A young man with a strong family history of sudden cardiac death and channelopathy

Recurring tachycardia and syncope in a young person

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Summary

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited cardiac arrhythmia in the absence of structural cardiopathy with a strong potential for sudden cardiac death (SCD). A patient with a worrisome family history of SCD and genetically proven CPVT in various family members was found to have CPVT with exaggerated cathecolaminergic burden and stress-induced complex cardiac arrhythmias. The arrhythmias are mediated by delayed after-depolarisation. The antiarrhythmic effect of the β-blocker metoprolol was insufficient. The patient refused other antiarrhythmic drugs. He received an implantable cardioverter defibrillator (ICD), which was effective in treating the recurring arrhythmia. Vigorous physical activity and high emotional stress must be avoided by these patients. The case underlines the importance of ICD in patients with recurring syncopes, a strong family history of SCD with a genetically proven CPVT in various family members.

Key Words: catecolaminergic polymorphic ventricular tachycardia; inherited cardiac arrhythmia

Introduction

Sudden cardiac death (SCD) is a devasting event. In a prospective study [1] the addition of genetic testing to autopsy investigation found an annual incidence of SCD of 1.3 cases per 100 000 persons 1 to 35 years of age, 72% of the cases were boys or young men. At present approximately 30% of patients are genotype negative. A clinically relevant cardiac mutation was detected in 27% of cases and identified an inherited cardiac disease in 13% of the families in which unexplained SCD occurred. The genetic defects that cause catecholaminergic polymorphic ventricular tachycardia (CPVT) may be linked to mutations in chromosome 1 (115,700,007,768,781, reverse strand GRCh38: CM000663.2) [2]. Thus far, two genetic variants have been identified [3,4]. The detected mutations involve Ca^{2+} handling, mostly in ryanodine (Ry) isoforms, less frequently in the Ca^{2+}-binding protein calsequestrin (CASQ2), or the integral proteins triadin 1 and junctin (JCN) [3, 4]. Defects in proteins of this junctional Ca^{2+} signalling complex induce irregular Ca^{2+} flow and electrical instability at the sarcoplasmic reticulum (SR) of cardiac (and muscular) myocytes. The electrical dysfunction is complex and leads to a SR "perceived $Ca2^+$ overload", the so called "Ca^{2+} overload paradox", with a consequent decreased threshold to Ca^{2+} and predisposition to arrhythmia [3, 4]. Experts in basic research and pharmacology [3, 4] write that "technically" CPVT is not a "true" cardiac channelopathy, because it is an inherited genetic arrhythmia encoding a channel-related protein and not the channel itself. However, ryanodine receptors actually are part of the Ca^{2+} channels that control Ca^{2+} flow out of the SR protein and cause CPVT. Furthermore, there is a phenotypic and therapeutic overlap with long QT syndrome (LQTS) and short QT syndrome (SQTS). It is therefore clinically correct to accept CPVT as a channelopathy. CPVT is characterised by a structurally normal heart with a myocardial substrate that is highly disposed to ventricular arrhythmias, typically triggered by adrenergic stimulation, especially physical exertion or emotional stress. Patients with CPVT have an entirely normal-looking ECG at rest, but clinical exercise, or stress testing with adrenaline, may provoke several arrhythmias and ventricular tachycardia (VT), characteristically in a bidirectional or polymorphic pattern. Ventricular ectopic beats in CPVT are mediated by delayed after-depolarisation.

Case report

A 23-year-old Caucasian male patient was referred because of syncope during jogging. His first symptoms of cardiac arrhythmia began at the age of 12 years, during physical effort. There was a worrisome familial anamnesis for SCD in the paternal family. A *CASQ2* mutation had been detected in the paternal family. The father, an uncle and a cousin died suddenly, at the ages of 29, 34 and 27, respectively, and an aunt had been fitted at the age of 36 with an implantable cardioverter defibrillator (ICD) for secondary prophylaxis. The patient had refused a genetic test. He was in excellent clinical conditions and jogged regularly at least twice a week. There were no classic cardiovascular risk factors. A laboratory check-up did not detect any pathology. The resting ECG was normal. At echocardiographic examination

there was no structural cardiopathy. A 24-hour dynamic ECG, recorded during jogging, detected 98 runs of tachyarrhythmia with frequent and complex atrial ectopic beats and paroxysmal atrial fibrillation, and some premature ventricular beats (fig. 1a, 1b, 1c, and 1d). The atrial ectopic beats were polymorphic and probably derived from increased automaticity. Some premature ventricular beats were also seen. Paroxysmal tachycardic atrial fibrillation was detected. A cyclo-ergometric stress test elicited marked horizontal ST downsloping in the left precordial leads, without chest pain. The ECG (fig. 2) recorded in the post-exercise recovery phase shows VT with a rate of 125 beats/min. The VT lasted almost 2 min. The diagnosis of VT is confirmed by the atrioventricular dissociation in the second QRS complex in V4–V5. In the fifth minute of the recovery phase the ECG (fig. 3a) showed slow intraventricular conduction in the posterior fascicle, exp-

laining the appearance of left axis deviation and a slightly broader QRS complex. In the follow-up (recovery) phase a negative T-wave was recorded in aVF and in V3–V6 (fig. 3b). The QRS morphology returned to normal after 15 min. The disappearance of the T negativity confirmed the hypothesis of T-wave memory due to VT [5, 6]. A pharmacological stress test with adrenaline would have confirmed the catecholaminergic aetiology of the arrhythmia, but in this case it was considered unnecessary.

Treatment

Clinical therapy for CPVT traditionally has relied on reducing precipitating circumstances (vigorous physical activity and high emotional stress must be avoided in those patients), high-dose noncardioselective β-adrenergic blockade and adhesion to therapy [3, 4]. In addition to blunting whole-body adrenergic tone,
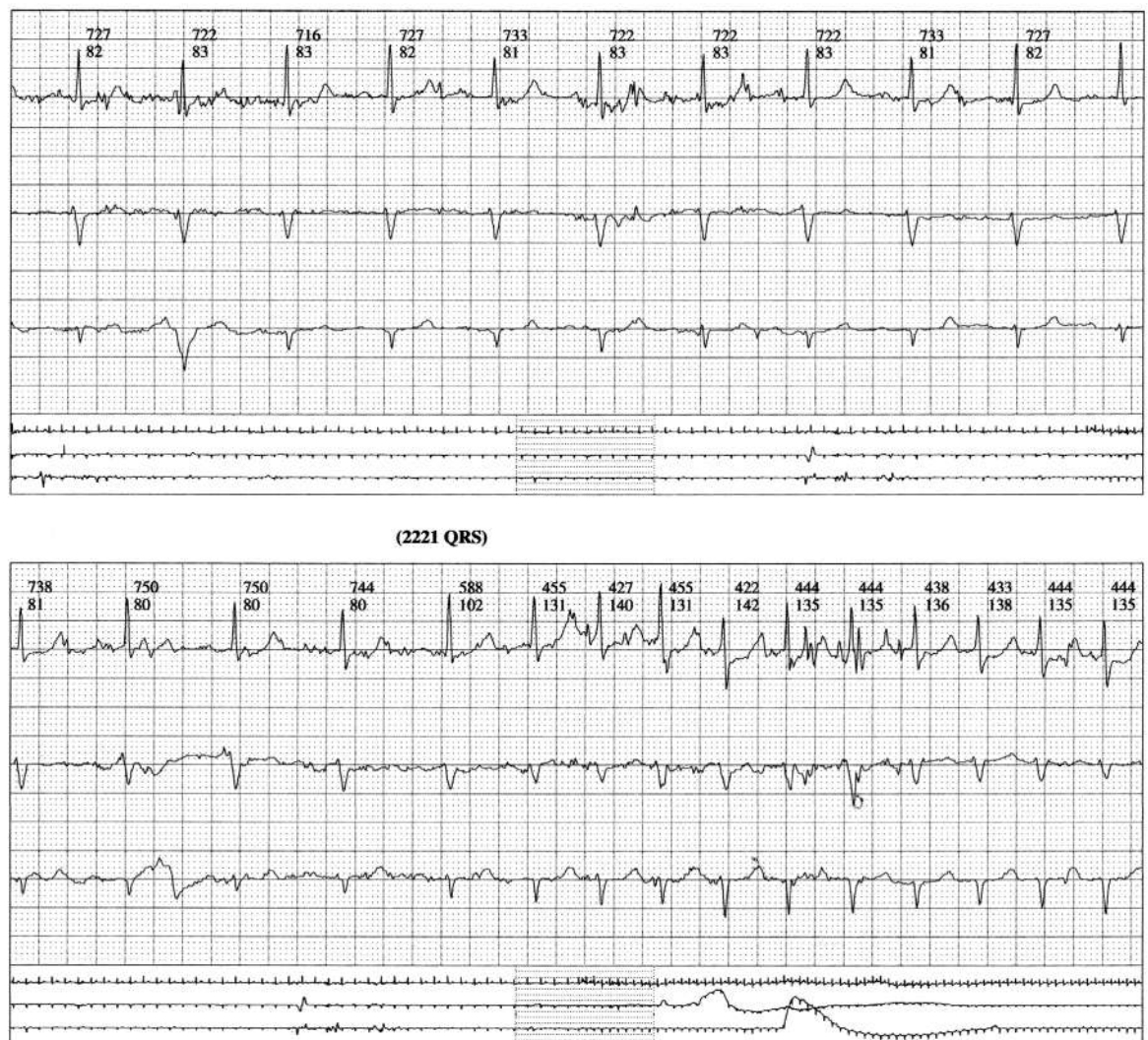

(2221 QRS)

Figure 1a: Dynamic ECG recording during jogging. Beginning of the tachycardic arrhythmia. Symptomatic long run long lasting tachyarrhythmia (2221 QRS complexes). Begining of atrial ectopic beats of undetermined origin (probably automatic aetiology). Heart rate up to 170/min.
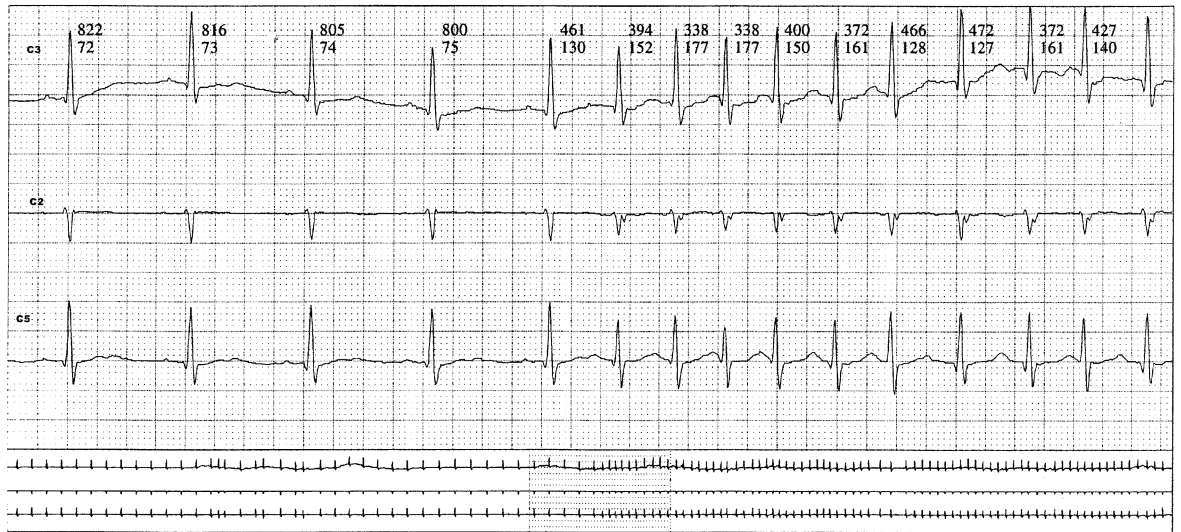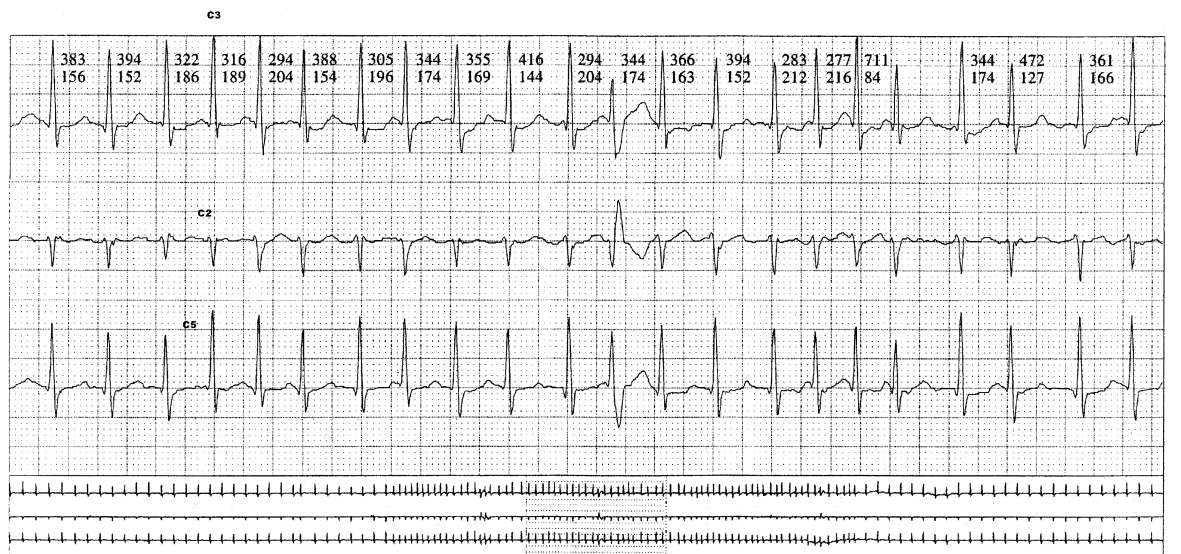
Figure 1b: Dynamic ECG recording during jogging. Change from atrial arrhythmia to paroxysmal atrial fibrillation.
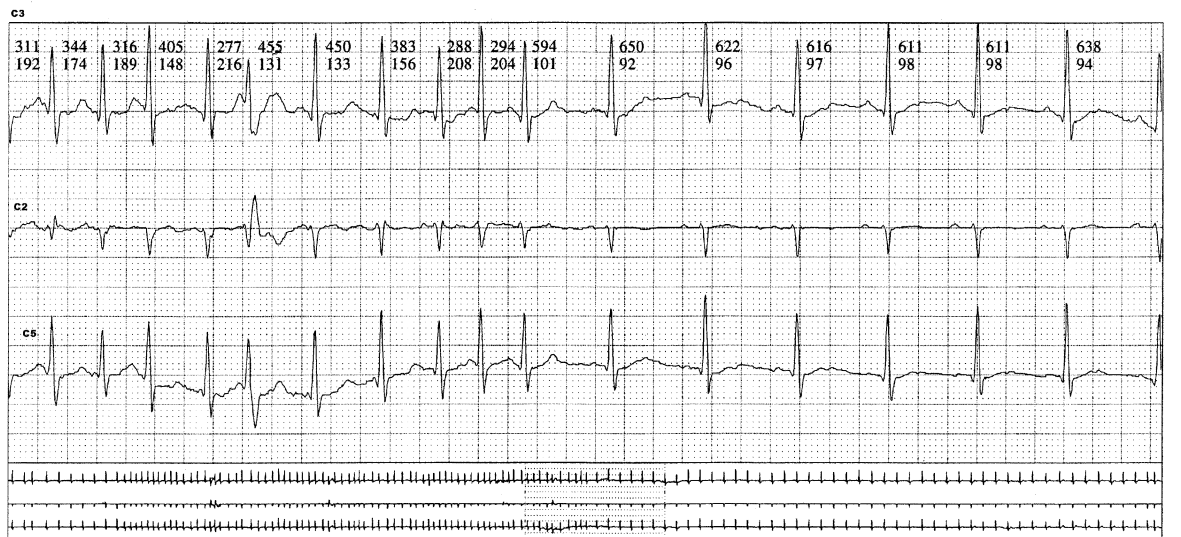

End of the supraventricular episode

Figure 1c: Dynamic ECG recording during jogging. Paroxysmal atrial fibrillation.
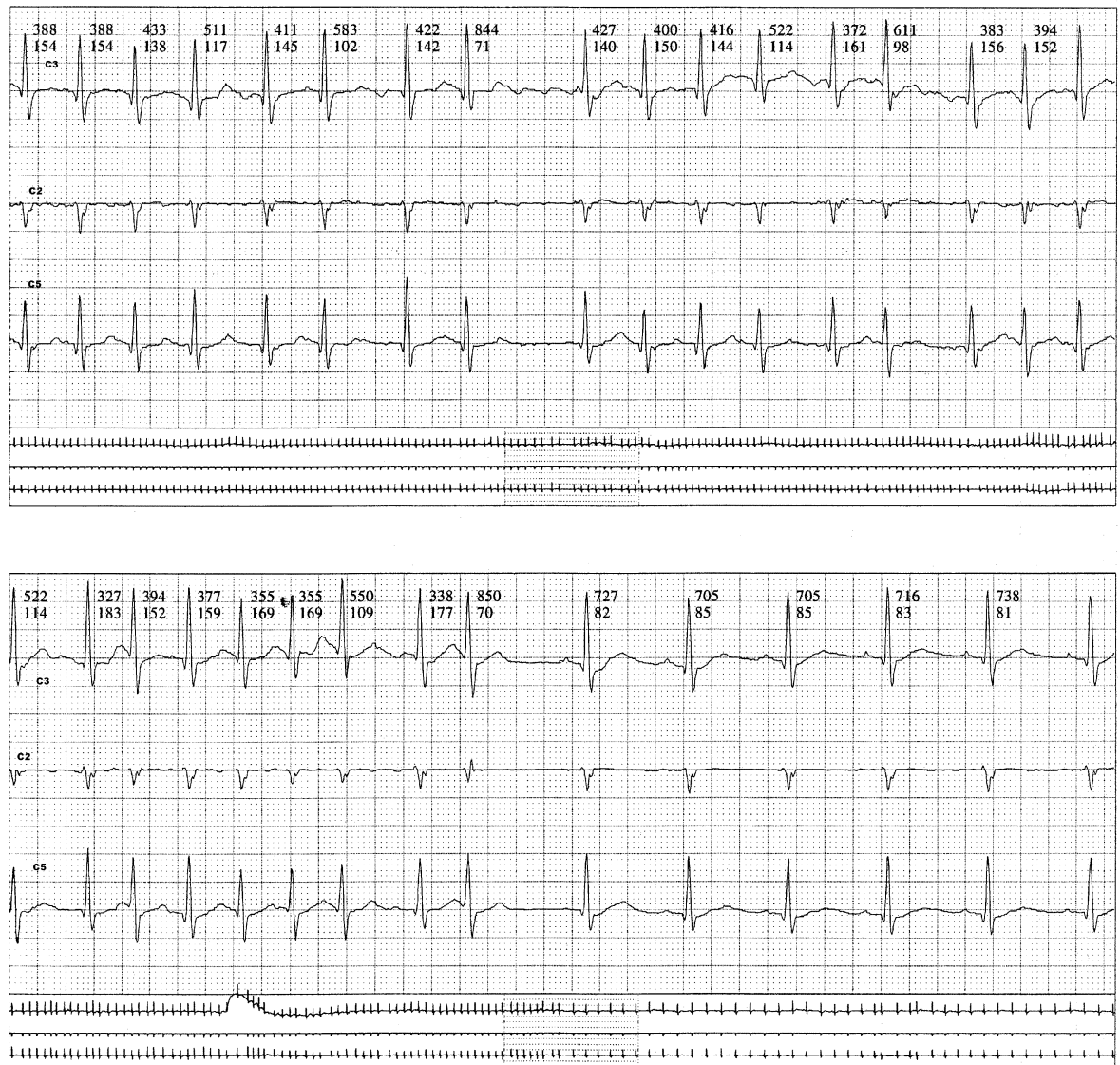
Figure 1d: Dynamic ECG recording during jogging. Termination of atrial fibrillation.

β-blockers modulate the heart rate-dependent overload of Ca^{2+} in cells and may directly reduce the type-1 Ca^{2+} channel current. Ca^{2+} channel blockers have also been used and have been shown in small studies to partially protect patients from exertion-induced arrhythmic events [3, 4]. This patient was treated with metoprolol retard, the dose being slowly adjusted to 200 mg/day. The patient refused to stop his sporting activity. He was instructed to adhere to the therapy and to reduce the intensity of jogging. The frequency of symptoms decreased. However, repeated dynamic ECG recording showed that arrhythmia persisted. It has been shown [4] that the Na^+-channel blocking drug flecainide inhibits RyR2 activity and reduces spontaneous SR Ca^{2+} release. It also seems to have significant antiarrhythmic effects in *CASQ2* models and small clinical series, suggesting that the effects of flecainide, the

role of *CASQ2* in CPVT, or both are still incompletely understood. Some patients with CPVT may require combination medical therapy, with high-dose β-blockers plus flecainide, verapamil, or both. However, despite polytherapy there continues to be a significant rate of cardiac events. Side-effects of medical polytherapy may be important. Our patient refused therapy with either verapamil or flecainide because the combined therapy had been ineffective and poorly tolerated by his relatives. The use of nonpharmacologic therapies is warranted for medically refractory cases. Minimally invasive left cardiac sympathetic denervation has been reported by several groups to be effective for selected patients with CPVT, although the numbers treated with this technique are still small. Because of the catecholaminergic nature of the disease and the patient's worrisome familial history of SCD,

the risk of arrhythmic storm was of particular concern. The implantation of an ICD was considered and the patient accepted an invasive cardiac diagnostic procedure. At ventriculography no structural pathology was detected and biventricular function was normal. Coronarography did not detect a coronary artery disease. The patient received an ICD.

At 1-year follow-up, under therapy with metoprolol retard, recurring supraventricular and ventricular tachycardic runs occurred during jogging and were success-

fully treated by appropriate ICD discharges. Atrial fibrillation did not recur. Vigilant programming of ICDs and discussions to minimise medication non-compliance are vital because even an inappropriate shock can trigger an electrical storm with multiple shocks. The patient has now returned to his country of birth. He was instructed to be strictly followed up by a local cardiologist experienced in arrhythmias and ICD therapy.
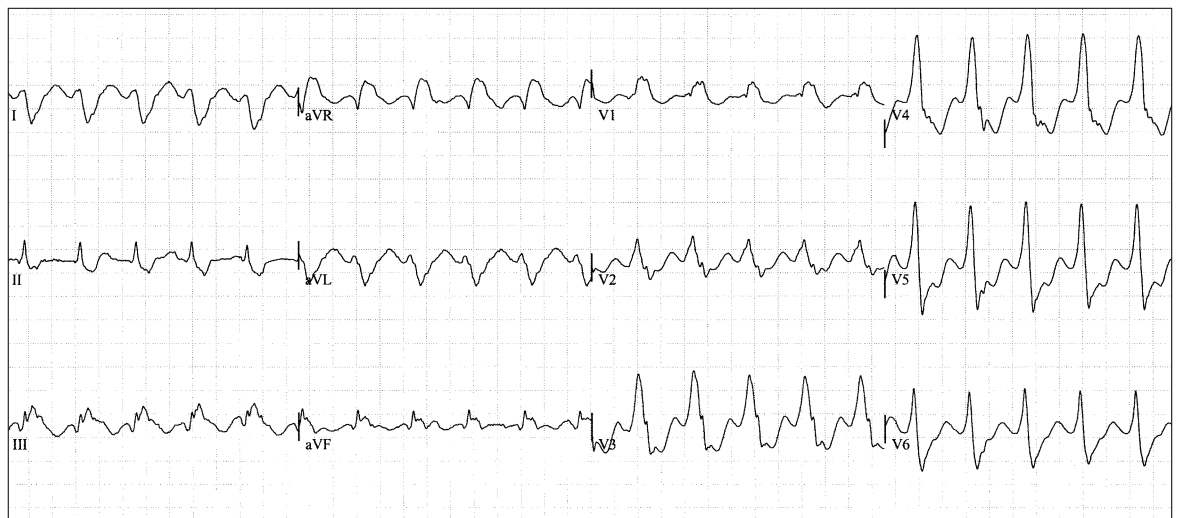

Figure 2: Ventricular tachycardia (rate 125/min) with biphasic right bundle branch block morphology in V1 and V4–V5. The atrioventricular dissociation in the second QRS complex in V4–V5 confirms the diagnosis of ventricular tachycardia.

Figure 3a: ECG changes in the recovery phase of the stress test. In the fifth minute of recovery the ECG detects slow intraventricular conduction in the posterior fascicle, explaining the appearance of the left axis deviation and a slightly broader QRS complex.
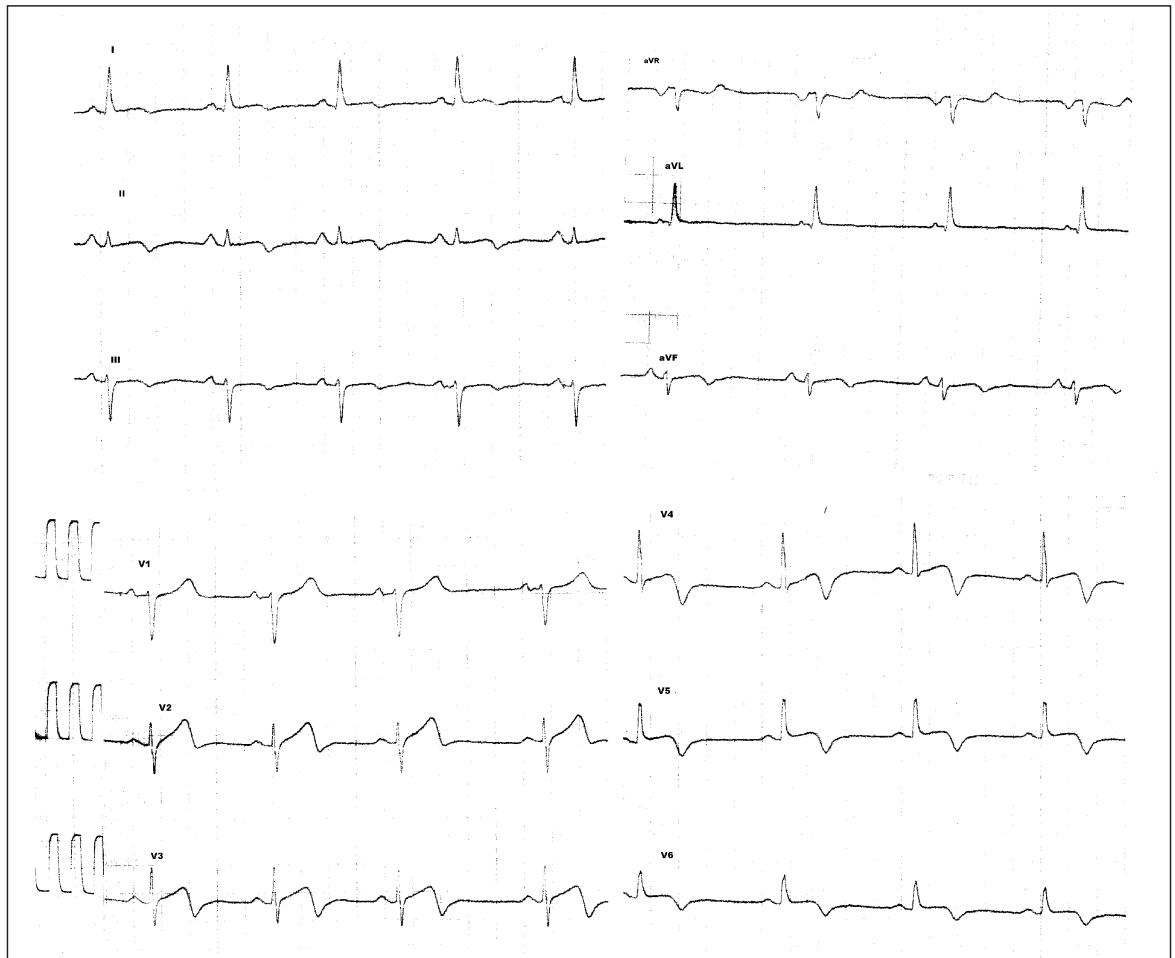
Figure 3b: ECG changes in the recovery phase of the stress test. The QRS morphology returns to normal. Negative T-waves are present in aVF and V3–V6. The disappearance of the T negativity confirm the hypothesis of T-wave memory due to ventricular tachycardia.

Discussion

This patient has a CPVT and a worrisome history of SCD and a channelopathy. Stress testing showed ST down-sloping, QRS conduction disturbances, after-repolarisation arrhythmias and secondary (memory-induced) T negativity. These changes prove relevant catecholaminergic activation. In the absence of myocardial ischaemia and/or dilatative cardiomyopathy, similar arrhythmias are found in patients with exaggerated sympathetic stimulation, such as patients with cerebral haematoma. These ECG changes indicate a high risk for SCD.

The past 20 years have witnessed an incredible advancement in in the role of genetics on cardiac arrhythmias [3, 4]. The case underlines the importance of ICD in patients with recurring syncopes, a worrisome family history of SCD with a genetically proven CPVT in different family members.

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