Systematic Assessment of Patients With Unexplained Cardiac Arrest

Cardiac Arrest Survivors With Preserved Ejection Fraction Registry (CASPER)

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Background—Cardiac arrest without evident cardiac disease may be caused by subclinical genetic conditions. Provocative testing to unmask a phenotype is often necessary to detect primary electrical disease, direct genetic testing, and perform family screening.

Methods and Results—Patients with apparently unexplained cardiac arrest and no evident cardiac disease (normal cardiac function on echocardiogram, no evidence of coronary artery disease, and a normal ECG) underwent systematic evaluation that included cardiac magnetic resonance imaging, signal-averaged ECG, exercise testing, drug challenge, and selective electrophysiological testing. Diagnostic criteria were based on accepted criteria or provocation of the characteristic clinical features for long-QT syndrome, catecholaminergic polymorphic ventricular tachycardia, Brugada syndrome, early repolarization, arrhythmogenic right ventricular cardiomyopathy, coronary spasm, and myocarditis. Sixty-three patients in 9 centers were enrolled (age 43.0 ± 13.4 years, 29 women). A diagnosis was obtained in 35 patients (56%): Long-QT syndrome in 8, catecholaminergic polymorphic ventricular tachycardia in 8, arrhythmogenic right ventricular cardiomyopathy in 6, early repolarization in 5, coronary spasm in 4, Brugada syndrome in 3, and myocarditis in 1. Targeted genetic testing demonstrated evidence of causative mutations in 9 (47%) of 19 patients. Screening of 64 family members of these patients identified 15 affected individuals who were treated (24%). The remaining 28 patients (44%) were considered to have idiopathic ventricular fibrillation.

Conclusions—Systematic clinical testing, including drug provocation and advanced imaging, results in unmasking of the cause of apparently unexplained cardiac arrest in >50% of patients. This approach assists in directing genetic testing to diagnose genetically mediated arrhythmia syndromes, which results in successful family screening. (Circulation. 2009;120:278-285.)

Key Words: heart arrest ■ diagnosis ■ catecholamines ■ genetics ■ magnetic resonance imaging

Cardiac arrest in the absence of evident structural heart disease is uncommon, with a broad differential diagnosis that includes subclinical cardiomyopathy, primary electrical disorders, and idiopathic ventricular fibrillation.1–5 Growing recognition of the clinical features of uncommon genetic conditions that lead to cardiac arrest has reduced the number of cases that remain unexplained.

Clinical Perspective on p 285

Cardiac ion channel disorders that result in “primary electrical disease” may be difficult to diagnose unless overt ECG abnormalities are present.6–12 Subclinical QT prolongation, ST-segment shifts, or ventricular arrhythmias may be electrocardiographically subtle or intermittent.13–18 Although an implantable cardioverter defibrillator (ICD) is indicated in patients who have had a cardiac arrest without a correctable cause,19 optimal management to reduce recurrence requires a diagnosis. In addition, screening of family members is dependent on recognition of a phenotype that allows case finding, targeted genetic testing, and prophylactic intervention. We describe the yield of sequential noninvasive and invasive testing in.

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conjunction with targeted genetic testing in patients in a national registry of unexplained cardiac arrest.

Methods

Patients

Patients were eligible for enrollment if they had experienced an unexplained cardiac arrest with documented cardiovascular collapse with ventricular tachycardia or fibrillation that required direct-current cardioversion or defibrillation to restore sinus rhythm. Follow-up testing demonstrated normal left ventricular function (left ventricular ejection fraction ≥50%) and normal coronary arteries. Patients were excluded if they had a resting corrected QT interval (QTc) >460 ms (for men) or a QTc >480 ms (for women)20,21 or if a reversible cause of cardiac arrest such as marked hypokalemia or drug overdose was present. Investigators and coordinators performed a consultation/assessment whenever possible to determine whether drug overdose was present. Investigators and coordinators performed a consultation/assessment whenever possible to determine whether drug overdose was present.

Methods

Patients were enrolled between January 1, 2004, and October 1, 2008, in 8 adult and 1 pediatric electrophysiology center across Canada. During the recruitment period, the 9 involved centers enrolled 63 patients, during which time they implanted 1,877 secondary-prevention ICDs (3.4%). On the basis of projections from the systematic data from a single year, an estimated 105 patients were enrolled during which time they implanted 1,877 secondary-prevention ICDs (3.4%).

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, transesophageal echocardiography, and coronary angiography. Those who met inclusion criteria were enrolled and underwent additional testing, including signal-averaged ECG, exercise testing, cardiac magnetic resonance imaging, and intravenous adrenaline and procainamide challenge. Electrophysiological testing was performed with a standard technique, with up to 3 ventricular extrastimuli at 2 drive cycle lengths for induction of ventricular arrhythmias.24 Electrophysiological testing was used on a discretionary basis but was not applied routinely because of its limited utility in primary electrical disease.25–28 Voltage mapping, right ventricular angiography, and right ventricular biopsy were conducted in select cases when occult ARVC was suspected.29,30

Symptom-limited exercise testing was performed with a modified or standard Bruce protocol. The signal-averaged ECG was considered positive if it met published criteria.31 Cardiac magnetic resonance imaging (MRI) findings were reviewed with an MRI expert to assess for evidence of ARVC. ARVC was diagnosed when findings met task force criteria32 based on the results of the MRI in conjunction with other imaging modalities, monitoring, electrophysiological testing, and family history. Early repolarization was defined as an elevation of the QRS-ST junction (J point) in at least 2 leads, as close to the point of cardiac arrest as was available for review. The amplitude of J-point elevation had to be at least 1 mm (0.1 mV) above the baseline level, either as QRS slurring (a smooth transition from the QRS segment to the ST segment) or notching (a positive J deflection inscribed on the S wave) in the inferior lead (II, III, and aVF), lateral lead (I, aVL, and V4 to V6), or both.33–35 Coronary spasm was diagnosed when patients experienced ≥2 mm of transient ST elevation during inpatient telemetry, variably associated with nonsustained polymorphic ventricular tachycardia in conjunction with ST elevation, and angiographic evidence. Provocative testing with ergonovine or acetylcysteine was not performed.

Adrenaline and procainamide infusions were performed through a peripheral intravenous line with continuous ECG monitoring. Adrenaline was administered starting at 0.05 μg·kg⁻¹·min⁻¹, increased to 0.10 and 0.20 μg·kg⁻¹·min⁻¹ in 5-minute intervals.37–39 Twelve-lead ECGs were performed at baseline and just before each dose increment. The infusion was discontinued if systolic blood pressure fell below 80 mm Hg or exceeded 200 mm Hg; if monitoring detected nonsustained ventricular tachycardia or polymorphic ventricular tachycardia, >10 premature ventricular contractions per minute, or previously absent T-wave alternans; or for patient intolerance due to headache or nausea.40 If symptoms persisted after discontinuation, metoprolol 2.5 to 5 mg was administered intravenously over 1 minute. The QT interval and heart rate were measured at the end of each 5-minute period, and the QTc was calculated with the Bazett formula.41 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 Ackerman et al39 and Shimizu et al,38,42 QTc prolongation of ≥50 ms was considered abnormal, consistent with LQTS.

After a 30-minute washout period, procainamide 15 mg/kg (to a maximum of 1 g) was infused at 50 mg/min to assess for development of new or increased ST elevation in the anterior precordial leads consistent with Brugada syndrome.13,43,44 ECGs were recorded every 15 minutes for 1 hour during procainamide infusion in standard precordial lead positions. ST 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.35,44 A test was considered positive if there was an increase in STₚ, elevation >1 mm or if there was >1 mm of new STₚ, segment elevation in response to procainamide.13

Genetic Testing

Targeted genetic testing was performed on the basis of phenotype detection in patients after systematic clinical testing. Genetic testing was performed on suspected culprit genes (for LQTS: KCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2; for Brugada syndrome: SCN5A; for ARVC: Pkp2 and Dsp; and for catecholaminergic...
polymorphic ventricular tachycardia (CPVT); RyR2 selected exons 2 to 4, 6 to 15, 17 to 20, 39 to 49, 83, 84, 87 to 97, and 99 to 105). Genomic DNA isolated from blood lymphocytes was screened by temperature-gradient capillary electrophoresis and/or direct DNA sequencing. In temperature-gradient capillary electrophoresis analysis (SpectruMedix, State College, Pa), polymerase chain reaction–amplified DNA samples were separated by capillary electrophoresis under 2 temperature gradient conditions (50° to 58° and 55° to 63°). Samples that contained mutations were identified on the basis of altered electrophoretic patterns of heteroduplexes caused by their different melting equilibriums and electrophoretic mobilities. Samples that contained heteroduplexes then underwent direct DNA sequencing.

**Statistical Analysis**

Continuous variables were compared by use of a 2-tailed Student t test for continuous variables and χ² test for categorical variables. Statistical analysis was performed with SAS software version 9.1 (SAS Institute, Cary, NC) by the authors (LJG). P values <0.05 were considered significant. All results are expressed as mean±SD.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

**Results**

Sixty-three patients met inclusion criteria for the study and underwent investigation at 9 centers across Canada. The mean age was 43.0±13.4 years (range 14 to 79 years); 29 patients were female (46%). A specific diagnosis was obtained in 35 patients (56%; Table 1). Age, sex, previous symptom history, and baseline ECG findings were similar in the 2 groups. Thirty-five percent of patients had experienced syncope before their index event. Fifty-seven patients (90%) received an ICD after testing or were tested without an MRI after the ICD was implanted.

The spectrum of diagnosed conditions is illustrated in Figure 2. Among the 35 diagnosed patients, LQTS was detected in 8 patients (23%), CPVT in 8 (23%), ARVC in 6 (17%), early repolarization in 5 (14%), coronary spasm in 4 (11%), Brugada syndrome in 3 (9%), and myocarditis in 1 (3%). The positive diagnostic testing that led to diagnosis is summarized in Figure 3. Provocative testing had the highest yield of the components of testing, with abnormal findings in 18 patients (60%; 29% overall).

Among the 8 LQTS patients, adrenaline infusion was used to diagnose LQTS in 5 patients, in whom the QTc was prolonged by 117±42 ms. Application of the updated 30-ms absolute QT prolongation cutoff of Vyas et al reclassified the epinephrine test as normal in 2 of the 5 patients, who had a QTc of 546 and 558 ms during infusion. Imaging was negative in both patients. One patient died of malignancy before genetic testing could be performed, and the second patient has a sibling with dramatic QTc prolongation and has not yet had genetic testing. QTc prolongation was seen during exercise in 3 patients, with genetic confirmation in 3. Among the 8 CPVT patients, 7 had polymorphic ventricular ectopy during adrenaline infusion, 4 of whom also had ectopy during treadmill testing. One patient had exercise-induced polymorphic ventricular tachycardia and did not have an adrenaline infusion.

The diagnosis of ARVC in 6 patients was based on a combination of an abnormal signal-averaged ECG in 3, genetic testing in 2, an abnormal voltage map in 2, a diagnostic biopsy in 1, and right ventricular premature ventricular contractions during adrenaline infusion in 1. Coronary spasm was diagnosed in 4 patients, associated with >2 mm of ST elevation in all 4 patients during inpatient telemetry; nonsustained polymorphic ventricular tachycardia was diagnosed in conjunction with ST elevation in 3 patients; and angiographic evidence of spasm or occlusion was seen in 3 patients (Figure 4). Provocative testing with ergonovine or acetylcholine was not performed. Procainamide induced ST elevation that was consistent with a type 1 Brugada ECG in 3 patients. Myocarditis was detected

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**Table 1. Baseline Characteristics of the Study Population**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Idiopathic VF (n=28)</th>
<th>Diagnosed (n=35)</th>
<th>All Patients (n=63)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>43±13</td>
<td>44±15</td>
<td>43±13</td>
<td>0.54</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>11 (39)</td>
<td>18 (51)</td>
<td>29 (46)</td>
<td>0.34</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>71±14</td>
<td>74±18</td>
<td>72±15</td>
<td>0.66</td>
</tr>
<tr>
<td>QT, ms</td>
<td>394±43</td>
<td>389±38</td>
<td>390±38</td>
<td>0.86</td>
</tr>
<tr>
<td>QTc, ms (range)</td>
<td>422±31 (372–482*)</td>
<td>425±30 (372–495*)</td>
<td>422±30 (372–495*)</td>
<td>0.72</td>
</tr>
<tr>
<td>Symptoms before cardiac arrest</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palpitations</td>
<td>5 (18)</td>
<td>4 (11)</td>
<td>9 (14)</td>
<td>0.49</td>
</tr>
<tr>
<td>Syncope</td>
<td>9 (32)</td>
<td>13 (37)</td>
<td>22 (35)</td>
<td>0.63</td>
</tr>
<tr>
<td>Presyncope</td>
<td>2 (6)</td>
<td>5 (14)</td>
<td>7 (11)</td>
<td>0.35</td>
</tr>
<tr>
<td>ICD</td>
<td>26 (93)</td>
<td>31 (89)</td>
<td>57 (90)</td>
<td>0.57</td>
</tr>
</tbody>
</table>

VF indicates ventricular fibrillation.

*All 3 patients with QTc >480 ms had subsequent ECGs after recovery from cardiac arrest that demonstrated normal QTc intervals.
This prospective multicenter study has demonstrated that systematic, rigorous clinical testing, including drug provocation, can determine the cause of unexplained cardiac arrest in more than half of all patients. Two thirds of diagnosed cases were based on primary electrical disease, and a third had a structural basis. In 47% of patients in whom a clinical diagnosis was ascertained, targeted genetic testing identified disease-causing mutations. This strategy is important for the index case and family members to direct family screening, influence drug avoidance, and prescribe disease-specific adjuvant therapy. Indirectly, it may also influence device decisions such as the provision of atrial pacing support in type 3 LQTS (LQT3) or Brugada syndrome and direct drug or ablation therapy in ARVC.

The most common underlying substrate of cardiac arrest is ischemia and/or left ventricular dysfunction, both of which were excluded in the present study. In addition, patients with overt LQTS and ARVC were excluded, but clearly, they constitute an important component of patients with cardiac arrest with preserved left ventricular function. The 63 patients in the present study represent a small proportion of the overall cardiac arrest population; however, they represent an important cohort in light of the potential genetic basis for their events and implicit risks to family members.

Systematic use of testing that focused on provocation was key to arriving at a diagnosis. The highest yield of testing lay in exercise and drug-challenge findings, particularly QT prolongation in LQTS and complex ventricular ectopy in CPVT. This is consistent with the single-center pilot study that preceded the present study, in which CPVT was diagnosed most often from adrenaline challenge. The multicenter nature of the present study in a larger population demonstrated a broader range of primary electrical disease diagnoses, with more prevalent LQTS and Brugada syndrome. Although the number of diagnoses is small, this confirms that the mechanism of subclinical inherited causes of cardiac arrest reflect specific molecular defects that may warrant consideration with targeted provocative testing. A recent report used erythromycin to provoke $T_{peak} - T_{end}$ prolongation in patients with type 2 LQTS (LQT2), which was not performed in the present cohort. Further development of provocation protocols is clearly warranted, because almost half of the present cohort remained “idiopathic” after assessment.

Cardiac monitoring during short-term follow-up demonstrated evidence of coronary spasm in 4 cases, an unexpected mechanism of cardiac arrest within the target population. Coronary spasm is a well-recognized cause of cardiac arrest, but it typically precipitates infarction or is manifest with recognizable symptoms in a suspicious substrate. Dramatic ST-segment elevation was seen in all 4 cases, with ventricular arrhythmia in 3. Pharmacological challenge was not performed in the present study cohort, although it is an established provocative test to induce coronary spasm. Because it may precipitate infarction, arrhythmias, and even death, it is not performed systematically in most catheterization laboratories. The observation in the present cohort suggests a greater role for ergonovine or acetylcholine challenge aimed at provoking coronary spasm.

Advanced cardiac imaging was useful in detecting occult structural causes of cardiac arrest in the present cohort. In particular, MRI should be performed before ICD implanta-
Figure 4. Serial rhythm strips over 2 minutes in a 46-year-old man with recent cardiac arrest. Mild luminal irregularity was noted on coronary angiography, with normal left ventricular function. Routine telemetry 72 hours after presentation demonstrated asymptomatic dramatic ST-segment changes in conjunction with ventricular ectopy and nonsustained polymorphic ventricular tachycardia with a resultant diagnosis of coronary spasm-induced cardiac arrest.
tion; it was useful primarily in detection of ARVC and myocarditis. In the coordinating center (Ontario, Canada), MRI scanning in this population includes functional imaging, T1- and T2-weighted imaging, and gadolinium enhancement to detect fat replacement (T1) and inflammation (T2 and gadolinium).

Screening for mutations responsible for the genetic conditions that cause cardiac arrest may detect a potentially causative mutation in the minority of cases, but at present, this is not a feasible approach outside of a research environment. In overt cases of primary electrical disease, genetic screening is positive in only 5% to 60% of cases.50,51 These yields represent selection bias, because many sporadic cases without affected family members have not been genotyped. The findings from the present study are in keeping with this, because phenotype-directed testing yielded a genetic correlate in 47% of patients.

Limited screening of the 30 patients with idiopathic ventricular fibrillation demonstrated apparent disease-causing mutations in 2 of the 10 patients who had screening, both of which represented ARVC genes. Although the diagnosis of ARVC is not based on an overt phenotype, ARVC is an eclectic condition that often manifests without a structural correlate.52 Further study is needed in this area in a larger population to explore the yield of ARVC-directed genetic testing in an idiopathic ventricular fibrillation cohort with nondiagnostic clinical findings, supported by the suspicious imaging and voltage mapping results in 2 idiopathic ventricular fibrillation patients that were inconclusive. Molecular autopsy has demonstrated a comparable yield when genetic testing is applied to apparently unexplained sudden death.53,54

At present, genetic testing can only be advocated as adjunctive to phenotypic testing in unexplained cardiac arrest. Improved phenotypic recognition is needed to provide insight into the mechanism of cardiac arrest to 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 is the norm and simple medical therapy is typically effective in the prevention of initial symptoms.9,17

### Study Limitations

The number of cases in the present study was relatively small, an inherent problem in studying uncommon diseases. Nonetheless, the present study is based on a prospective multicenter experience and supports accessible, simple testing, including provocative drug infusions and MRI, as diagnostically useful. The observations in the present cohort are clearly contingent on survival of cardiac arrest and may not apply to the large proportion of fatal cardiac arrests that are unexplained after autopsy. Use of an alternate sodium channel blocker such as ajmaline may have enhanced detection of Brugada syndrome; unfortunately, procarainamide is the only intravenous sodium channel blocker available in Canada. Early repolarization has demonstrated an emerging association with cardiac arrest, with an incompletely understood arrhythmogenic mechanism. Further research will undoubtedly clarify this mechanism and the clinical significance of the ECG observation. We believe that the arguable inclusion of such patients and that diagnosis in the study reflected the incremental

### Table 2. Test Findings in the 9 Patients With Positive Genetic Testing

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Sex</th>
<th>Heart Rate, bpm</th>
<th>QTC, ms</th>
<th>Diagnosis</th>
<th>Adrenaline</th>
<th>Procarainamide</th>
<th>Genetic Test</th>
<th>Additional Test of Interest of</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>37</td>
<td>Female</td>
<td>68</td>
<td>434</td>
<td>CPVT</td>
<td>Abnormal</td>
<td>Not done</td>
<td>RyR2*: Ala1136Val,† Gly1885Glu, Gln2956Arg</td>
<td>Exercise-induced PVCs</td>
<td>PMVT with adrenaline</td>
</tr>
<tr>
<td>2</td>
<td>43</td>
<td>Female</td>
<td>86</td>
<td>455</td>
<td>ARVC</td>
<td>Abnormal</td>
<td>Abnormal</td>
<td>DSP: Thr2595Ile†</td>
<td>Borderline SAECG</td>
<td>QT prolongation with both drug infusions</td>
</tr>
<tr>
<td>3</td>
<td>51</td>
<td>Male</td>
<td>65</td>
<td>416</td>
<td>ARVC</td>
<td>Normal</td>
<td>Normal</td>
<td>PKP2: Asp26Asn</td>
<td>PVCs with exercise</td>
<td>MRI not performed due to ICD; SAECG normal</td>
</tr>
<tr>
<td>4</td>
<td>23</td>
<td>Female</td>
<td>69</td>
<td>461</td>
<td>LQT2</td>
<td>Abnormal</td>
<td>Abnormal</td>
<td>KCNH2: Arg1007His†</td>
<td>Exercise-induced QT prolongation</td>
<td>QT prolongation with both drug infusions</td>
</tr>
<tr>
<td>5</td>
<td>27</td>
<td>Female</td>
<td>52</td>
<td>413</td>
<td>CPVT</td>
<td>Not done</td>
<td>Not done</td>
<td>RYR2: Met3978Ile†</td>
<td>Exercise-induced PMVT</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>38</td>
<td>Male</td>
<td>90</td>
<td>392</td>
<td>Brugada</td>
<td>Abnormal</td>
<td>Not done</td>
<td>SCNSA: 2953_2954insC†</td>
<td>Abnormal SAECG</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>52</td>
<td>Female</td>
<td>76</td>
<td>450</td>
<td>Brugada</td>
<td>Abnormal</td>
<td>Not done</td>
<td>SCNSA: Ala997Thr†</td>
<td>Abnormal SAECG</td>
<td>QT prolonged and PVCs with exercise</td>
</tr>
<tr>
<td>8</td>
<td>72</td>
<td>Male</td>
<td>50</td>
<td>383</td>
<td>LQT2</td>
<td>Normal</td>
<td>Borderline</td>
<td>KCNH2: Lys897Thr (homozygous), KCNE1 Gly38Ser</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>53</td>
<td>Female</td>
<td>85</td>
<td>433</td>
<td>LQT3</td>
<td>Normal</td>
<td>Normal</td>
<td>SCNSA: Pro2006Ala</td>
<td>Follow-up ECGs showed intermittent QT prolongation</td>
<td></td>
</tr>
</tbody>
</table>

PVCs indicates premature ventricular contractions; PMVT, polymorphic ventricular tachycardia; and SAECG, signal-averaged ECG.

*Heterozygote for the A1136V and G1185E variants and homozygous for Q2958R.

†Novel mutations.
assessment for a wide array of diagnostic outcomes in apparent idiopathic ventricular fibrillation. Finally, a comprehensive genetic screen was not performed on all patients. Although this may have been ideal, genetic testing is of uncertain yield and is costly. Scarce genetic testing resources are currently directed at families with multiple affected members. Application of the results to the larger number of family members is a clear goal of the present study and is currently under way.

Conclusions

Apparently unexplained cardiac arrest can be explained in half of all patients with the use of systematic noninvasive and invasive testing, in particular drug provocation and advanced imaging. This approach assists in directing genetic testing to diagnose genetically mediated arrhythmia syndromes such as LQTS, CPVT, and ARVC.

Acknowledgment

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Disclosures

None.

References


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In the article by Krahn et al, “Systematic Assessment of Patients With Unexplained Cardiac Arrest: Cardiac Arrest Survivors With Preserved Ejection Fraction Registry (CASPER),” which appeared in the July 28, 2009 issue of the journal (*Circulation*. 2009;120:278–285), the current Table 2 is not correct and should be replaced by the following table:

The change has been made to the current online version of the article. The authors regret the error.

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<td>Abnormal</td>
<td>DSP: Thr2595Ile†</td>
<td>Borderline SAECG</td>
<td>QT prolongation with both drug infusions</td>
</tr>
<tr>
<td>3</td>
<td>51</td>
<td>Male</td>
<td>65</td>
<td>416</td>
<td>ARVC</td>
<td>Normal</td>
<td>Normal</td>
<td>PKP2: Asp26Asn</td>
<td>PVCs with exercise</td>
<td>MRI not performed due to ICD; SAECG normal</td>
</tr>
<tr>
<td>4</td>
<td>23</td>
<td>Female</td>
<td>69</td>
<td>461</td>
<td>LQT2</td>
<td>Abnormal</td>
<td>Abnormal</td>
<td>KCNH2: Arg1007His†</td>
<td>Exercise-induced QT prolongation</td>
<td>QT prolongation with both drug infusions</td>
</tr>
<tr>
<td>5</td>
<td>27</td>
<td>Female</td>
<td>52</td>
<td>413</td>
<td>CPVT</td>
<td>Not done</td>
<td>Not done</td>
<td>RYR2: Met3978Ile†</td>
<td>Exercise-induced PMVT</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>38</td>
<td>Male</td>
<td>90</td>
<td>392</td>
<td>Brugada</td>
<td>Not done</td>
<td>Abnormal</td>
<td>SCN5A: 2953_2954insC†</td>
<td>Abnormal SAECG</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>52</td>
<td>Female</td>
<td>76</td>
<td>450</td>
<td>Brugada</td>
<td>Not done</td>
<td>Abnormal</td>
<td>SCN5A: Ala997Thr†</td>
<td>Abnormal SAECG</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>72</td>
<td>Male</td>
<td>50</td>
<td>383</td>
<td>LQT3</td>
<td>Borderline</td>
<td>Normal</td>
<td>KCNH2: Lys897Thr (homozygous), KCNE1 Gly383Ser</td>
<td>QT prolonged and PVCs with exercise</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>53</td>
<td>Female</td>
<td>LQT3</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>SCN5A: Pro2006Ala</td>
<td>Follow-up ECGs showed intermittent QT prolongation</td>
<td></td>
</tr>
</tbody>
</table>

PVCs indicates premature ventricular contractions; PMVT, polymorphic ventricular tachycardia; and SAECG, signal-averaged ECG.

*Heterozygote for the A1136V and G1185E variants and homozygous for Q2958R.
†Novel mutations.