

Catecholaminergic Polymorphic Ventricular Tachycardia: The Cardiac Arrest Where Epinephrine Is Contraindicated

David Bellamy, MBChB¹; Gabrielle Nuthall, MBChB, FRACP, CICM^{2,3};

Stuart Dalziel, MBChB, FRACP, PhD^{4,5}; Jonathan R. Skinner, MD, MRCP (UK), FRACP, FHRS^{1,5,6}

Objectives: To raise awareness among pediatric intensive care specialists of catecholaminergic polymorphic ventricular tachycardia; an uncommon cause of polymorphic ventricular tachycardia and ventricular fibrillation arrest in children and young adults where epinephrine (adrenaline), even when given according to international protocols, can be counter-productive and life-threatening. We review three cases of cardiac arrest in children, later proven to be catecholaminergic polymorphic ventricular tachycardia related, where delay in recognition of this condition resulted in significantly longer resuscitation efforts, more interventions, and a longer time to return of spontaneous circulation.

Design: Retrospective case series.

Setting: Tertiary children's hospital.

¹Green Lane Paediatric and Congenital Cardiac Services, Starship Children's Hospital, Auckland, New Zealand.

²Paediatric Intensive Care Unit, Starship Children's Hospital, Auckland, New Zealand.

³Department of Paediatrics Child and Youth Health, the University of Auckland, Auckland, New Zealand.

⁴Children's Emergency Department, Starship Children's Hospital, Auckland, New Zealand.

⁵Departments of Surgery and Paediatrics: Child and Youth Health, the University of Auckland, Auckland, New Zealand.

⁶Cardiac Inherited Disease Group, Auckland City Hospital, Auckland, New Zealand.

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Each child is enrolled in the Cardiac Inherited Disease Registry, part of which gives consent for publication of deidentified data. In addition, although there are no identifying features (name, year of birth, etc.) and no photos, each family has reviewed this article and consent has been obtained for publication from the guardians of each of the three children.

For information regarding this article, E-mail: jkskinner@adhb.govt.nz

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Patients and Results: Three previously well children 4, 5, and 10 years old presented with cardiac arrest triggered by light activity, partial water immersion, and running, respectively. Initial resuscitation was bystander cardiopulmonary resuscitation and community defibrillation in all three cases. Electrocardiograms revealed multifocal ventricular ectopy, and in two (4 and 10 yr old), this correlated with repeated administration of epinephrine during repeated ventricular tachycardia and ventricular fibrillation cardiac arrest resuscitation cycles. This ultimately resolved immediately (at 78 and 140 min, respectively) with IV opiates once catecholaminergic polymorphic ventricular tachycardia was suspected. During recovery, on extracorporeal membrane oxygenation, epinephrine challenge in two children induced polymorphic ventricular tachycardia, bidirectional ventricular tachycardia, and ventricular fibrillation, which was cardioverted with flecainide in the 4-year-old. The third case was recognized early as catecholaminergic polymorphic ventricular tachycardia and was managed by avoiding epinephrine and using opiates and general anesthesia after the initial (single) cardioversion, and had a much better clinical course, without recourse to extracorporeal membrane oxygenation. All three carried de novo RyR2 (cardiac ryanodine) mutations.

Conclusions: Those involved in resuscitation of young people should be aware of catecholaminergic polymorphic ventricular tachycardia and be suspicious of persistent ventricular ectopy, polymorphic, or bidirectional ventricular tachycardia during resuscitation. Appropriate management is avoidance of epinephrine, administration of general anesthesia, IV opiates, and consideration of flecainide. (*Pediatr Crit Care Med* 2018; XX:00–00)

Key Words: arrhythmia; cardiopulmonary resuscitation; catecholaminergic polymorphic ventricular tachycardia; pediatric resuscitation

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a genetic condition with an estimated prevalence of 1 in 10,000 (1, 2), characterized by epinephrine (adrenaline)-induced polymorphic ventricular tachycardia (VT) leading to syncope and sudden death in children and adolescents. Genetic tests in those who died from sudden

unexplained death (autopsy negative) under 35 years old reveal this condition almost as commonly as long QT syndrome (3, 4). Common triggers include exercise or emotion (1, 5–8). Outpatient diagnosis depends on exercise-induced ventricular ectopy, bidirectional, or polymorphic VT (2, 9). Epinephrine challenges have been used to demonstrate provocation of polymorphic or bidirectional VT (9–11). Genetic testing reveals mutations in the cardiac ryanodine receptor gene (RyR2) in 50–60% of those with CPVT (1, 2, 6–9, 12). Long-term treatments for CPVT are β -blockers, flecainide, and left cardiac sympathetic denervation (2, 7, 13–17) with implantable cardiac defibrillator (ICD) indicated in some patients (1, 2, 9, 15, 18).

Epinephrine is recommended as part of current advanced cardiopulmonary resuscitation (CPR) guidelines (19–22). Here we describe three children who presented following cardiac arrest, ultimately proven to be due to CPVT, where the clinical course was either made worse through the administration of epinephrine and/or improved by the use of opiate analgesia and/or general anesthesia with avoidance of epinephrine. In two of these cases, we also describe how epinephrine testing while on extracorporeal membrane oxygenation (ECMO) was used to diagnose CPVT, and in one where flecainide stopped the VT.

Each subject is enrolled in the consent-based and ethically approved Cardiac Inherited Disease Registry New Zealand, which permits deidentified publication of clinical and genetic information. Because some potentially identifying features are presented, signed informed consent was obtained from each of the parents after they reviewed the article.

CASES

Case A

A 4-year-old boy (approximately 20 kg) collapsed while playing outside with another young child, unwitnessed by any adults. An estimated 2–4 minutes passed before CPR was started by an adult family member. Ambulance staff arrived 5 minutes after initiation of CPR and found the child in asystole. Return of spontaneous circulation occurred 10 minutes after initiation of chest compressions and bag-mask ventilation only. On route to hospital at 23 minutes after CPR was started, he had another cardiac arrest, described as pulseless electrical activity (PEA). At this time, the first bolus of IV epinephrine (0.2 mg~0.01 mg/kg) was given, after which he went into ventricular fibrillation (VF) and was shocked with 100 J into sinus bradycardia at 50–60 beats/min.

In the emergency department, at 34 minutes, he was breathing spontaneously with a sinus bradycardia of 40 beats/min and poor peripheral perfusion, he received two further boluses of 0.2 mg IV epinephrine, 3 and 7 minutes later. There were frequent multimorphic ventricular extrasystoles (VEs). At 46 minutes, he had another VF arrest, at which point CPR was recommenced then two 100 J shocks, IV saline (10 mL/kg), and calcium (1 mL/kg 10% calcium gluconate) were given. After this, he was intubated and ventilated. He was still in VF after the intubation, and with CPR continuing, an additional 0.2 mg epinephrine bolus was given at 56 minutes with another direct current (DC) shock and amiodarone (10 μ g/kg), after which he

reverted to sinus rhythm at 110 beats/min for around 6 minutes, but with intermittent ventricular ectopy.

At 64 minutes, he had another low output arrest with sinus rhythm but very weak/absent central pulses and interspersed runs of VT. A fifth epinephrine bolus was given followed by an epinephrine infusion was started at 0.05 μ g/kg/min. In addition, he received IV magnesium, lignocaine, and saline boluses and had a further 0.2 mg epinephrine bolus 10 minutes later, after which the epinephrine infusion was increased to 0.5 μ g/kg/min. The rhythm alternated between sinus bradycardia and rapid polymorphic VT.

At 78 minutes on the advice of a pediatric electrophysiologist, the epinephrine infusion was stopped and 200 μ g (10 μ g/kg) of fentanyl was given IV. This dramatically altered the course of events. Within minutes, CPR was ceased as he had a return of spontaneous circulation with a sinus bradycardia of 50 beats/min and mean blood pressure of 75–85 mm Hg. Following the resuscitation, he was put on ECMO because of severe metabolic acidosis (pH, 6.9; lactate, 6.1 mmol/L), hypoxemia, and poor myocardial function (ejection fraction, 18%).

In total, he received six epinephrine boluses, an epinephrine infusion, and 4 DC shocks for VF.

The 12 lead electrocardiogram was normal and the left ventricular function returned rapidly to normal while on ECMO. There were no features to suggest myocarditis, and there was no family history of sudden death or syncope.

After 24 hours on ECMO, with stable hemodynamic and metabolic parameters, and good ejection on echocardiography, an epinephrine challenge was done to confirm the diagnosis of CPVT. An infusion was started at 0.2 μ g/kg/min which induced polymorphic VT. A flecainide bolus of 40 mg over a few minutes led to gradual resolution of the tachycardia, confirming the diagnosis (Figs. 1–3).

An ICD was inserted, and regular atenolol and flecainide were started. Genetic testing confirmed a de novo RyR2 mutation (p.Ser2246Leu), absent in both parents. His ICD has not fired in 12 months of follow-up.

Case B

Case B, a 10-year-old girl (weight 30 kg), had a background of presumed epileptic seizures associated with exercise. While running, she was witnessed to collapse, followed by a brief seizure. She was found to be pulseless and not breathing. CPR was initiated by bystanders for 8 minutes before ambulance staff arrived. DC shock (150 J) was delivered for VF, and 0.8 mg (~0.03 mg/kg) IV epinephrine was given. Return of spontaneous circulation was recorded after 20 minutes, and she was transported to the local hospital. A second VF arrest occurred at 38 minutes, on arrival at the hospital, with delivery of a 70 J DC shock and return of spontaneous circulation. IV magnesium and amiodarone were given, and a propofol infusion was started. She had another VF arrest and received seven recorded DC shocks, but no epinephrine. She returned to sinus rhythm at 81 beats/min, with occasional ventricular ectopy and remained stable for over an hour on a propofol infusion.



Figure 1. Series of 12 lead electrocardiograms. All recorded at 25 mm/s. Initiation of ventricular tachycardia with epinephrine challenge.

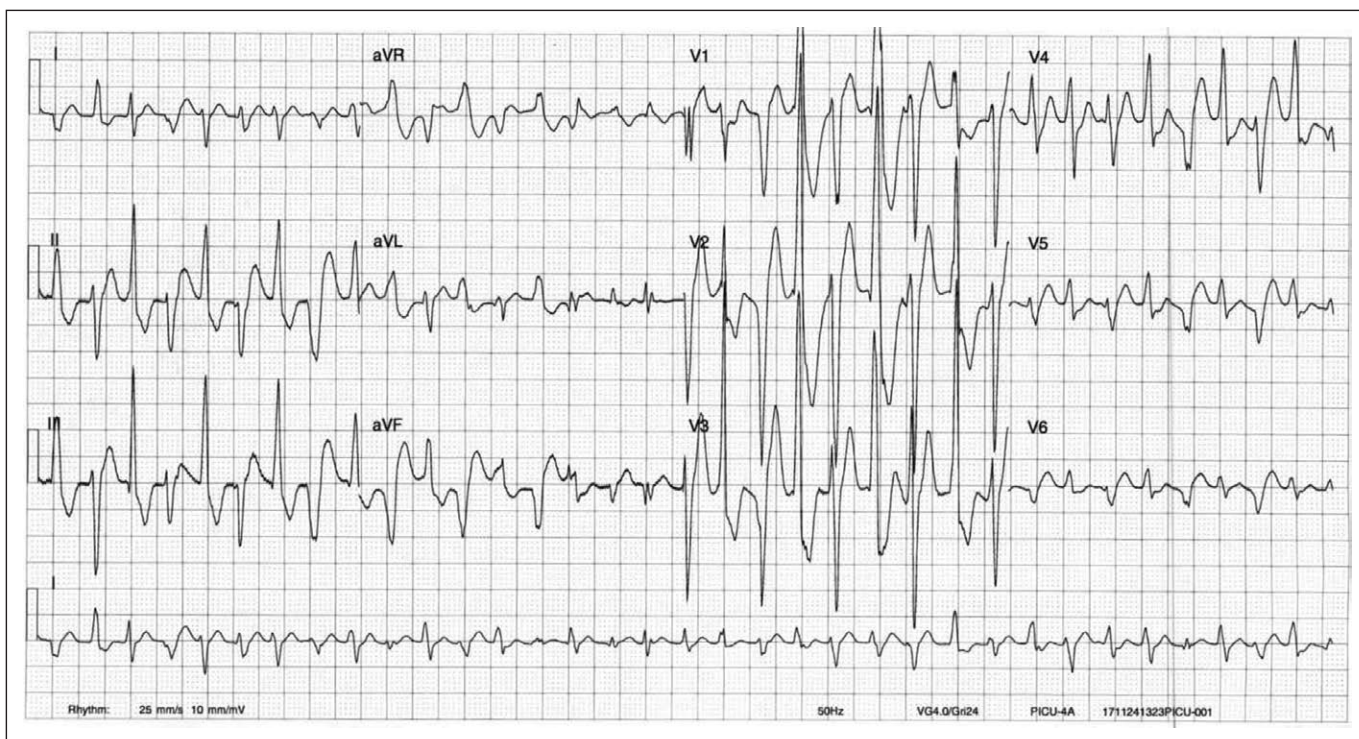


Figure 2. Series of 12 lead electrocardiograms. All recorded at 25 mm/s. More organized, bidirectional ventricular tachycardia after the commencement of the flecainide infusion.

At 2 and 3 hours, she had further VF arrests receiving five and four DC shocks, respectively. She was given IV magnesium, amiodarone, and after her cardiac rhythm stabilized, she was started on an amiodarone infusion. She received no epinephrine during these resuscitations.

She was transferred to the PICU at a tertiary children's hospital following the third VF arrest and proceed to have three further arrests in the next 8 hours with frequent multimorphic ventricular ectopy between arrests. Another arrest occurred at 9 hours, and she received 5 DC shocks and an IV epinephrine

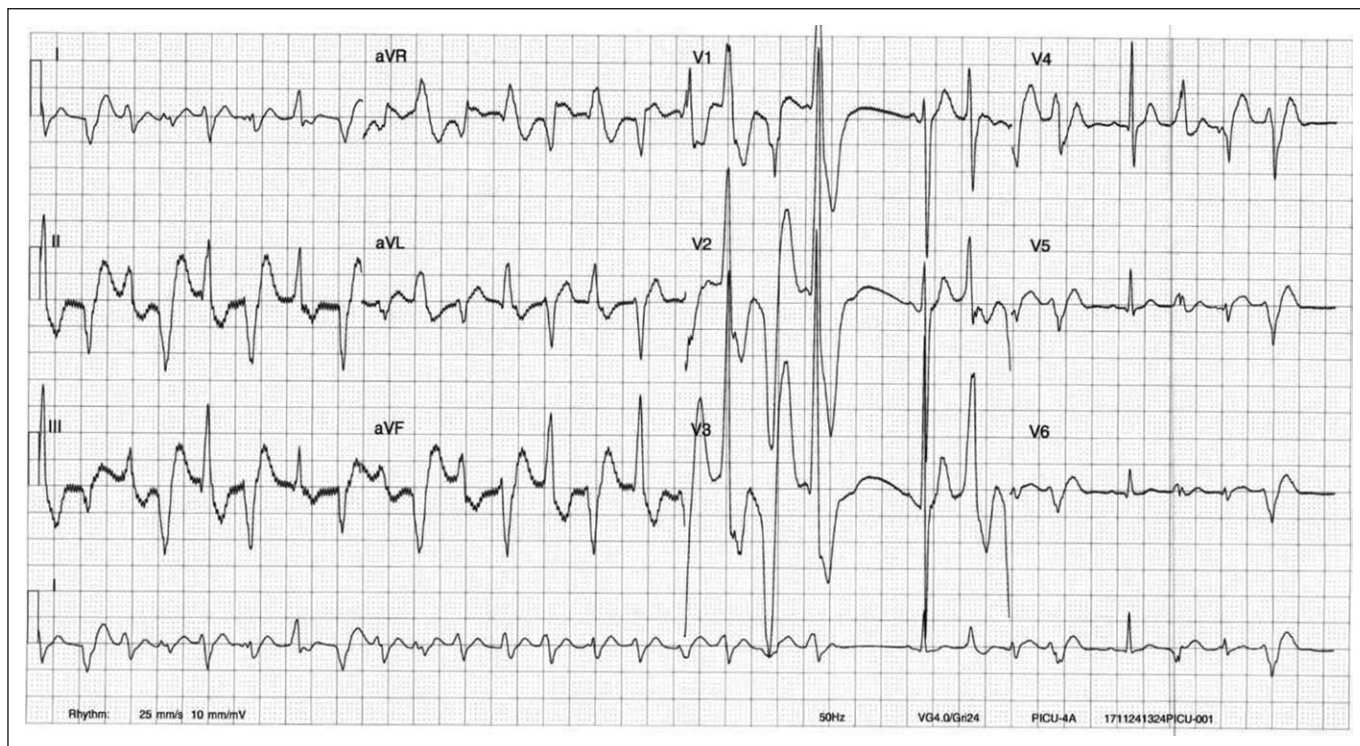


Figure 3. Series of 12 lead electrocardiograms. All recorded at 25 mm/s. Termination of ventricular tachycardia during flecainide administration, resolving here to frequent ventricular ectopy and after this into sinus rhythm.

bolus, IV magnesium, and atropine. She was started on an epinephrine infusion at 0.05 $\mu\text{g}/\text{kg}/\text{min}$, up titrated to 0.2 $\mu\text{g}/\text{kg}/\text{min}$. After the infusion was started, she received two further epinephrine boluses and four further DC shocks over 10 minutes. Specialist pediatric electrophysiology advice was sought, CPVT was suspected, and at 20 minutes into the arrest, IV fentanyl (10 $\mu\text{g}/\text{kg}$) was given, continuous IV epinephrine was stopped, and the VT/VF storm settled over 2 minutes. A final VF arrest occurred 40 minutes later, which resolved with a DC shock, IV lignocaine, magnesium, and further fentanyl (10 $\mu\text{g}/\text{kg}$).

She was started on ECMO as she had very poor ventricular function, poor cardiac output, and bradycardia. Family history was negative, the resting electrocardiogram was normal, the heart was structurally normal on echocardiography, and there was nothing to suggest myocarditis.

To confirm the suspicion of CPVT, while stable on ECMO, she received a 0.2 mg epinephrine bolus, then a 0.2 $\mu\text{g}/\text{kg}/\text{min}$ infusion of epinephrine which caused a short run of ventricular bigeminy and finally a 0.5 $\mu\text{g}/\text{kg}/\text{min}$ infusion that caused self-reverting VT/VF (Figs. 4 and 5).

She underwent a left cardiac sympathectomy, had an ICD implanted, and was started on nadolol and flecainide; genetic testing confirmed a de novo RyR2 mutation (p.Ser2246Leu), absent in both parents. She had no further episodes of cardiac arrest, and her ICD has not fired in 74 months of follow-up.

Case C

Case C, a 5-year-old girl, weighing 17 kg, was climbing down into the water from the back of a boat to the point where her legs were submerged in water when she became suddenly

unresponsive, and fell backward into the water. She was pulled back onto the boat, and CPR was started by a family member. A nurse who was nearby continued CPR “more aggressively.” An estimated 10 minutes passed before a nearby automatic external defibrillator was located and applied. A shockable rhythm was identified, and a shock delivered. CPR was continued until emergency services arrived by helicopter approximately 15 minutes following the arrest, she was breathing spontaneously, and CPR was stopped. She was taken to the local hospital with a Glasgow Coma Score of 7, where an electrocardiogram showed polymorphic broad complexes at 200 beats/min. The electrocardiogram was faxed to specialists at the tertiary children’s hospital and reviewed by the electrophysiology specialist. CPVT was suspected, and the local team was advised to avoid epinephrine and anesthetise her and deliver opiates. This suspicion was based on key features in the history—particularly that the child was previously well and that loss of consciousness occurred in water, along with the presence of multimorphic ventricular ectopy on the electrocardiogram (Figs. 1–5). She was treated with fentanyl (10 $\mu\text{g}/\text{kg}$) followed by rocuronium, intubation, and ventilation at which point her rhythm stabilized and her tachycardia resolved. A fentanyl infusion (3 $\mu\text{g}/\text{kg}/\text{hr}$) was started. She was transferred to the ICU at the tertiary children’s hospital. She had no further arrests, nor any ventricular ectopy. She underwent cerebral cooling but did not require ECMO. Family history was negative, the resting electrocardiogram was normal, and the heart was structurally normal on echocardiography.

Case C had a hybrid ICD inserted and was started on nadolol and flecainide; genetic testing revealed a denovo RyR2

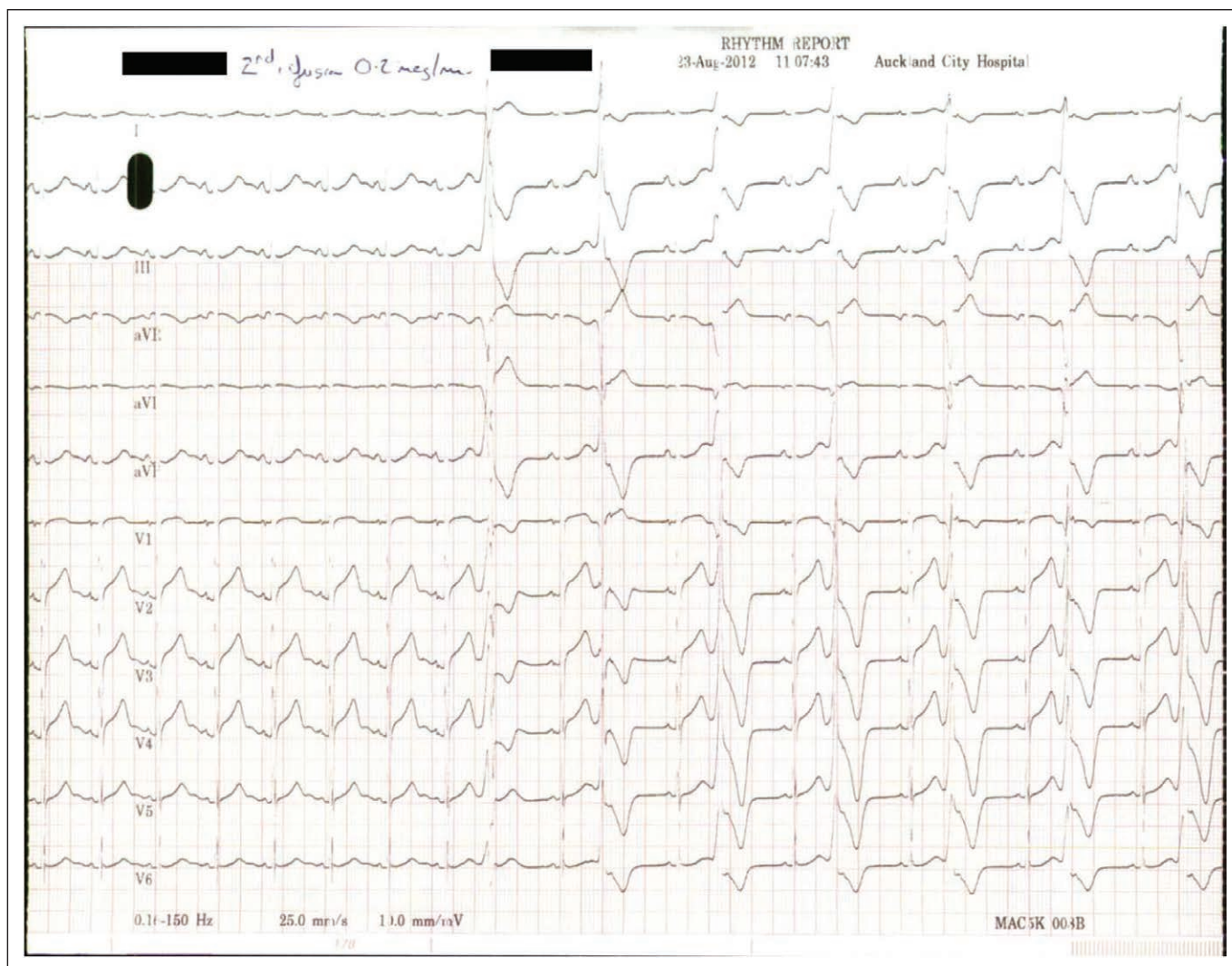


Figure 4. Series of 12 lead electrocardiograms. All recorded at 25 mm/s. Ventricular bigeminy following epinephrine infusion at 0.2 $\mu\text{g}/\text{min}$.

mutation (p.Gly4140Glu). She had no further episodes of arrest, and her ICD has not fired in 43 months of follow-up.

DISCUSSION

The first two cases presented here show that the repeated use of epinephrine was ineffective and likely contributed to VT/VF storms over many hours. A comparison with the third case, where epinephrine was avoided, and fentanyl delivered early, led to a dramatically better clinical course.

CPVT thus presents a unique challenge to resuscitators who work with children and adolescents because it must be managed differently from other types of arrhythmias. Most cases are children between 4 and 14 years old (although presentation at age >40 yr and in infants is recognized), and occur with some level of activity, especially swimming, or with fright or excitement (23). There is usually frequent ventricular ectopy between arrests. There is a male predominance. Aside from frequent ectopy, these characteristics are also common among children who suffer cardiac arrest secondary to long QT syndrome type 1 (6, 11, 24), a condition in which epinephrine

is not contraindicated during resuscitation attempts, even though exercise, swimming, and excitement are known triggers for long QT type 1 in particular. The finding of bidirectional VT, as demonstrated in **Figure 2**, is practically pathognomonic for CPVT (1, 5, 9, 24, 25), although it has been associated with Andersen-Tawil syndrome (25) and digoxin overdose (26).

Once recognized, the optimum therapies available are IV opiates and general anesthetics (which are useful treatments in any VT/VF storm anyway). In CPVT, these work to reduce the catecholaminergic stimulation to break the cycle that triggers the VT. The dose of IV fentanyl used in our cases, 10 $\mu\text{g}/\text{kg}$, is a high dose which may not be familiar to emergency physicians who commonly use a tenth of the dose for analgesia. However, this high dose is required to reduce the catecholaminergic stimulation. Hypotension and low cardiac output can be difficult to manage because catecholamines should be avoided, and ECMO may have to be considered to support cardiac output and blood pressure. Adjunct medications for rhythm control include flecainide and β -blockers (27). Long-term management includes long-term β -blockade, flecainide, left

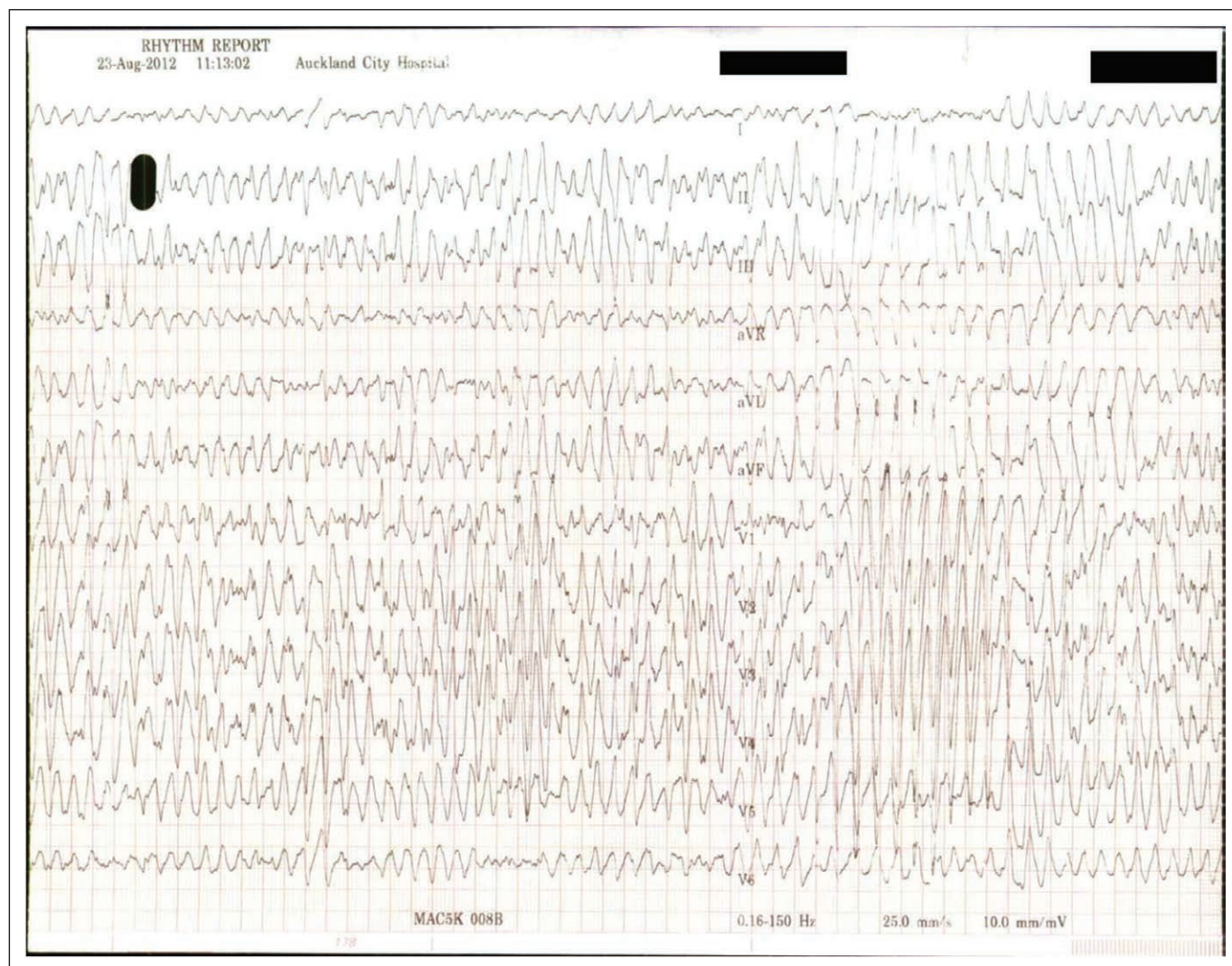


Figure 5. Ventricular fibrillation following epinephrine infusion at 0.5 $\mu\text{g}/\text{min}$.

cervical sympathetic denervation, and ICDs (1, 14, 16–18, 24). Flecainide has been shown to have a specific effect in CPVT in a mouse model in reducing sarcoplasmic calcium release (16). In CPVT, the intracellular calcium levels typically cascade out of control with an adrenergic stimulus making cardiomyocytes highly excitable and vulnerable to dysrhythmia. The therapeutic effect of flecainide in the mouse has been replicated in humans (with or without the typical RyR2 gene mutations), so much so that in combination with β -blockers an ICD may sometimes be withheld even after a cardiac arrest (14–17).

An awareness that epinephrine may sometimes be proarrhythmic in other acute cardiac deterioration is important; examples may include myocarditis or acute myocardial ischemia (such as due to anomalous coronary arterial supply). Epinephrine may also induce paradoxical hypotension during the acute management of cardiac arrest due to obstructive hypertrophic cardiomyopathy (28). In such cases, β_1 -adrenergic effects increase contractility and thus the outflow obstruction, whereas β_2 -adrenergic effects reduce systemic vascular resistance. Similarly, in quetiapine poisoning,

the drug's α -adrenergic blockade allows epinephrine's potent β_2 -adrenergic effects on the peripheral vasculature to dominate, worsening vasodilation (29). It is worthy of note that an initial rhythm of asystole, sometime after a cardiac arrest, does not exclude a primary VF or polymorphic VT event. We have previously reported a case of CPVT where syncope correlated with polymorphic VT, recorded by an implanted digital loop recorder; the device only activated when prolonged asystole was detected after this (30). The finding of PEA in the first case in this series is unusual and presumably reflected an acutely hypoxic myocardium. Thus neither asystole nor PEA at presentation in a young person with a sudden unexpected cardiac arrest excludes CPVT.

CPVT is an important differential diagnosis of any young person (typically 3 to 40 yr old) who has suffered an unexplained sudden cardiac arrest. Features which should raise suspicion include the following: 1) victim was previously well; 2) cardiac arrest occurred during a physical activity (especially in water) or with excitement; 3) electrocardiogram shows frequent VEs (usually but not always multimorphic); 4) VEs

become more frequent (or join to form VT) with epinephrine, and become less frequent with opiates and anesthesia; and 5) bidirectional VT (where ventricular complex QRS axis alternate by 180°) is virtually pathognomonic when seen but is not needed for the diagnosis (Fig. 3).

An algorithm has been proposed for the investigation of such patients in the ICU (11). Confirmation of the diagnosis, even if the patient has suffered brain death and treatment may be withdrawn, will guide further investigations and prognosis for surviving family (10, 11). During epinephrine or isoprenaline infusions, flecainide should be immediately available. In the event of good neurologic recovery, an exercise test is diagnostic (2, 9, 11).

CONCLUSIONS

A high suspicion for CPVT is important for all clinicians responsible for the emergency resuscitation of children and young adults (24). In the context of unremitting ventricular arrhythmia, not responding appropriately to standard resuscitation measures, IV opiates and general anesthesia, potentially flecainide, and the avoidance of epinephrine, can be life-saving.

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