Exercise testing: the catecholaminergic polymorphic ventricular tachycardia crystal ball?

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This editorial refers to ‘The role of stress test for predicting genetic mutations and future cardiac events in asymptomatic relatives of catecholaminergic polymorphic ventricular tachycardia probands’ by M. Hayashi et al., on page 1344

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a fascinating inherited arrhythmia syndrome characterized by autosomal dominant transmission of adrenergically induced ventricular tachycardia (VT) associated with syncope and sudden death. First described clinically in the late 1970s,1,2 we have discovered many interesting insights about the disease over the past three decades. Clinical diagnosis is currently based on the observation of stress-induced polymorphic or bidirectional VT in the absence of structural heart disease or a prolonged QT interval.3 Diagnosis can be confirmed by the detection of mutations in the gene encoding the cardiac ryanodine receptor channel (RyR2) or the gene encoding cardiac calsequestrin (CASQ2) in ~60% of symptomatic patients.4–7

Catecholaminergic polymorphic ventricular tachycardia has a malignant prognosis, with a recent study reporting an overall 8-year fatal or near-fatal event rate of 13%.8 Moreover, the same study reported an alarmingly high rate of arrhythmic events,8,9 consistent with other studies.17,18 The authors are to be commended for their clear description of a relatively large population of CPVT gene carriers, advancing our understanding of the variable phenotype of this disease.

There are several important caveats to the diagnostic utility of stress testing that are raised by the present study. Firstly, the optimal criteria for defining a positive stress testing have not been established for CPVT. In the present study, the authors chose inclusive criteria for defining a positive stress test. This proved to be a valid choice in asymptomatic relatives, because of the disappointing 22% sensitivity of using non-sustained VT as a positive test. Sensitivity was increased to 50% without an appreciable change in specificity by including bigeminy or couplets as a positive test for predicting the presence of mutations, consistent with other studies.17,18 The authors are to be commended for their clear description of a relatively large population of CPVT gene carriers, advancing our understanding of the variable phenotype of this disease.
CPVT in a much larger population, who are unlikely to represent our conventional concept of a monogenic familial sudden death disorder.

Secondly, the authors acknowledge the limitations of a ‘one-off’ exercise test. Although exercise tests were only repeated in a limited number of patients, three relatives with an initially negative result had a positive repeat test, with one of these patients experiencing syncope during follow-up. Therefore, exercise testing may need to be repeated periodically in patients with an initial negative test.

Finally and most importantly, the results of the present study confirm that a positive exercise test is highly predictive of CPVT, but that a negative test is unreliable for ‘ruling out’ CPVT. Sensitivity may have been improved by the addition of pharmacological adrenergic challenge, which was performed in only one patient in the present study. In our limited experience, epinephrine challenge has a higher yield than treadmill testing in unmasking complex ventricular ectopy in cardiac arrest survivors with a presumptive diagnosis of CPVT, though the absence of confirmatory genetic testing in some patients suggests that epinephrine may be less specific than treadmill testing. Lastly, the ideal form of exercise testing is not addressed. Most protocols of exercise testing use graduated exercise with either a bicycle or treadmill, developed to create a progressive metabolic workload to provoke ischaemia in patients with coronary artery disease. This approach does not recapitulate the ecletic nature and extent of exertion associated with symptoms in CPVT such as swimming (and drowning!), thus warranting exploration and further study in larger cohorts.

The authors also observed a trend towards a higher rate of cardiac events (predominantly syncope) in asymptomatic relatives with a positive stress test (44%) compared with patients with a negative stress test (13%). The association was perhaps even more clinically significant because more patients with a positive stress test were offered beta-blockade compared with those with a negative stress test. This was an interesting observation and in agreement with other recent studies that have found a higher rate of events in those with ‘provocable’ ventricular arrhythmia. However, the study also raised concerns with over-reliance on exercise testing as a risk-stratifying tool, since two patients with a negative stress test who were not treated with beta-blockers had cardiac events during follow-up. Therefore, we would strongly caution against placing too much emphasis on the results of the stress test in guiding therapy. This potential problem is highlighted by the present study where 11 of the 16 patients with CPVT and a negative stress test were prescribed beta-blocker therapy, whereas only 6 of the 16 CPVT patients with a negative stress test were treated with beta-blockers, perhaps reflecting the influence of exercise testing results on an individual physician’s preference in prescribing beta-blockers. Thus, we agree with the authors that restriction of strenuous physical activity and beta-blockers should be offered to all relatives until the results of genetic testing are known, since the overall event rate in asymptomatic patients is high, and events occur in patients with negative stress testing.

Catecholaminergic polymorphic ventricular tachycardia remains a disease with an unacceptably high rate of fatal events despite advances in its diagnosis and management. The systematic evaluation of diagnostic investigations and novel therapies will require ongoing collaboration between investigators, perhaps via the establishment of a multicenter patient registry, analogous to those which have promoted the understanding of other inherited arrhythmia syndromes such as long QT syndrome and Brugada syndrome.

Based on the current results, one must conclude that exercise test alone does not replace genetic testing, especially in relatives of genotype-positive probands where genetic testing is relatively straightforward. This is particularly the case in the current genetic era, where access to family specific screening is cost-effective, rapid, and typically definitive. Although exercise testing may be a more valuable diagnostic tool in relatives of probands with genotype-negative CPVT, the utility of stress testing in this group appears to be an adjunct to genetic testing for both diagnostic and prognostic purposes, but not a surrogate.

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References


