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PERSISTENT VENTRICULAR FIBRILLATION DURING THERAPEUTIC HYPOTHERMIA AND PROLONGED HIGH-DOSE VASOPRESSOR THERAPY: CASE REPORT

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☐ **Abstract—Background: Recent emphasis on high quality prehospital cardiopulmonary resuscitation has resulted in more out-of-hospital cardiac arrest victims surviving to the emergency department. As such, standardized in-hospital post-cardiac arrest care is necessary to assure optimal neurological recovery. Although therapeutic hypothermia has arisen as a key component in the post-cardiac arrest care paradigm, its interaction with other therapies remains poorly defined. Objective: The purpose of this communication is to demonstrate a potential interaction between therapeutic hypothermia and routinely administered resuscitation medications. Case Report: We present a case of idiopathic ventricular fibrillation in a previously healthy 36-year-old man who developed persistent ventricular fibrillation in the setting of mild therapeutic hypothermia and high doses of routine resuscitation medications. Conclusion: This case illustrates the importance of understanding the potential interaction between therapeutic hypothermia and resuscitation medications along with the need for a systematic and standardized, multi-disciplinary approach to post-cardiac arrest care. © 2009 Elsevier Inc.**

☐ **Keywords—therapeutic hypothermia; ventricular fibrillation; dopamine; dobutamine; drug metabolism**

INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) remains a leading cause of death in the United States. Although overall survival rates remain low, many communities have realized substantial improvements in meaningful survival after OHCA. This has occurred primarily through emergency medical services (EMS) systems focusing on delivering high quality cardiopulmonary resuscitation (CPR) (1,2).

Therapeutic hypothermia (TH) is currently an American Heart Association (AHA) 2005 Guideline IIa therapy for adult victims who remain unconscious after a ventricular fibrillation (VF) arrest in the out-of-hospital setting (3). Although TH has been a resuscitation treatment since the 1950s, it was not until the concept of mild TH (32–34°C) reemerged in the late 1990s that the true benefit was realized (4,5). Two landmark studies by Bernard et al. and the Hypothermia After Cardiac Arrest group demonstrated improved survival and neurological outcomes after TH in patients who survived OHCA with an initial rhythm of VF (4,6). Several additional studies support and substantiate these findings (7–9). In a meta-analysis of the three randomized trials evaluating the benefit of TH in the treatment of VF OHCA, Holzer et al. found a number-needed-to-treat of 6 to allow one additional patient to leave the hospital with a favorable neurological recovery (7). Despite the guideline recommendation and the aforementioned published evidence, a standardized approach to post-cardiac arrest care including TH is not routinely practiced in the United States. As such, many emergency

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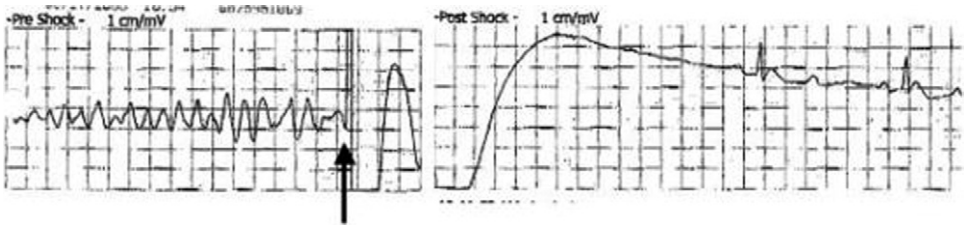

Figure 1. Rhythm strip demonstrating the single defibrillation captured on the automated external defibrillator used by the patient's coworkers.

physicians (EPs) have little experience with the associated concepts and treatments (10).

As EPs gain more firsthand experience with TH, many of the currently unanswered questions regarding the details of TH will be answered. The purpose of this article is to demonstrate a potential interaction between TH and routinely administered resuscitation medications.

CASE REPORT

A previously healthy 36-year-old man was brought to the Emergency Department (ED) by ambulance after coworkers witnessed him suddenly collapse and stop breathing. Coworkers called 9-1-1 and initiated CPR. An on-site automated external defibrillator utilized by the man's coworkers delivered one shock (Figure 1). EMS arrived approximately 4 min later and found the patient in asystole. Parademics followed a minimally interrupted cardiac resuscitation protocol. The patient received a total of 2 mg intravenous (i.v.) epinephrine and 2 mg i.v. atropine and had return of spontaneous circulation 11 min into the field resuscitation without further defibrillation. He remained unconscious and was orally intubated with a standard 8.0 endotracheal tube. Paramedics administered a 100 mg i.v. lidocaine bolus followed by a 2 mg/min lidocaine drip.

On arrival in the ED, the patient's vital signs included a blood pressure of 115/60 mm Hg, heart rate of 127 beats/min, core temperature of 37.0°C (98.6°F), and oxygen saturation of 100% while being bag-valve-mask ventilated. On physical examination, the pupils were equal and reactive to light. The chest was clear to auscultation; examination of the heart revealed clear heart sounds without rubs, gallops, or murmurs. There was no jugular venous distention. Rigid posturing of the extremities was noted on neurological examination.

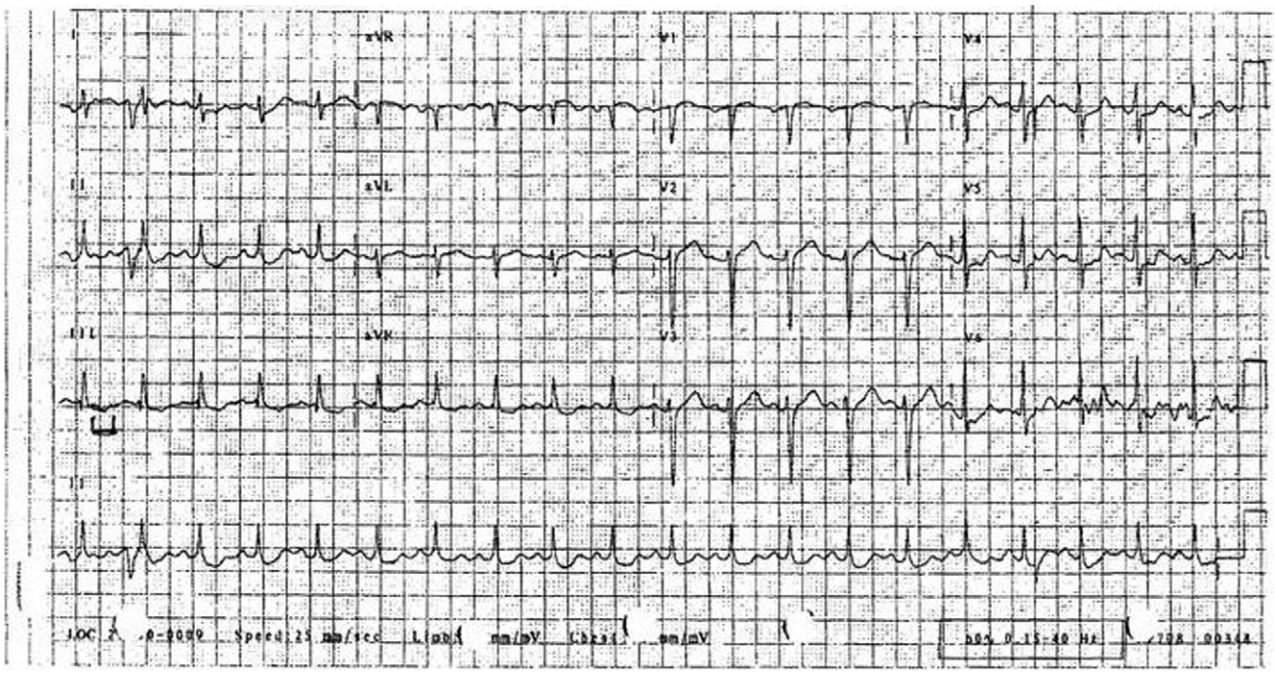

Figure 2. Electrocardiogram demonstrating sinus tachydcardia at the time of arrival in the emergency department.

The initial electrocardiogram revealed sinus tachycardia at 120 beats/min (Figure 2). The portable chest radiograph showed clear lung fields with normal heart and mediastinal silhouettes. Initial arterial blood gas revealed pH of 7.38, pCO_2 of 37, pO_2 of 346, and bicarbonate of 21.5. Complete blood count and chemistry-7 panels were normal. His cardiac markers were: total CPK (creatine phosphokinase) of 155, CPK-MB of 3.8, and troponin I of < 0.10 ng/mL. The urine drug screen was negative and the urinalysis was normal.

TH was induced while the patient was in the ED through a closed-loop i.v. catheter and a Coolgard 3000™ fluid circulator (Alsius, Irvine, CA) 2 h after the initial collapse. Intravascular temperature was maintained at 33.5°C. Propofol was administered for sedation and 10 mg of vecuronium was administered to prevent shivering. The lidocaine drip was continued at 2 mg/min and 325 mg of aspirin was administered per rectum.

The patient was transferred to the intensive care unit (ICU) with a core temperature of 33.5°C. Three hours after collapse the patient began experiencing recurrent episodes of VF (Figure 3.) The following i.v. medications were initiated: 5 μg/min of epinephrine, 8 μg/kg/min of dobutamine, and 8 μg/kg/min of dopamine. Bedside delivery of extracorporeal membrane oxygenation (ECMO) support and the placement of an intra-aortic balloon pump were required. A left heart catheterization was performed and demonstrated normal coronary anatomy without evidence of an obstructive lesion. A bedside two-dimensional echocardiogram demonstrated septal and ventricular akinesis with an ejection fraction of 15%.

Over the course of 9 h in the ICU, VF recurred persistently with just brief intervals of normal sinus rhythm (NSR). He received 122 defibrillations at settings between 200 and 300 J of biphasic energy. During the ongoing 9-h resuscitation, totals for the following i.v. medications were administered: 4.4 mg of epinephrine, 164 mg of dobutamine, 120 mg of dopamine, 795 mg of amiodarone, and 64 mg of procainamide.

Twelve hours after arrival, the patient was transferred to another facility to be evaluated for potential heart transplantation. He arrived at the receiving hospital in persistent VF with a core temperature of 33.5°C. It was proposed by the receiving physicians that either the considerable dosages of cardiac medications or TH was causing refractory VF. All vasoactive and beta adrenergic agents were abruptly discontinued and TH was withdrawn. The patient was again defibrillated with 200 J of biphasic energy and he converted to and remained in NSR. Propofol was discontinued and the patient remained unresponsive. His pupils were reactive.

On hospital day 2, his ejection fraction had increased to 75%. On day 3, after ECMO support and the intra-aortic balloon pump were removed, sedation was discontinued and he was successfully extubated. He remained in NSR. Upon regaining consciousness the patient had impaired short-term memory which gradually resolved over the next 7 days. On hospital day 10, an automatic implantable cardioverter defibrillator (AICD) (Medtronic, Minneapolis, MN) was placed and the patient had a full

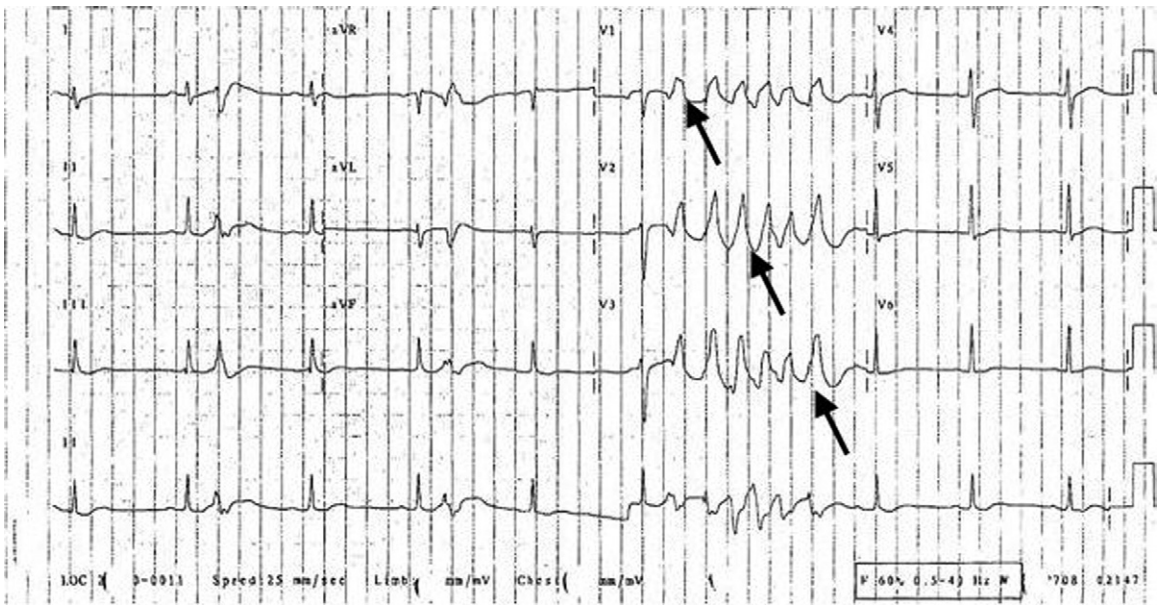

Figure 3. Electrocardiogram performed in the intensive care unit demonstrating one self-limiting episode of ventricular fibrillation.

neurological recovery and was discharged home. One year after discharge he is back at work full-time.

DISCUSSION

Idiopathic Ventricular Fibrillation

Idiopathic ventricular fibrillation (IVF) is defined as cardiac arrest in the absence of structural heart disease or identifiable causes of VF (11). It occurs in 1–9% of OHCA survivors (11). The mean age is 35–40 years, and 70–75% of the patients are male (11). IVF is a diagnosis of exclusion, making it necessary to rule out all possible causes of VF (12). This patient underwent cardiac magnetic resonance imaging, myocardial biopsy, channelopathy genetic screening, and evaluation for dysrhythmogenic right ventricular dysplasia, all of which were normal. AICDs are currently the treatment of choice, and ongoing annual evaluations for cardiomyopathy are recommended (10,11).

Persistent Ventricular Fibrillation

One of the major challenges in persistent VF is that patients resuscitated from a VF arrest are at risk of refibrillation by a variety of mechanisms (13). Initially, focal ionic and metabolic changes create electrical myocardial heterogeneity, leading to slow conduction and micro-reentry circuits (14). These conditions can be further complicated by hyperkalemia, increased cyclic adenosine monophosphate, disturbed calcium metabolism, and disrupted electrical coupling between cells (14). Myocardial stunning as a result of numerous defibrillations, as occurred with our patient, also makes termination of the ventricular dysrhythmia progressively more difficult (15). Ventricular fibrillation in this patient eventually terminated after the simultaneous cessation of both TH and cardiac life-support medications, making it difficult to determine which factor was the primary cause.

Is TH Pro-dysrhythmic at Temperatures between 32° and 34°C?

Therapeutic hypothermia is a relatively new treatment modality for many practitioners (10). In 2005, it received the status of guideline therapy by the American Heart Association; however, details regarding its potential complications and interactions with other therapies need further delineation (3). To date, the literature demonstrates that a core body temperature < 32°C is associated with refractory VF, whereas mild TH at 32–34°C is not (4,16). Several studies have demonstrated no evidence that TH poses a higher risk for dysrhythmias than normothermic therapy (4,17,18). The Hypothermia after Cardiac Arrest group performed a blinded assessment of 275 patients who were either maintained at a normothermic temperature or treated for 24 h with mild TH at 32–34°C. There was no statistically significant difference between the two groups in the rate of dysrhythmias: 32% (44/138) in the normothermic group compared to 36% (49/135) in the group treated with mild TH. In this study, TH was discontinued to mitigate dysrhythmias in 3/137 cases (6). Bernard et al. studied 77 patients who were assigned to treatment with TH at 33°C for 12 h vs. normothermia. Although numerical data were not published, the authors assert that clinically significant dysrhythmias did not develop as a result of TH (4).

Etiology of Persistent VF

Based on published evidence, we believe that the cause of persistent VF in our patient was excessive dopamine and dobutamine. At intermediate doses (2–5 μg/kg/min), dopamine stimulates β-receptors, producing positive inotropic effects (19). The adverse effects are associated with excessive sympathomimetic activity and include dysrhythmia, tachycardia, hypertension, anginal pain, nausea, vomiting, and headache (20). Dobutamine stimulates myocardial β_1-adrenergic receptors at doses with a positive inotropic effect (2.5–10 μg/kg/min) (19). The major side effects of dobutamine are dysrhythmia and excessive tachycardia (19). The Heart Failure Society of America guidelines recommend that if worsening tachydysrhythmias develop during administration of dobutamine, discontinuation or dose reduction should be considered (21). Dopamine is contraindicated in patients with uncorrected cardiac dysrhythmias, including ventricular fibrillation or ventricular tachycardia (22).

Dopamine and dobutamine are primarily metabolized by catechol-o-methyl transferase and monoamine oxidase, which are in highest concentration in the liver and kidneys (19). The effect of TH on the clearance of exogenous catecholamines and cardiac life support medications has not been specifically evaluated, however, studies have demonstrated diminished liver metabolism by enzymes such as cytochrome P-450 during TH (23–25). Tortorici et al. described four medications found in higher-than-expected concentrations in patients cooled within the therapeutic range (24). Additionally, animal studies have demonstrated reduced glomerular filtration, leading to reduced excretion of parent drugs or their metabolites during TH (26). The specific impact of TH

on the metabolism and excretion of resuscitation medications deserves further analysis.

CONCLUSION

We believe that this patient benefited from an integrated system of care encompassing all links in the AHA chain of survival, including the newest link, therapeutic hypothermia. As therapeutic hypothermia becomes more commonly accepted and utilized in clinical practice its interactions with other therapies and substantial benefits will become better understood.

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