resolved with administration of 5 mg IV metoprolol (Figure 2). Four of the 9 patients with adrenaline-induced, nonsustained ventricular tachycardia (44%) had isolated ectopy without nonsustained ventricular tachycardia on treadmill exercise. Procainamide infusion unmasked a latent Brugada sign in 2 patients with a ≥2-mm concave ST-segment elevation in V1 and V2. One patient had a borderline response to procainamide, with a 1-mm ST-segment elevation. This patient was assigned a diagnosis of idiopathic ventricular fibrillation because the ST-segment response was not interpreted as diagnostic. Of the 2 responders, 1 was Southeast Asian and the other was white.

Overall, adrenaline unmasked evidence of CPVT in 50% of the 10 patients with that final diagnosis in the complete absence of telemetry or exercise-induced ectopy, including isolated PVCs, representing an incremental diagnosis in 28% of the UCA population. Similarly, procainamide unmasked 1 non-Asian patient, representing 6% of the UCA population.

The QT interval was modestly prolonged in response to both adrenaline and procainamide. The adrenaline QTc increased by 31±23 ms, to 458±22 ms (P=0.0013). Two patients had an absolute QT prolongation of 90 ms, but the QTc increased by only 36 and 49 ms. No patient had a QTc prolongation >65 ms. The procainamide QTc increased by 20±24 ms, to 451±23 ms (P=0.027). The longest QTc recorded during either infusion was 493 ms. The final diagnosis was CPVT in 10 patients (56%), Brugada syndrome in 2 (11%), and idiopathic ventricular fibrillation in 6 (33%). Family members underwent testing in accordance with the scheme depicted in Figure 1. In the 8 symptomatic patients, symptomatic polymorphic ventricular ectopy during treadmill testing was observed in 7 members of a single family and in 1 additional patient (Figures 3 and 4). A single asymptomatic
family member had similar findings on treadmill testing. One symptomatic patient with palpitations, syncope, and a family history of sudden death had right ventricular outflow tract PVCs on electrophysiological study, a positive tilt test, and a completely negative workup for arrhythmogenic right ventricular cardiomyopathy. The adrenaline and procainamide challenge results were negative. Of interest, 2 girls aged 12 and 14 years were asymptomatic at first assessment with negative testing. Syncope and presyncope 4 years later led to repeated assessment. Both patients manifested previously absent polymorphic ventricular ectopy on exercise testing, similar to their mother. Symptoms and exercise-induced PVCs resolved after $\beta$-blockade. The results of testing in the 3 groups are summarized in Table 2.

The remaining 47 family members underwent testing according to the protocol in Figure 1. Three patients had exercise-induced polymorphic ventricular tachycardia and were diagnosed with CPVT (see previous section). A 46-year-old man from Thailand whose brother had died suddenly at age 43 had a negative noninvasive workup and 1 mm of intermittent saddle-back ST-segment elevation in lead V2. He had a positive response to procainamide infusion (Figure 2). All 3 patients with a positive procainamide test result had normalization of the ST segments with isoproterenol infusion. Only 2 of 21 families offered testing had 1 affected family member. One CPVT family had 10 affected family members, and 1 Brugada family had 2 affected family members.

**Figure 3.** Bidirectional followed by a polymorphic ventricular tachycardia in an 18-year-old female subject with a previous UCA who was given low-dose adrenaline. Exercise testing demonstrated only occasional, isolated, monomorphic PVCs. Despite discontinuation of the infusion, tachycardia accelerated and an appropriate ICD shock was delivered, followed by 5 mg of intravenous metoprolol, which terminated the recurrent polymorphic ventricular tachycardia. Abbreviations are as defined in text.

**Figure 4.** ECG recorded during exercise testing in a 38-year-old female subject with previous palpitations, remote syncope, and a family history of exercise-related sudden death. Her 14-year-old daughter experienced recurrent exertional syncope and subsequent cardiac arrest and was diagnosed with CPVT. This ECG was recorded during routine screening. The patient was minimally symptomatic. Abbreviations are as defined in text.

**Treatment and Follow-Up**

$\beta$-Blockers were prescribed to all CPVT patients and were titrated to the elimination of ventricular tachycardia and a marked reduction in ventricular ectopy on repeated exercise testing. The target reduction in peak heart rate was at least 30 beats/min. In the UCA patients, clinical and ICD follow-up demonstrated 1 to 10 appropriate shocks in 4 CPVT patients during 35±37 months of follow-up. An ICD was also implanted in a CPVT patient who had not experienced cardiac arrest. She has received appropriate shocks every 6 to 12 months over 8 years of follow-up, despite $\beta$-blockade, thoracoscopic cardiac sympathectomy, and extension of the interval to detect ventricular fibrillation settings on the ICD. In the affected family members, $\beta$-blockers suppressed exercise-induced ventricular ectopy in both CPVT patients, and the Brugada syndrome patient declined electrophysiology testing and consideration of an ICD.

Two deaths occurred during 57±45 months of follow-up. The first occurred in a 12-year-old boy from the large CPVT kindred, who experienced 3 episodes of syncope during vigorous exercise. He had a family history of exertional syncope and sudden death. Exercise testing demonstrated frequent PVCs, and he was advised not to exercise pending an electrophysiological assessment. He died suddenly while running the bases during a baseball game.

The second patient had a UCA at age 13 and received an ICD. After referral to our center at age 18, low-dose adren-
tachycardia. Autopsy in both cases did not reveal any structural abnormalities. Immediate recurrence of rapid polymorphic ventricular tachycardia that led to an appropriate ICD discharge, which resolved with 5 mg of intravenous aline (0.10 μg·kg⁻¹·min⁻¹) induced nonsyncopal polymorphic ventricular tachycardia that led to an appropriate ICD discharge, which resolved with 5 mg of intravenous metoprolol. Seventeen months later, she experienced sudden death. ICD interrogation demonstrated appropriate ICD recognition and therapy, with exhausted therapies because of immediate recurrence of rapid polymorphic ventricular tachycardia. Autopsy in both cases did not reveal any structural abnormalities.

**Discussion**

UCA may ultimately be explained through a manifested phenotype with long-term follow-up or provocative testing. Potential explanations include arrhythmogenic right ventricular cardiomyopathy, LQTS, Brugada syndrome, and CPVT.3–7 When these conditions are not diagnosed, the arrest is attributed to idiopathic ventricular fibrillation.11,20 The underlying cardiac ion channel disorder may be overtly manifest, in which case the presenting symptoms are attributed to the recognized phenotype. The present study suggests that thorough noninvasive and subsequent provocative testing with adrenaline and procainamide may unmask a latent explanation in two thirds of cases. The most common explanation was CPVT in 56%.

The prevalence of these conditions is clearly dependent on genetic factors in the local population and the inclusion criteria of the present study. Patients with overt LQTS and arrhythmogenic right ventricular cardiomyopathy were excluded from the present study, but they clearly constitute an important component of patients who experience cardiac arrest with preserved left ventricular function. During the recruitment period for the present study, 3 patients with resuscitated cardiac arrest were identified who had overt LQTS and who were excluded from this study. No patient with known LQTS experienced sudden death.

Screening for mutations responsible for the genetic conditions that cause cardiac arrest may detect a potentially causative mutation in the minority of cases, but this is not a feasible clinical approach. In overt cases of LQTS, genetic screening is positive in only 60% of cases.42,43 This number is even lower (15%) in recognized cases of Brugada syndrome and is unknown in CPVT.5,44,45 These figures represent selection bias, because many sporadic cases without affected family members have not been genotyped. For this reason, genetic testing currently can only be adjunctive to phenotypic testing in UCA. Improved phenotypic recognition is needed to provide insight into the mechanism of cardiac arrest for patients, their families, and physicians. Furthermore, directed genetic testing when a phenotype is unmasked or at least suspected may provide both an explanation and a concrete screening tool for family members when the phenotype is difficult to detect. This is particularly relevant in genetically based primary electrical disease, in which variable phenotypic penetrance has been reported.11,19

In this limited series of UCA patients, a small proportion of them had affected family members. The predominant phenotype unmasked by testing was CPVT, which contrasts with the findings of previous studies. This rare condition may be sporadic or familial.5,9,37,44–47 The present study suggests that adrenaline may be more effective than exercise testing at unmasking diagnostic polymorphic ventricular ectopy and tachycardia, because exercise testing was suggestive in only half of the patients who responded to adrenaline, many with only occasional exercise-induced, isolated ectopy, which was not considered diagnostic. This incremental finding may relate to a combination of sympathetic stimulation and vagal withdrawal during exercise that is less arrhythmogenic than a pure catecholamine trigger during adrenaline infusion in the presence of presumed normal vagal tone.

A single case of nonsustained ventricular tachycardia during adrenaline infusion of 27 controls was reported by Ackerman et al.31 There have been no other reported arrhythmias during adrenaline infusion in healthy controls in multiple case series involving 143 subjects.32,48–50 Nonetheless, the false-positive rate of adrenaline infusion remains uncertain, suggesting caution in the interpretation of the response during infusion, particularly when the degree of ventricular ectopy is not compelling. Brugada syndrome was seen in only 11% of UCA patients. The prevalence of Brugada syndrome is highly variable, based on published reports.39–41 We have seen only 3 other cases of overt Brugada syndrome during the recruitment period for the present study. This finding is concordant with the highly variable nature of the ST-segment abnormalities in and regional prevalence of Brugada syndrome.6,13,14 We did not monitor multiple V1 and V2 lead positions during procainamide infusion or use alternative sodium channel blockers, which have been reported to increase sensitivity.12 Future studies will incorporate this component.

Although family screening was not comprehensive, those family members who pursued testing had a low likelihood of manifesting disease. Only 1 large kindred was identified, with screening of affected family members. Given the noninvasive nature of the screening performed, it seems sensible to recommend the approach outlined in Figure 1, followed by directed aggressive testing based on findings in the proband. This screening approach for both UCA survivors and their families is readily available in most cardiac centers. Despite the published safety of adrenaline infusion, the single case of sustained arrhythmia suggests that infusions should be performed in an acute monitoring setting with resuscitation equipment immediately available. The prognosis of those family members with negative screening was excellent in our population, although the number of patients involved does not exclude a small risk.

**Limitations**

The number of cases of UCA in this study was relatively small, an inherent problem in studying relatively uncommon
diseases. Nonetheless, this study supports simple testing, including adrenaline and procainamide infusions, as diagnostically useful. The observations in this cohort are clearly contingent on surviving cardiac arrest. Clearly, the observed diagnoses may not apply to the large proportion of cardiac arrest cases that are fatal and still unexplained after autopsy. A larger study that includes nonsurvivors with a genetic screen would be useful for evaluating whether the diagnoses and demographics suggest a survival advantage based on patient or disease characteristics. As indicated earlier, the true false-positive rate of adrenaline infusion is uncertain, although current observations in the context of previous cardiac arrest remain compelling. A Canadian registry is currently under way to prospectively evaluate patients with UCA. Use of an alternative sodium channel blocker such as ajmaline might have enhanced detection of Brugada syndrome. Unfortunately, procainamide is the only intravenous sodium channel blocker available in Canada. Second, a comprehensive genetic screen was not performed in all UCA patients. Although this might have been the ideal, genetic testing is of uncertain yield and costly. Scarse genetic testing resources should be directed at families with multiple affected members. The phenotype recognition arising from the present study suggests that this should be a focus of further study. This is a component of the currently enrolling Canadian registry. This finding is clearly specific to the population studied and may be influenced by the prevalence of the explanatory conditions in the area of referral. Similar to the autopsies series of sudden death in athletes, the prevalence of conditions such as arrhythmogenic right ventricular cardio-myopathy and Brugada syndrome is influenced by region.

Conclusion

The etiology of apparent UCA can be unmasked by systematic noninvasive and invasive testing, in particular, adrenaline and procainamide infusions. This approach assists in directing genetic testing to diagnose latent repolarization syndromes such as CPVT and the Brugada syndrome.

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References


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