Low doses of intravenous epinephrine for refractory sustained monomorphic ventricular tachycardia

Aimé Bonny, Antonio De Sisti, Manlio F Márquez, Richard Megbemado, Françoise Hidden-Lucet, Guy Fontaine

Abstract
We report three cases of sustained monomorphic ventricular tachycardia (VT) in the setting of coronary artery disease, resistant to beta-blockers in two patients and to amiodarone in all, successfully terminated by low doses of intravenous (IV) epinephrine. VT was the first manifestation of coronary artery disease in one patient, whereas the other two patients had a previous history of myocardial infarction and were recipients of an implantable cardioverter-defibrillator (ICD). One of these two patients experienced an arrhythmic storm. All had hemodynamic instability at the time of epinephrine administration. A single slow administration of IV epinephrine (0.5 to 1 mg administered over 30 to 60 s) restored sinus rhythm after 30-90 s with only minor side effects. In the ICD patient with recurrent VT and several cardioversions due to transformation of VT to ventricular fibrillation, epinephrine injection led to the avoidance of further shocks. Although potentially harmful, low doses of IV epinephrine used alone or in combination with beta-blocker treatment and electrical cardioversion may be an alternative effective therapy for sustained monomorphic VT refractory to amiodarone. The role of epinephrine in the termination of VT should be studied further, especially in patients pre-treated with amiodarone in combination with beta-blockers.

© 2012 Baishideng. All rights reserved.

Key words: Ventricular tachycardia; Epinephrine; Cardiopulmonary resuscitation; Ischemic heart disease; Coronary artery disease; Amiodarone

INTRODUCTION
Sustained ventricular tachycardia (VT) is common in coronary heart disease, usually occurring in the setting of acute myocardial ischemia/infarction or later as scar-related arrhythmia.

Catecholamines have been described in the treatment of VT in the past in both animal and human models[1-3]. In clinical practice, however, their use is restricted to a few indications. Epinephrine is indicated in the setting of cardiopulmonary resuscitation for shock-resistant ventricular fibrillation (VF), pulseless electrical activity or asystole[6,7]. Currently, isoproterenol is recommended
as an antiarrhythmic treatment for arrhythmic storm in Brugada syndrome[6].

Acute therapy for sustained VT depends on hemodynamic tolerance. In the case of VT with hemodynamic instability, electrical cardioversion is the standard of care. In cases of recurrence, intravenous (IV) amiodarone is the drug of choice. However, resistance to this drug, even in association with a beta-blocker, has been described[9-11].

We report three cases of coronary heart disease presenting with hemodynamically unstable sustained monomorphic VT, resistant to beta-blockers and amiodarone, in which arrhythmias were rapidly terminated by single-bolus low doses of IV epinephrine.

**CASE REPORT**

**Patient 1**

A 47-year-old man, a smoker without past medical history, was admitted to the Cardiac Care Unit (CCU) due to severe fatigue and palpitations. Physical examination was normal with the exception of a heart rate (HR) of 170 beats/min. Blood pressure (BP) was 125/86 mmHg. A VT was documented on a standard 12-lead electrocardiogram (ECG) (Figure 1). An IV dose of 300 mg amiodarone administered over 5 min failed to stop VT, and the patient then developed hemodynamic instability with a drop in BP to 89/46 mmHg, and profuse sweating without loss of consciousness. Because of rapid hemodynamic alteration and no available anesthesiologist to perform sedation for electrical cardioversion according to the protocol of this remote medical hospital, a single slow infusion of epinephrine (1/10 000, 1 mg within 1 min) was administered. VT stopped within 30 s. Termination was preceded by an increase in BP up to 130/84 mmHg and a slight increase in VT rate from 170 to 180 beats/min (Figure 2). The side effects of epinephrine were chest discomfort, nausea, and anxiousness. ECG in sinus rhythm (SR) after cessation of VT showed a pathologic Q wave in inferior leads (Figure 3). Echocardiography performed in SR showed a dilated left ventricle (62 mm), and left ventricular ejection fraction (LVEF) of 40% with inferior wall akinesia. Troponin I was slightly elevated at 0.82 ng/mL. No electrolyte disturbances were observed. Coronarography showed occlusion of the middle segment of the right coronary artery and a bare-metal stent was implanted. Continuous ECG monitoring did not record any ectopic ventricular beat in the following days. The patient was discharged seven days later.

**Patient 2**

A 64-year-old male was admitted to the CCU due to sustained VT with a HR of 140 beats/min (Figure 4A). Past medical history showed an inferior myocardial infarction (MI) with low ejection fraction and an implantable cardioverter-defibrillator (ICD) for secondary prevention. He was on bisoprolol 10 mg daily associated with amiodarone 200 mg daily added three months prior for recurrent non-sustained VT. On arrival, he was conscious and had a palpable pulse although BP was 85/50 mmHg; ICD interrogation was not attempted due to unavailability of this expertise at the time of patient management. One slow-rate infusion of IV epinephrine (1/10 000; 0.5 mg in 30 s) was then administered. VT termination occurred approximately 30 s after the end of the epinephrine infusion. Cessation was preceded by a slight increase in the VT rate (from 140 to 148 beats/min). During epinephrine administration the patient experienced brief
chest discomfort and headache. Twelve-lead ECG in SR displayed pathologic Q waves in inferior and lateral leads (Figure 4B). Troponin I was slightly elevated (0.57 ng/mL). Serum electrolytes were within normal limits. Two-D echocardiography indicated a LVEF of 35%. Coronary angiography revealed a restenosis of the right coronary artery and a sub-occlusion of the ostium of a marginal artery. A drug-eluting stent was implanted in both lesions. An ICD interrogation before discharge did not register any arrhythmic event as the programming VT zone (150 beats/min) was higher than the patient’s VT (140 beats/min). No further episodes of VT were observed during hospitalization, and the patient was discharged seven days later.

**Patient 3**

A 67-year-old man was admitted to the CCU due to an arrhythmic storm. The patient had a previous history of two MI (inferior and anterior) with a large akinetic area in the anterior wall and a low ejection fraction (LVEF < 20%). He was on chronic treatment with carvedilol (12.5 mg twice daily) and amiodarone (200 mg daily). An ICD had been implanted for primary prevention. As the patient developed permanent atrial fibrillation and remained symptomatic despite an optimal pharmacological regimen, the ICD was upgraded to CRT-D because of the need for chronic ventricular pacing. Four months previously, the patient had been admitted for syncope. At that time, ICD interrogation confirmed an arrhythmic storm. Coronary angiography showed an occlusion of the first marginal artery, but no intervention was performed due to the absence of viability. He underwent successful radiofrequency catheter ablation of two inducible monomorphic VTs. Four months later, the patient was re-admitted to the CCU due to another arrhythmic storm.

On admission to the CCU, a tachycardia with a VT pattern was recorded (Figure 5). BP was 90/45 mmHg. No electrolyte disturbance was observed. Troponin I was within normal limits. Once in the CCU, he experienced six more appropriate ICD shocks within 5 min. The underlying rhythm was VT with a HR of 140-150 beats/min. The ICD was programmed with one VT zone from 130 to 200 and the VF zone > 200 beats/min. Appropriate ICD shocks were delivered, but were followed by recurrence of the VT. Amiodarone (150 mg IV over 15 min) failed to terminate VT and decreased BP to 70/40 mmHg. Different protocols of direct manual overdrive pacing also failed to interrupt VT. One “aggressive” attempt transformed VT to VF managed by the ICD. Less than 60 s later, the VT reappeared. BP steadily continued to decrease down to 65/30 mmHg. A bolus IV injection of epinephrine (1/10,000, 0.5 mg in 30 s) was administered while his BP was continuously monitored. Following a BP increase up to 125/85 mmHg, VT terminated within 90 s, preceded by a small shortening of VT cycle length (Figure 6). Treatment was supplemented by amiodarone IV (300 mg over 20 min) and atenolol IV (25 mg over 15 min). The next day, he underwent coronary angioplasty of the first marginal artery. The patient remained free of arrhythmias.

**DISCUSSION**

We illustrated three cases of drug-resistant sustained monomorphic VT with hemodynamic instability, in which the arrhythmia was terminated with IV epinephrine. All patients had coronary heart disease, but whether acute coronary syndrome was concerned is difficult to state. Indeed, a moderate troponin increase is also seen after tachyarrhythmias and post-VT ECGs did not show either ST-segment elevation or depression. Amiodarone...
When to use epinephrine in sustained VT

In cases of drug-resistant poorly tolerated VT, immediate external electrical cardioversion must be attempted. However, there are cases in which VT recurs immediately after the shock, and cardioversion involves the need for anesthesia when the patient is still conscious. Although shocks delivered by ICD often effectively terminate VT, in some patients VT can restart quickly, as the ICD is unable to prevent arrhythmia. In this context of arrhythmic storm, sedation and anti-arrhythmic drugs are of great interest. However, in the setting of coronary disease, either acute phase or scar-related VT, effective drug therapy is limited to lidocaine, mexiletine, sotalol or lidocaine as anti-arrhythmic drugs. The standard of care for sustained VT with a cycle shortening before interruption is noted.

Possible mechanisms of VT reduction by epinephrine

Two possible mechanisms may underlie the interruption of a monomorphic sustained VT by low doses of intravenous epinephrine.

Effects on BP, baroreceptor stimulation and coronary perfusion: Epinephrine has an alpha-sympathomimetic effect by which systemic BP is known to increase. This increase in BP could have two different effects. The rise in BP could result in better coronary artery perfusion, thus inhibiting ischemia-induced VT (patient 1). Alternatively, a baroreceptor-mediated increase in parasympathetic tone via the carotid body could lead to VT termination via vagal stimulation. The latter hypothesis is difficult to demonstrate because vagal myocardial innervation is not completely defined in humans. Finally, a direct effect of epinephrine on coronary perfusion, through coronary vasodilatation, is a possible mechanism in ischemia-related VT.

Modification of conduction properties: Conduction velocity and refactoriness of the myocardium are modified in opposite ways by epinephrine and beta-blockers and/or amiodarone. Adrenaline-dependent increased conduction velocity with shortening of VT cycle length could be responsible for extinction of the circuit by a simple mechanism of head-tail conjunction. Considering a circus movement reentry as the mechanism of the VT, the acceleration of the VT by epinephrine will translate into progressive shortening of the excitable gap until it will be so short that the “head” meets the “tail”, and then the circuit becomes extinct. This being the case, termination of the VT will be preceded by a faster epinephrine-induced, small transient VT acceleration and then the circuit becomes extinct. This being the case, termination of the VT will be preceded by a faster epinephrine-induced, small transient VT acceleration in all 3 patients. A change in myocardial fiber stretch by epinephrine could also modify the circuit components favoring VT interruption.

On the other hand, amiodarone could limit the refractoriness shortening of epinephrine which, combined with an increased conduction velocity determined by epinephrine itself, might be responsible for tachycardia interruption because of a residual refractoriness prolongation of part of the circuit. Tonet et al. have shown that beta-receptor blockade by beta-blocker agents and chronic amiodarone therapy converts VT to SR via prolongation of the refractory period and cycle length. Thus, pre-treatment with amiodarone might enhance the effectiveness of IV epinephrine which, reducing repolarization dispersion, interrupts reentry and could be useful in cases of electrical storm.

Detailed analysis of the cases reported herein can support both hypotheses. In all patients, elevation of BP preceded VT termination, suggesting a mechanism of better coronary artery perfusion or parasympathetic...
stimulation. Otherwise, in all patients, the cycle length of the VT shortened just before the return to SR, suggesting a modification in myocardial conduction properties with an increase in conduction velocity and a subsequent shortening of the VT cycle length able to induce reentry interruption by a head-tail conjunction mechanism. All patients were previously treated with amiodarone, whose antiarrhythmic properties mainly concern refractoriness prolongation, especially when taken on a chronic basis. A possible intricate electrophysiological mechanism could also be conjectured, that is, a residual prolonged refractoriness by beta-blocker and amiodarone pre-treatment combined with increased velocity when epinephrine is administered.

Precautions on the use of epinephrine for VT

The most frequent and clinically significant side effects of IV epinephrine were not observed in our patients, which may be explained by the lower doses (≤ 1 mg) used. The potential complications of epinephrine while performing cardiopulmonary resuscitation were described for doses greater than those that are the standard. VF induction in subjects treated with bolus or continuous infusion of epinephrine for severe hypotension or cardiogenic shock have been reported, and the conversion of VT to VF is a matter of real concern. It is of interest to note that in experimental models of chronically infarcted canine hearts, selective beta1-adrenergic stimulation alone does not cause dispersion of myocardial refractoriness and does not cause significant proarrhythmia. Also, in dogs with experimentally induced myocardial infarction, infusion of isoproterenol increases the incidence of inducible VT, but does not facilitate the induction of VF. In any case, given the potentially harmful intervention in the setting of coronary heart disease, further research to explore the mechanism of action, its effectiveness and its safety is mandatory. In our patients, evidence of acute ischemia was modest compared to the expected effects of epinephrine. The most frequent and clinically significant side effects of IV epinephrine were not observed in our patients, which may be explained by the lower doses (≤ 1 mg) used. The potential complications of epinephrine while performing cardiopulmonary resuscitation were described for doses greater than those that are the standard. VF induction in subjects treated with bolus or continuous infusion of epinephrine for severe hypotension or cardiogenic shock have been reported, and the conversion of VT to VF is a matter of real concern. It is of interest to note that in experimental models of chronically infarcted canine hearts, selective beta1-adrenergic stimulation alone does not cause dispersion of myocardial refractoriness and does not cause significant proarrhythmia. Also, in dogs with experimentally induced myocardial infarction, infusion of isoproterenol increases the incidence of inducible VT, but does not facilitate the induction of VF. In any case, given the potentially harmful intervention in the setting of coronary heart disease, further research to explore the mechanism of action, its effectiveness and its safety is mandatory. In our patients, evidence of acute ischemia was modest compared to the expected effects of epinephrine.

Clinical implications

It is well known that spontaneous episodes of VT can accelerate, slow, or even terminate spontaneously. However, in all cases, the termination of a long-duration (> 2 h) VT was rapidly observed after 90 s or less following epinephrine administration, preceded by a shortening of the VT cycle length before SR restoration, strongly suggesting an epinephrine-related effect. Although the use of sympathomimetic amines to treat sustained monomorphic ischemic VT could be questionable, mainly because its rationale is against the current paradigm of the pathophysiology of ischemic VT as well as the wide availability of appropriate drugs and external cardioversion, the effect observed in our cases merits further investigation. Remote medical centers and under-resourced countries with difficulties providing ACLS management may be concerned. We might also speculate on a possible protective effect of amiodarone and beta-blocking treatment for the prevention of the degenerative arrhythmic effects of epinephrine itself. In fact, VT cycle length was slightly shortened in all patients, without any change in VT morphology or VF degeneration.

Study limitations

Some limitations merit consideration. First, as these are only three observational cases, this remains a non-conclusive assessment of the efficacy and safety of this unconventional “heroic” intervention. Second, although all subjects had beta-blocker and/or amiodarone resistant VT, another antiarrhythmic drugs such as lidocaine or mexiletine were not attempted before the epinephrine regimen. Third, the treatment of patients 1 and 2 is not a conventional one and should not, therefore, be advocated at the first intention. Fourth, one of the questions raised by our observations is whether VT was actually self-limiting or truly stopped by the epinephrine injection; however, the rapid onset of action in a longstanding sustained monomorphic VT serves to consider it a direct effect of epinephrine.

Conclusion

Low dose IV epinephrine may terminate sustained monomorphic VT refractory to amiodarone used alone or in combination with beta-blockers and electrical cardioversion. Although potentially harmful, epinephrine may be an alternative effective therapy for refractory VT, particularly in remote medical centers and low income countries where advanced cardiac life support is under-provided. This treatment requires a clinical study.

ACKNOWLEDGMENTS

The authors are indebted to Ms Corine Tachtitis for editing the manuscript for English usage.

REFERENCES

1. Gold H, Corday E. Vasopressor therapy in the cardiac arrhythmias. N Engl J Med 1959; 260: 1151-1156
2. Greenspan W, Shahgalian ZL. The use of vasopressors in cardiac arrhythmias, particularly ventricular tachycardia. Am J Cardiol 1961; 7: 707-713
3. Kravetz RE, Kagan A, Fremont RE. Termination of rapid ventricular tachycardia with metaraminol (Aramine). Am J Cardiol 1962; 10: 579-582
4. Brown J. Termination of ventricular tachycardia after methoxamine. Crit Care Resusc 2001; 3: 259-261
5. Amitzur G, Shenukar N, Leor J, Novikov I, Eldar M. Effects of adrenaline on electrophysiological parameters during short exposure to global ischemia. A ventricular fibrillation study in isolated heart. Cardiovasc Drugs Ther 2002; 16: 111-119
6. Travers AH, Rea TD, Bobrow BJ, Edelson DP, Berg RA, Sayre MR, Berg MD, Chameides L, O’Connor RE, Swor RA. Part 4: CPR overview: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2010; 122: S676-S684
7. Nolan JP, Soar J, Zideman DA, Biareset D, Bossaert LL, Deakin C, Koster RW, Wylie J, Böttiger B. European Resuscita-
Bonny A et al. Low doses IV epinephrine for refractory sustained monomorphic VT

Saunders Company, 2000: 300-314

Chase PB, Kern KB, Sanders AB, Otto CW, Ewy GA. Effects of graded doses of epinephrine on both noninvasive and invasive measures of myocardial perfusion and blood flow during cardiopulmonary resuscitation. Crit Care Med, 1993; 21: 413-419

Franz MR, Cima R, Wang D, Profit D, Kurz R. Electrophysiological effects of myocardial stretch and mechanical determinants of stretch-activated arrhythmias. Circulation, 1992; 86: 968-978

Kirchhof P, Degen H, Franz MR, Eckardt L, Fabritz L, Milberg P, Laer S, Neumann J, Breithardt G, Haverkamp W. Amiodarone-induced postpolarization refractoriness suppresses induction of ventricular fibrillation. J Pharmacol Exp Ther, 2003; 305: 257-263

Tovar OH, Jones JL. Epinephrine facilitates cardiac fibrillation by shortening action potential refractoriness. J Mol Cell Cardiol, 1997; 29: 1447-1455

Tovar OH, Bransford PP, Jones JL. Probability of induction and stabilization of ventricular fibrillation with epinephrine. J Mol Cell Cardiol, 1998; 30: 373-382

Tonet J, Himbert C, Johnson N, Jouven X, Halimi F, Fontaine G. Prolongation of ventricular refractoriness and ventricular tachycardia cycle length by the combination of oral beta-blocker-amiodarone in patients with ventricular tachycardia. Pacing Clin Electrophysiol, 2000; 23 (Part II): 565

Tonet J, Frank R, Fontaine G, Grosgeorge Y. Efficacy of the combination of low doses of beta-blockers and amiodarone in the treatment of refractory ventricular tachycardia. Arch Mal Coeur Vaiss, 1989; 82: 1511-1517

Naor EM, Russell AM. A preliminary analysis of surgical trends in Maine: 1974–1975. J Maine Med Assoc, 1979; 70: 277-277

Thames MD, Kontos HA. Mechanisms of baroreceptor-induced changes in heart rate. Am J Physiol, 1970; 218: 251-256

Morady F, DiCarlo LA, Krol RB, Baerman JM, de Buiteler M. Acute and chronic effects of amiodarone on ventricular refractoriness, intraventricular conduction and ventricular tachycardia induction. J Am Coll Cardiol, 1986; 7: 148-157

Callaham M, Barton CW, Kayser S. Potential complications of high-dose epinephrine therapy in patients resuscitated from cardiac arrest. JAMA, 1991; 265: 1117-1122

Nelson SD, Coyne K. Electrophysiologic effects of selective B1 adrenergic stimulation in the late phase of myocardial infarct healing. Int J Cardiol, 1992; 36: 95-102

Hunt GB, Ross DL. Effect of isoproterenol on induction of ventricular tachyarrhythmias in the normal and infarcted canine heart. Int J Cardiol, 1990; 29: 155-161

S- Editor Cheng JX | L- Editor Webster JR | E- Editor Li JY