Epinephrine Infusion in the Evaluation of Unexplained Cardiac Arrest and Familial Sudden Death

From the Cardiac Arrest Survivors With Preserved Ejection Fraction Registry

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Background—Epinephrine infusion may unmask latent genetic conditions associated with cardiac arrest, including long-QT syndrome and catecholaminergic polymorphic ventricular tachycardia (VT).

Methods and Results—Patients with unexplained cardiac arrest (normal left ventricular function and QT interval) and selected family members from the Cardiac Arrest Survivors with Preserved Ejection Fraction Registry (CASPER) registry underwent epinephrine challenge at doses of 0.05, 0.10, and 0.20 µg/kg per minute. A test was considered positive for long-QT syndrome if the absolute QT interval prolonged by ≥30 ms at 0.10 µg/kg per minute and borderline if QT prolongation was 1 to 29 ms. Catecholaminergic polymorphic VT was diagnosed if epinephrine provoked ≥3 beats of polymorphic or bidirectional VT and borderline if polymorphic couplets, premature ventricular contractions, or nonsustained monomorphic VT was induced. Epinephrine infusion was performed in 170 patients (age, 42±16 years; 49% men), including 98 patients with unexplained cardiac arrest. Testing was positive for long-QT syndrome in 31 patients (18%) and borderline in 24 patients (14%). Exercise testing provoked an abnormal QT response in 42% of tested patients with a positive epinephrine response. Testing for catecholaminergic polymorphic VT was positive in 7% and borderline in 5%. Targeted genetic testing of abnormal patients was positive in 17% of long-QT syndrome patients and 13% of catecholaminergic polymorphic VT patients.

Conclusions—Epinephrine challenge provoked abnormalities in a substantial proportion of patients, most commonly a prolonged QT interval. Exercise and genetic testing replicated the diagnosis suggested by the epinephrine response in a small proportion of patients. Epinephrine infusion combined with exercise testing and targeted genetic testing is recommended in the workup of suspected familial sudden death syndromes.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00292032.

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Key Words: catecholaminergic polymorphic ventricular tachycardia ■ diagnosis ■ long-QT syndrome ■ genetic testing
its exercise and genetic correlates in a national registry of UCA and familial sudden death.

**Methods**

**Patients**

Details of the Cardiac Arrest Survivors with Preserved Ejection Fraction Registry (CASPER) registry have previously been reported. Briefly, CASPER is a national registry in 11 centers that examines phenotype-genotype correlation and assesses test performance in familial sudden death and UCA. Cardiac arrest patients were eligible for enrollment if they had experienced an UCA with documented cardiovascular collapse, with ventricular tachycardia (VT) or fibrillation requiring direct current (DC) 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 permitted to have transient left ventricular dysfunction or QT prolongation immediately after the cardiac arrest if these resolved promptly. Additional study groups were included cardiac arrest patients’ first-degree relatives and first-degree relatives of unexplained sudden death victims. In total, 4 populations underwent epinephrine infusion: (1) cardiac arrest probands as described above; (2) first-degree relatives of the cardiac arrest proband; (3) first-degree relatives of an unexplained sudden cardiac death (SCD) before the age of 60 with a negative autopsy, presumed arrhythmic; and (4) syncope with documented polymorphic ventricular tachycardia (PMVT).

Investigators and coordinators performed a consultation/assessment to determine whether reversible causes, including drug overdose or a proarrhythmic effect, were present or reviewed the medical record when the arrest was no longer acute. Patients were excluded if they had a resting QTc >450 ms and women had a QTc >480 ms immediately after the cardiac arrest, if imaging demonstrated evidence of hypertrophic cardiomyopathy, if their resting or exercise ECGs. A small number of patients declined testing because of the perceived risks (not quantified).

Epinephrine infusion was performed through a peripheral intravenous line with continuous ECG monitoring. Intravenous epinephrine challenge was performed according to the Mayo Clinic (Ackerman) protocol as previously described, with continuous monitoring at doses of 0.05, 0.10, and 0.20 μg/kg per minute. 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, exceeded 200 mm Hg, if monitoring detected nonsustained VT or PMVT, or previously absent T-wave alternans, or patient intolerance because of headache and nausea. 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 by the site investigator who was unaware of genetic findings at the end of each 5-minute period, and the QTc was calculated using the Bazett formula. 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 TP segment. U waves were excluded from the measured QT interval.

Epinephrine infusion was considered positive for LQTS if the absolute QT prolonged by ≥30 ms at 0.10 μg/kg per minute and borderline if the QT prolongation was 0 to 29 ms (Figure 1). The test was considered positive for CPVT if epinephrine provoked ≥3 beats of polymorphic VT or bidirectional VT and borderline if polymorphic coupllets, premature ventricular contractions, or nonsustained monomorphic VT was induced (Figure 2).

**Testing Procedures**

Patients underwent evaluation as described in the previous published algorithm, including noninvasive and invasive testing in cardiac arrest probands and noninvasive testing in relatives. The extent of testing was based on investigator discretion, taking into account the presentation/trigger in the patient or family member, the findings from previous testing, and the residual index of suspicion. Epinephrine was typically carried out in a cardiac arrest survivor unless a diagnosis was previously obtained. Family members underwent epinephrine infusion when a suspicion arose from other testing, either in their family proband or from their resting or exercise ECGs. A small number of patients declined testing because of the perceived risks (not quantified).

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Symptom-limited exercise testing was performed with a modified or standard Bruce protocol. A positive exercise test for LQTS was defined as an end-recovery QTc >455 ms based on a recently validated algorithm (4–6 minutes into recovery). Targeted genetic testing was performed on the basis of phenotype detection after clinical testing was complete. Testing was accessed on the basis of clinical testing from commercial vendors (n=54; Familion-Transgenomic, Omaha, NE, and GenDx, Gaithersburg, MD; \(KCNQ1\), \(KCNH2\), \(SCN5A\), \(KCNE1\), \(KCNE2\), and additional genes based on generation of testing). Limited research testing assessed 8 patients, with 3 major genes in 3 patients (\(KCNQ1\), \(KCNH2\), \(SCN5A\)) and single gene in 5 patients. Genomic DNA was isolated from blood lymphocytes and screened with direct sequencing performed on suspected culprit genes.

Investigators were asked to review the entire patient record, including the nature and context of symptoms, family history, and the results of clinical and genetic testing, and render a working diagnosis and a qualitative descriptor of the strength of the diagnosis as definite, probable, and possible based on the weight of the evidence. The working diagnosis could be revised over time based on events during follow-up, repeat clinical or genetic testing, or determination of previously unrecognized diagnoses such as early repolarization or short-QT syndrome. Testing of family members of cardiac arrest victims was pursued after investigation of the index arrest patient was complete. This led to tailoring of investigations based on the findings in cardiac arrest patients.

Statistics
Continuous variables were compared by use of a 2-tailed Student \(t\) test, and \(\chi^2\) test was used for categorical variables. Fisher exact testing was performed when cell sizes were ≤5. Multiple continuous variables were compared using ANOVA. Test performance was assessed with calculation of sensitivity, specificity, positive and negative predictive values, and likelihood ratios. Statistical analysis was performed using GraphPad Prism software version 5 for Mac (La Jolla, CA) by the authors (A.K.). Analysis was not stratified by patient group. \(P<0.05\) was considered significant. All results are expressed as mean±SD.

Results
One hundred seventy patients underwent epinephrine infusion, including 58% UCA patients, 21% UCA relatives, 18% SCD relatives, and 4% patients with syncope and PMVT (Table 1). The mean age was 41.6±16.0 years (range 14–79 years), and 86 patients were women (51%). The heart rate increased with incremental epinephrine dosing, with minimal overall effect in the absolute QT interval (Figure 3). The target maximum dose of 0.20 \(\mu\)g/kg per minute was achieved in 164 patients (96.5%), with 0.10 \(\mu\)g/kg per minute in 2 patients (1.2%) and 0.05 \(\mu\)g/kg per minute in 4 patients (2.4%). Infusion did not achieve the maximum dose because of nonsustained
ventricular arrhythmias in 3 patients, diagnostic QT changes in 1, hypertension in 1, and chest discomfort in 1.

Based on the Ackerman protocol, the QT interval increased by ≥30 ms in 31 patients (18%) and 10 to 25 ms in 24 patients (14%) at an infusion rate of 0.10 μg/kg per minute. The QT interval increased by ≥30 ms in 18% of patients at 0.05 μg/kg per minute, 18% at 0.10 μg/kg per minute, and 21% at 0.20 μg/kg per minute (Figure 4).

In the 107 patients who had a correlated exercise test, the end-recovery QTc was longer in the Ackerman-defined positive epinephrine group compared with both borderline and negative patients (451±28 versus 432±28 versus 439±50 ms; ANOVA P=0.047; Figure 5, upper panel), although the correlation between epinephrine ΔQT and exercise end-recovery QTc was modest (R=0.20; P=0.042; Figure 5, bottom panel). Sixty-five of the 107 patients had normal findings on both tests. Using either the exercise test or the epinephrine test as a gold standard for the diagnosis of LQTS, both tests demonstrated good negative predictive value but low positive predictive value (Table 2). Fifty-seven patients underwent genetic testing for LQTS that included at least the 3 major genes (see Methods section), and positive findings were restricted to patients with a positive epinephrine challenge, whose QT interval prolonged by 30 to 90 ms. A pathogenic mutation or variant of unknown significance was found in only 20 of 22 epinephrine long-QT positive patients tested (sensitivity 20%; Table 3). All 4 patients underwent exercise testing; all were abnormal with an end-recovery QTc of 456 to 499 ms. Using a positive stress test or genetic test as a gold standard, epinephrine challenge had a sensitivity of 40%, specificity of 84%, positive predictive value of 0.5, and negative predictive value of 0.78.

Of the 31 patients with a positive adrenaline challenge test, integration of all baseline clinical testing, genetic studies, and clinical follow-up led to a working diagnosis of long QT in 22 patients (71%). Of the remaining 9 patients, a working diagnosis of idiopathic ventricular fibrillation (n=3) and normal (n=4) was based on lack of corroborating exercise and genetic information (n=7), arrhythmogenic right ventricular cardiomyopathy (n=1) based on genetic and imaging confirmation, and CPVT in 1 based on follow-up suppression of recurrent PMVT treated with shocks from an implantable cardioverter defibrillator. Of the 41 patients with a working diagnosis of LQTS, a borderline or abnormal epinephrine response was present in 35 patients (sensitivity including borderline tests=85%). To evaluate the epinephrine response in patients with no evidence or suspicion of long QT (no previous cardiac arrest, normal resting QTc, negative stress test for long QT, no known relative with long QT), the epinephrine result was positive in 8 of 36 patients (22%).

Epinephrine challenge for CPVT was positive in 7% and borderline in 5%. Among 18 epinephrine positive or borderline patients for CPVT who underwent exercise testing, exercise induced isolated premature ventricular contractions, couplets, or bigeminy in 14 (sensitivity 78%) but nonsustained VT in only 2. Twenty patients underwent genetic testing for CPVT (RyR2 sequencing), and only 1 of 8 epinephrine positive patients who had genetic testing had a mutation in the RyR2 gene (RyR2 M3978I, previously reported; sensitivity 13%). Eleven of 12 patients with a working diagnosis of CPVT had an abnormal or borderline response to epinephrine (n=7 and 4, respectively; 92% overall sensitivity). CPVT was diagnosed during follow-up in a single patient with exercise-induced syncope associated with nonsustained polymorphic VT; whose adrenaline infusion and genetic testing were negative but developed recurrent exercise-related polymorphic VT associated with implantable cardioverter defibrillator shocks that responded to high-dose β-blockade.

The diagnostic yield of epinephrine infusion was not different when cardiac arrest patients were compared with the familial sudden death comparator (all other patient groups...
combined, $\chi^2 P=0.49$ for LQTS, $P=0.48$ for CPVT; online-only Data Supplement Figure SI).

**Discussion**

This prospective multicenter study has demonstrated that epinephrine infusion provokes abnormalities in a large proportion of patients with UCA or familial sudden death. These findings may suggest impaired repolarization reserve consistent with LQTS, which is not borne out in the majority of cases by manifest QT prolongation with exercise testing or conventional monogenic LQTS genetic findings. An ideal control population was not studied, but the rate of QT prolongation is in keeping with the small number of control patients studied in 2 previous series using the Ackerman protocol.6,9

Previous studies have applied epinephrine infusion to patients with genotyped LQTS or unaffected controls and suggested excellent test performance in discriminating LQTS patients from controls, and LQT1 as the dominant-positive response. These findings have stemmed from 2 high-profile research centers with a long history of LQTS-related research. Although the Shimizu protocol differs from the Ackerman protocol in the current study by using bolus dosing,18,19 the findings are consistent with those by Ackerman et al6,7,9 in both detection and genotype prediction of LQTS. This may reflect a polarized population of study, with clear evidence of phenotypic and genotypic LQTS or healthy control status. These groups also assessed patients with borderline and normal QT intervals who were gene

| Table 2. Test Performance Using Epinephrine and Subsequently Exercise Testing as the Gold Standard for Diagnosing LQTS |
|-----------------|-----------------|-----------------|
|                | Epinephrine positive | Epinephrine negative |
| Exercise positive | 11               | 18               |
| Exercise negative | 13               | 65               |
| Exercise to epinephrine Gold standard | 24               | 83               |
| Sensitivity        | 46%              | 78%              |
| Specificity       | 38%              | 83%              |

LQTS indicates long QT syndrome; PPV, positive predictive value; NPV, negative predictive value. See text for discussion.

| Table 3. Genetic Test Results in 4 Patients With Positive Epinephrine Challenge for LQTS |
|-----------------|-----------------|-----------------|-----------------|
| Age/Sex        | Diagnosis       | Baseline QT/HR | 0.10 mg/kg per min QT/HR |
|                | Ventricular Arrhythmias | Genetic Finding | Exercise Test Result |
| 29/male        | LQTS            | 410 ms          | 450 ms           |
|                | None            | Pathogenic KCNH2 3256 ins G 1086 Pro frameshift 32X |
|                | No exercise test |
| 22/female      | LQTS            | 420 ms          | 480 ms           |
|                | PVCs            | Pathogenic KCNH2 Arg 1007 His |
|                | End recovery QTc 482 ms |
| 52/female      | LQTS            | 440 ms          | 470 ms           |
|                | None            | KCNJ2 VUS Thr 400 Met |
|                | End recovery QTc 456 ms |
| 15/male        | LQTS            | 390 ms          | 480 ms           |
|                | None            | KCNQ1 VUS Pro 631 Arg |
|                | End recovery QTc 499 ms |

LQTS indicates long QT syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia; VUS, variants of unknown significance; nsPMVT, nonsustained polymorphic ventricular tachycardia; PVCs, frequent premature ventricular contractions; bpm, beats per minute; ICD, implantable cardioverter defibrillator.

A total of 61 patients had genetic testing for LQTS because of epinephrine infusion results, exercise testing, or clinical suspicion.

*This patient had polymorphic ventricular tachycardia with appropriate ICD shocks during follow-up, with subsequent positive genetic testing. See text for discussion.
carriers and found that the test was excellent at unmasking latent QT prolongation with paradoxical prolongation of the absolute QT interval, with specificity >90%. The current study suggests that sensitivity is likely retained with respect to the degree of QT prolongation in the 4 patients with genetic evidence of LQTS, but calls into question the specificity.6-8,9 This is particularly the case because first-degree relatives had a similar response rate to the cardiac arrest patients, who would have been expected to represent an enriched sample with a higher positive yield of testing. Assigning a working diagnosis of LQTS because of an isolated apparently abnormal epinephrine test by definition forms a circular argument, diminishing the specificity of the test because no other corroborating evidence is necessary to arrive at the diagnosis and thus compare with an accepted gold standard. Until a clear gold standard can be adopted in conjunction with comprehensive testing of all patients, the observations can only lead to the conclusion that epinephrine challenge provokes abnormalities that cannot be validated by any of the putative gold standards.

The bolus infusion of Shimizu et al reported 100% specificity of a QTc prolongation of ≥30 ms in identifying mutation carriers.18,19 None of the 12 unaffected family members or 15 controls had QTc prolongation ≥30 ms. In a systematic study of 24 healthy volunteers, Magnano et al20 did not detect paradoxical QT prolongation or a QTc >600 ms at a low dose of epinephrine or with isoproterenol but did see prominent U waves and QT prolongation at higher doses of epinephrine (0.20 μg/kg per minute). In contrast, the Ackerman protocol use of paradoxical prolongation of the absolute QT interval of ≥30 ms was sensitive for LQTS (particularly LQT1) but was less specific, seen in 6 of 27 controls (22%) in a preliminary study and 18% of patients referred for LQTS evaluation who were considered genotype negative.6,9 In that subset that most closely resembles healthy controls (normal QTc, negative stress test, and no previous cardiac arrest), the yield of epinephrine challenge was 22%, consistent with the reports of Ackerman et al.1 The latter group may represent an analogous group to the current study population, although more than half of the current population had experienced a cardiac arrest. This suggests the need to study a larger number of healthy controls to establish the specificity of the paradoxical response in an at-risk population.

Multiple investigators have demonstrated the use of exercise testing in unmasking evidence of LQTS, particularly when the resting QTc is not evidently prolonged.16,17,21-28 Exercise testing in the current study demonstrated a modest correlation with adrenaline results, suggesting that neither test is ideal in evaluating familial sudden death syndromes. This is further hampered by genetic testing results, which were frequently informative.

Epinephrine infusion provoked ventricular arrhythmias that suggested CPVT in a much smaller proportion of patients. The likelihood of provoking ventricular arrhythmias in healthy controls has been reported as very low, with no arrhythmias noted in controls in 2 large series by Shimizu et al.,18,19 isolated premature ventricular contractions in 3 of 44 controls by Vyas et al.,9 and bigeminy in 1 patient. These data suggest that those patients with complex ectopy provoked by epinephrine in the current study may in fact have latent CPVT. These individuals clearly do not fall into the classic definition of CPVT, which presents in a malignant fashion in adolescence with a relatively high yield of detection of mutations in the RyR2 gene. A recent series that includes some of the current patients has proposed that an adult-onset form of CPVT may exist, with later presentation and a low yield of genetic testing.10

Finally, test utility is best derived in a clearly defined population with an evident gold standard. This was clearly the case for epinephrine infusion for LQTS.6,7,9,18,19 Application of the assessed test to an undiagnosed population that is at risk for the target disorder then translates into real-world test utility in the context of clinical uncertainty. The current study could be interpreted to indicate prevalent impaired repolarization reserve, but an alternate interpretation is that epinephrine challenge is sensitive but not specific and that results should be interpreted with caution in the absence of corroborating evidence that the provoked abnormalities resonate with the clinical presentation. Our interpretation of the current findings is that exercise testing is a more physiological test to unmask repolarization abnormalities than epinephrine infusion when LQTS is suspected. The recognition that recovery is an ideal period to detect QTc prolongation has simplified our previous focus on the complex signals and acquisition artifact that is often present during exercise. The pregenomic Schwartz score was a first thoughtful attempt to quantify a continuum of dose response. Replication of the current study in the whole genome era with dual testing is predicted to demonstrate that the term LQTS is indeed too simple and that a term such as QT arrhythmia propensity index may better capture the gradient of risk.

Larger-scale studies that include comprehensive genetic testing, such as a whole genome approach, combined with rigorous phenotype characterization, extended follow-up, and a large sample of healthy controls are necessary to determine the implications of the current findings. In the interim, β-blockers remain the mainstay of treatment for adrenergically mediated disorders, which are generally well tolerated and effective.29,30 Whether this is the treatment of choice in the current population will require further study.

Limitations

The number of cases in this study was relatively small, an inherent problem in studying uncommon diseases. Nonetheless, this study is based on a prospective multicenter experience, which is readily implemented in clinical practice. ECG interpretation can be challenging in this context. This study is limited by not capturing the subcomponents of the QT interval such as the Tpeak-Tend interval, which has been reported in previous studies and postulated to reflect dispersion of refractoriness.18,19 Nonetheless, these same studies reported similar prolongation of the QTend and QTpeak interval as well, supporting the use of the summative QTend interval in the current study. Other forms of adrenergic challenge were not evaluated, such as isoproterenol challenge, which has been proposed for CPVT.31 Finally, a comprehensive genetic screen with extended follow-up 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 a larger population is a clear goal of the current study, which is currently underway. A clear gold standard to test against is lacking in this realm, because both genetic sequencing and exercise testing are not without their own limitations. Further study in the entire genome era combined with long-term follow-up may increase the ability to discriminate between false-positive and true-positive epinephrine responses.

Conclusions

Epinephrine challenge provoked abnormalities, suggesting an arrhythmogenic substrate in a high proportion of patients, most commonly QT prolongation. Exercise and genetic testing infrequently replicated the basis of the epinephrine response. These data suggest a potential incremental role for epinephrine challenge in detecting reduced repolarization reserve but support the need for larger-scale assessment in a healthy control population to establish specificity and the utility of the test. Epinephrine infusion combined with exercise testing and targeted genetic testing is recommended in the workup of suspected familial sudden death syndromes.

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Disclosures

None.

References

Epinephrine infusion has been reported to show excellent sensitivity and specificity for detection of long-QT syndrome and catecholaminergic polymorphic ventricular tachycardia. We performed epinephrine infusion in 98 patients with unexplained cardiac arrest (normal left ventricular function and QT interval) and 72 selected family members from the Cardiac Arrest Survivors with Preserved Ejection Fraction Registry (CASPER) registry using the Mayo clinical escalating infusion protocol. Using the previously reported cutoff of an absolute QT interval prolongation by ≥30 ms at 0.10 μg/kg per minute, testing was positive for long-QT syndrome in 31 patients (18%) and borderline in 24 (14%). Testing for catecholaminergic polymorphic ventricular tachycardia was positive in 7% and borderline in 5%. Correlation with exercise test results was moderate, but it raises concern about the specificity of the provoked changes. Targeted genetic testing of a proportion of abnormal patients was positive in only 17% of long-QT syndrome patients and 13% of catecholaminergic polymorphic ventricular tachycardia patients. Thus, epinephrine challenge provoked abnormalities in a substantial proportion of patients, although exercise and genetic testing replicated the suggested diagnosis in a small proportion of patients. Despite concern regarding the specificity of the observations in this at-risk population, epinephrine infusion combined with exercise testing and targeted genetic testing is recommended in the workup of suspected familial sudden death syndromes.
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Supplemental Material

Figure 1. Proportion of patients with positive and borderline testing for LQTS (upper panel, left) and CPVT (upper panel, right). The lower panel summarizes the diagnostic yield of epinephrine testing, separated by clinical presentation. The left panel indicates the number of patients with positive testing for LQTS, and the right for CPVT. There was no difference in proportions between the familial sudden death groups (Familial SD) and the unexplained cardiac arrest group (UCA) for LQTS (chi squared p=0.49) or CPVT chi squared p=0.048).