Syncope and Exercise-Related Ventricular Tachycardia

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Ann Noninvasive Electrocardiol 2012;17(2):146–150

CASE PRESENTATION

A 15-year-old girl, a varsity basketball player, reported that she experienced multiple episodes of syncope over the past several years, occurring every two to three months. These are always associated with mild-to-moderate physical exertion, such as dancing or gym class, or just after exercise. Typically, these episodes have begun with head tingling and blurriness of vision. Usually the amount of physical exertion at the time of syncope is mild to moderate. She denies any palpitations, dyspnea, or angina at any time, including before or after syncope. She admits to one episode of syncope while swimming several years ago. She had been diagnosed as most likely neurally mediated syncope (NMS) and was instructed to increase her dietary intake of sodium and hydration. The patient instituted these changes, but while jumping rope in front of her house, she passed out and was found by her father as she awoke.

Her medical history includes an uncomplicated birth and no unusual illnesses, hospitalizations, or surgeries. The patient does not take any medications. She has a maternal uncle who died in his sleep when he was in his 50s. An ECG can be seen in Figure 1. During an exercise treadmill test, the patient exercised for 13.5 minutes with a modified Bruce protocol before stopping for fatigue.

She developed increasingly frequent premature ventricular contractions (PVCs) throughout the exercise which appeared unifocal and never occurred more often than in bigeminy. These disappeared rapidly with recovery. A 24-hour Holter monitor showed 131 PVCs and 5 beats of supraventricular tachycardia. A waking and sleep-deprived electroencephalogram was normal. A transthoracic echocardiogram showed her heart to be normal in size and function with no significant valvular abnormalities with normal takeoff of coronary arteries.

The patient subsequently had another syncopal event which occurred when she was running to “catch the bus” in the morning. She felt lightheaded, squatted down, and then experienced a syncopal event. She was not wearing her event monitor at the time. An EP study performed documented polymorphic ventricular tachycardia (VT) with rapid degeneration into ventricular fibrillation with triple extra-stimuli (400.200.190.190 milliseconds) on an epinephrine drip. There were increased PVCs and a ventricular bigeminal as well as trigeminal rhythm once on epinephrine. An implantable loop recorder (ILR) was subsequently placed. Several months later, while playing basketball, the patient experienced lightheadedness and another syncopal event. ECG tracings of her loop recorder are shown in Figures 2A and B.

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Figure 1. Baseline ECG.

Dr Wilde: What is your interpretation of the clinical and ECG findings in this case and what further diagnostic or management strategy would you recommend?

Thank you for presenting this interesting case to me. This 15-year-old girl suffers from bottom line, exercise-related syncope, which must have started around age 10. The events do not occur during peak exercise but more at mild to moderate exercise levels and, interestingly, one event occurred while swimming. Notably her family history is negative for young (<40 years of age) sudden cardiac death or exercise-related arrhythmias, but no information is given on the size of the family (which is of importance for a critical appraisal of this information).

From the very beginning I would have been very suspicious on a malignant arrhythmia syndrome. NMS is very unusual during exercise, but can occur immediately after exercise. Moreover, NMS is extremely rare while swimming.

Before going into the details of the case it is important to note that almost all causes of exercise-related events (i.e., arrhythmias) are inherited in nature. Exceptions are mitral valve prolapse (not demonstrable in this case), aberrant coronary arteries (excluded), and coronary artery disease (very unlikely at this age). The remaining differential diagnostic possibilities include long QT syndrome (LQTS, exercise-related events occur typically in type 1), catecholaminergic polymorphic ventricular

tachycardia (CPVT), and a subclinical cardiomyopathy (arrhythmogenic cardiomyopathy [AC] or hypertrophic cardiomyopathy [HCM]). A normal echo does not exclude the latter possibilities but both become less likely. A MRI might be helpful in further investigating these possibilities.

Her baseline ECG is normal, although heart rate is relatively slow. The QTc interval is normal, but it is well known that it might only prolong during exercise or in the first minutes after exercise.¹ A normal QTc interval during exercise or in the first minutes thereafter makes LQTS entity highly unlikely.¹ There might be a hint of early repolarization in the inferior leads with a horizontal ST-segment which has been associated with malignant outcome.² It is described that during exercise increasingly monomorphic ventricular extrasystoles appear, at most in a bigeminal pattern. Similar ectopy occurred on an i.v. epinephrine drip. Finally, the internal loop recorder revealed intermittent polymorphic ventricular tachycardia during exercise associated with a syncopal event.

This case is most typical for CPVT, a diagnosis that should have been considered much earlier in time. Exercise-induced arrhythmias, already demonstrated at the first exercise test, are abnormal and should be considered a red flag (!) and certainly so when the medical history is further characterized by exercise-related syncope. Swimming-related events are typical for CPVT and

Figure 2. (A) Implantable loop recorder tracings recorded during early phases of exercise. (B) Implantable loop recorder tracings recorded while playing basketball.

not unusual the arrhythmias disappear at peak exercise (unpublished data), providing a good explanation for the clinical and electrophysiological findings. Genetic testing typically reveals a mutation in the Cardiac RyR(2) protein.³

As to management, immediate installment on maximal tolerated beta-blocker therapy is warranted (preferably nadolol or propranolol). Treatment efficacy can usually be monitored by exercise tests and any ectopy exceeding isolated extrasystoles should be considered an insufficient treatment result. As a potential second step I would add flecainide, which has been shown to very effective in high-risk patients.⁴ Left stellate ganglion ablation might be considered as a first invasive step in the presence of an insufficient response on combined drug treatment. (For review see van der Werf et al.⁵) ICD therapy could be considered, but it is very important to realize that in this condition it may prove to be pro-arrhythmic.⁵

Finally, immediate family members should be offered genetic testing in case the genetic test on your patient comes back positive or be offered clinical cardiological testing (exercise test) in case genetic testing is not possible or negative (which does not exclude the diagnosis CPVT).

FURTHER HISTORY

Based on the ILR data, the recommendations at this time were to admit the patient to the Pediatric Cardiology service for further evaluation and treatment, including the initiation of beta-blockers for her VT. An ICD was considered at that point, but refused by the family.

The patient sought further evaluation and treatment at another institution and underwent an EPS and VT ablation. At follow-up several months later, the patient had an exercise treadmill stress test which showed her usual bigeminy was present, as well as multifocal PVC pairing. A beta-blocker was still recommended and her restrictions regarding competitive sports were maintained since she was classified as having a catecholaminergic VT with complex presentation and history of several syncope episodes during exercise/stress. However, the patient and family preferred that she should not take beta blockade, and the patient continued to participate in sports activities.

The patient eventually graduated high school. She said she would start beta-blockers but declined an ICD at that time. Shortly thereafter, the patient

was in dance class and experienced a cardiac arrest. CPR was administered and an AED was attached to the patient with multiple shocks being delivered but were unsuccessful in resuscitating the patient.

Dr Wilde: Thank you for your insight so far. Would you please comment on the effectiveness of therapy for patients with CPVT, from pharmacologic agents to ICD? please also share with us your thoughts about the role of ablation for patients with CPVT.

The patient's outcome is of course very unfortunate and includes elements of inappropriate decisions by doctors and the patient herself (or her parents). The latter relates to not taking the advised beta-blocker therapy and not adhering to the appropriately given life style advises. The former relates to the immediate suggestion to implant an ICD and to the performed ablation therapy. As discussed in first term the diagnosis CPVT is highly likely and beta-blocker therapy should have been installed. Beta-blocker therapy is effective in the majority of patients but failure rates have been described in up to 35% of patients at 8 years' follow-up, with fatal events in 6% during the same time period.⁵ In the patient discussed an ICD "was considered" but should, in this disease entity, really be regarded as a last resort option. In the past few years several case reports have appeared describing a "proarrhythmic" effect of ICD therapy. (See van der Werf et al. 2011.⁵) Indeed, inappropriate shocks (i.e., shocks on atrial arrhythmias or shocks based on mal sensing) lead to fear, anger, and pain that may (and has been shown to) start up a vicious circle of true ventricular arrhythmias and ICD interventions and finally death. One should realize that there is no randomized trial that shows the benefit of ICD therapy in CPVT patients and given the above-described potential proarrhythmic effects there is a need for such a study before ICD can be implanted on a large scale.

In the meantime left stellate ganglion ablation and flecainide therapy have been described as successful treatment strategies in CPVT patients who present with an insufficient response on beta-blocker treatment.^{4,5} This patient would have qualified for either option and given its documented efficacy, also on the very long term in individual patients, would have probably been still alive. Ablation therapy has been described, but only successfully for atrial arrhythmias that triggered inappropriate ICD interventions.⁶ The pathophysiological mechanism of CPVT arrhythmias relates to calcium overload of myocardial cells triggering delayed

afterdepolarizations and associated arrhythmias and affects the whole heart. Recent mouse studies suggest that particularly Purkinje fibers exhibit a high sensitivity to calcium overload.⁷ Human studies suggest that the majority of initial ectopy originates from the RVOT area,⁸ in my view making a Purkinje fiber origin less likely by the way. However, whatever the exact arrhythmogenic mechanism, it is very unlikely that it is completely unifocal, preventing successful (ventricular) ablation therapy. In the two patients in whom it had been tried it proved to be unsuccessful.⁸

REFERENCES

1. Sy RW, van der Werf C, Chattha I, et al. Derivation and validation of a simple exercise-based algorithm for prediction of genetic testing in relatives of LQTS probands. *Circulation* 2011;124:2187–2194.
2. Tikkanen M, Junttila J, Anttonen O, et al. Early repolarization: Electrocardiographic phenotypes associated with favorable long-term outcome. *Circulation* 2011;123:2666–2673.
3. Medeiros-Domingo A, Bhuiyan ZA, Tester DJ, et al. Comprehensive open reading frame mutational analysis of the RYR2-encoded ryanodine receptor/calcium channel in patients diagnosed previously with either catecholaminergic polymorphic ventricular tachycardia or genotype negative, exercise-induced long QT syndrome. *J Am Coll Cardiol* 2009;54:2065–2074.
4. van der Werf C, Kannankeril PJ, Sacher F, et al. Treatment with flecainide reduces exercise-induced ventricular arrhythmias in patients with catecholaminergic polymorphic ventricular tachycardia. *J Am Coll Cardiol* 2011;57:2244–2254.
5. van der Werf C, Zwinderman AH, Wilde AAM. Therapeutic approach for patients with catecholaminergic polymorphic ventricular tachycardia: state of the art and future developments. *Europace* 2012;14:175–183.
6. Sumitomo N, Nakamura T, Fukuhara J, et al. Clinical effectiveness of pulmonary vein isolation for arrhythmic events in a patient with catecholaminergic polymorphic ventricular tachycardia. *Heart Vessels* 2010;25:448–452.
7. Herron TJ, Milstein ML, Anumonwo J, et al. Purkinje cell calcium dysregulation is the cellular mechanism that underlies catecholaminergic polymorphic ventricular tachycardia. *Heart Rhythm* 2010;7:1122–1128.
8. Sumitomo N, Harada K, Nagashima M, et al. Catecholaminergic polymorphic ventricular tachycardia: electrocardiographic characteristics and optimal therapeutic strategies to prevent sudden death. *Heart* 2003;89:66–70.