

Amiodarone Supplants Lidocaine in ACLS and CPR Protocols

Anna Mizzi, MD^{a,*}, Thanh Tran^b, Devanand Mangar, MD^b, Enrico M. Camporesi, MD^c

KEYWORDS

- Amiodarone • Ventricular tachyarrhythmias • Cardiac surgery
- ACLS protocol

Amiodarone is an antiarrhythmic medication used to treat and prevent certain types of serious, life-threatening ventricular arrhythmias. Amiodarone gained slow acceptance outside the specialized field of cardiac antiarrhythmic surgery because the side effects are significant. Recent adoption of amiodarone in the ACLS (Advanced Cardiac Life Support) protocol has somewhat popularized this class of antiarrhythmics. Its use is slowly expanding in the acute medicine setting of anesthetics. This article summarizes the use of amiodarone by anesthesiologists in the operating room and during cardiopulmonary resuscitation (CPR).

SUDDEN CARDIAC DEATH

In a population of 1000, the average annual occurrence of sudden cardiac death (SCD) is approximately 0.2%, but population-related frequency of cardiovascular disease in different areas of the country should be considered. There are approximately 400,000 to 450,000 recorded occurrences of SCD in the United States, which accounts for about 60% of all cardiovascular mortality in this country.¹ Holter studies further indicate that approximately 85% percent of SCDs are caused by ventricular tachyarrhythmias, both pulseless ventricular tachycardia (VT) and ventricular fibrillation (VF).

VT is a critical condition that can lead to VF. VT is characterized as monomorphic when waveforms are at a steady rate and amplitude, and polymorphic when they are inconsistently variable. VF is another critical condition whereby the ventricles tremble rather than contract. VF waveforms are inconsistent in rate and amplitude,

^a Department of Cardiothoracic and Vascular Anesthesia, San Raffaele Hospital, "Vita e Salute" University, Milan, Italy

^b Florida Gulf-to-Bay Anesthesiology, 1 Tampa General Circle, Suite A327, Tampa, FL 33606, USA

^c Department of Surgery/Anesthesiology, Florida Gulf-to-Bay Anesthesiology Associates & University of South Florida, 1 Tampa General Circle, Suite A327, Tampa, FL 33606, USA

* Corresponding author. 1 Tampa General Circle, Suite A327, Tampa, FL 33606.

E-mail address: anna.mizzi@alice.it

often more than 300 beats per minute and more than 0.2 mV in amplitude. The irregular rate and amplitude indicates the inconsistent and hectic electrical activity and contraction when the heart stops pumping. VF waveforms often weaken to asystole within 15 minutes.²

In countries with prosperous resources, such as the United States and Europe, cardiac arrest due to VT or VF is mostly caused by myocardial ischemia. As a consequence, major risk factors for SCD include those factors that can accelerate coronary artery disease. Other risk factors associated with SCD include age (typically 45–75 years), male sex, and dilated cardiomyopathy.²

Cardiac arrest due to VT or VF causes an interruption in oxygen supply that can lead to critical ischemic damage to the organs. This condition is life-threatening, and leads to death within minutes if untreated. The treatments for pulseless ventricular tachyarrhythmias include use of defibrillation and antiarrhythmic drugs.³

CARDIAC ACTION POTENTIALS

Cardiac action potentials are divided into fast-response action potential and slow-response action potential. Fast-response action potential, also known as nonpacemaker action potential, is found in nonnodal cardiomyocytes (atrial and ventricular myocytes, and Purkinje tissue). This action potential type relies on fast sodium channels for depolarization. Slow-response action potentials, on the other hand, also known as pacemaker action potentials, are found in nodal tissue, which consists of sinoatrial and atrioventricular nodes, and depend on calcium channels rather than sodium channels for depolarization (Fig. 1).⁴

Cardiac action potentials, in general, use sodium and calcium channels for depolarization, and potassium channels for repolarization. In fast-response action potential, phase 0 represents depolarization, whereby sodium channels open to enhance positive membrane potential. Phase 1 is the initial repolarization, when potassium channels open and allow outward K^+ current. There is, however, a slow increase in inward Ca^{2+} current during this time, impeding the repolarization seen in phase 2. This phase, however, lengthens the period of action potential, and is the only phase that shows a difference between cardiac action potentials and those of the nerves and skeletal muscle. Phase 3 is then the continuation of the repolarization, and phase 4 allows the action potential to return to resting membrane potential.⁴

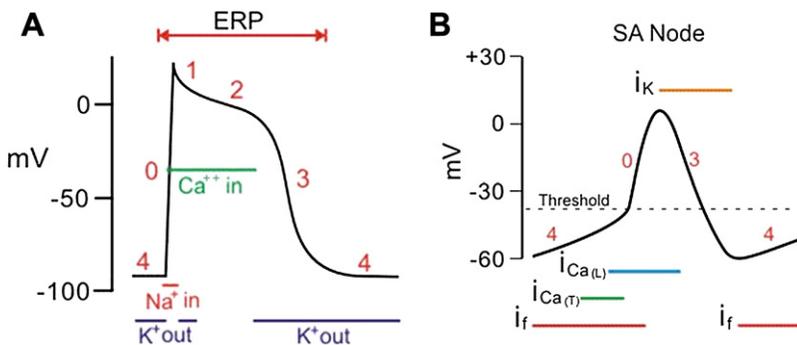


Fig. 1. Cardiac action potential. (A) Fast-response action potential (atrial and ventricular myocytes, and Purkinje tissue). (B) Slow-response action potential (sinoatrial and atrioventricular nodes). ERP, effective refractory period; SA, sinoatrial.

VAUGHAN WILLIAMS CLASSIFICATION

Antiarrhythmic drugs have different effects on action potentials, and are classified based on their mechanism of action. Many proposals have been made in classifying the antiarrhythmic drugs, but Vaughan Williams' classification seems to be the most used.⁵ There are 4 classes in Vaughan Williams' classification, which are shown in **Table 1**.

Class I

Class I antiarrhythmics act as sodium channel blockers. These antiarrhythmics attach to and block sodium channels accountable for rapid depolarization in fast-response cardiac action potentials. The faster the depolarization of a cell, the faster adjacent cells would be depolarized, causing a faster regeneration and conduction of action potentials between the cells. Blocking sodium channels would decrease the action potential conduction velocity, and this action is helpful in repressing irregular conduction that can cause tachycardias.

Table 1 Vaughan Williams classification for antiarrhythmic drugs	
CLASS I → Sodium Channel Blockers	
IA	<ul style="list-style-type: none"> • Moderate Na⁺ channel blocking effect with conduction impairment • Prolonged repolarization • QUINIDE, PROCAINAMIDE, DISOPYRAMIDE
IB	<ul style="list-style-type: none"> • Minimal Na⁺ channel blocking effect • Tendency for shortening repolarization • LIDOCAINE, MEXILETINE, TOCAINIDE
IC	<ul style="list-style-type: none"> • Marked Na⁺ channel blocking effect with significant conduction impairment (QRS prolonged) • No effect on repolarization • FLECAINIDE, PROPAFENONE, ETHMOZINE
CLASS II → β-Receptor Antagonists	
	<ul style="list-style-type: none"> • Depressed automaticity and conduction in slow-response cells • Impair calcium release to reduce contractility • No effect on repolarization • β-BLOCKERS
CLASS III → Potassium Channel Blockers	
	<ul style="list-style-type: none"> • Potassium channel blockade lengthens refractoriness by delaying recovery of membrane potential • Most agents are not purely potassium blockers and have properties of other classes • AMIODARONE, BRETILUM, AZIMILIDE, DOFETILIDE, IBUTILIDE
CLASS IV	
IVA → Calcium channel blockers	<ul style="list-style-type: none"> • Predominantly blocks calcium entry in slow-response cells only (SA and AV nodal cells) • No effect on repolarization • VERAPAMIL, DILTIAZEM
IVB → Adenosine receptor agonist	<ul style="list-style-type: none"> • Stimulation of adenosine receptor results in opening of potassium channels with predominant effect of hyperpolarization; This will depress automaticity in SA nodal cells and conduction in AV nodal cells • Minimal effect of shortening repolarization • ADENOSINE

Abbreviations: AV, atrioventricular; SA, sinoatrial.

Class I is further broken down to subclasses A, B, and C. These subclasses are based on the drugs' ability to alter action potential duration (APD) and effective refractory period (ERP). ERP is also known as absolute refractory period, and indicates the period in which, with an action potential already started, a new action potential cannot be started until the cell returns to resting membrane potential. Increasing or decreasing APD or ERP can increase or decrease arrhythmias based on the cause of the condition. Class IA increases APD and ERP, whereas class IB decreases APD and ERP, and IC has no effect on APD and ERP. Class IA drugs are classified as moderate sodium channel blockers, whereas IB drugs are weak and IC drugs are strong. Class IA drugs are used to treat atrial fibrillation, flutter, and supraventricular and ventricular tachyarrhythmias. Class IB drugs are used to treat ventricular tachyarrhythmias. Class IC drugs are used to treat life-threatening supraventricular and ventricular tachyarrhythmias.^{6,7}

Class II

Class II drugs are known as β -blockers. β -Blockers attach to β -adrenoceptors in cardiac nodal tissue, the conducting system, and contracting myocytes to block catecholamines (noradrenaline and adrenaline) from binding to the adrenoceptors. β -Blockers are further divided into β_1 -blockers and β_2 -blockers. The heart has both β -adrenoceptors, but β_1 predominate in number and function. β -Receptors bind norepinephrine released from sympathetic adrenergic nerves, as well as norepinephrine and epinephrine in the blood.

β -Blockers can reduce sympathetic influences that usually stimulate chronotropy (heart rate), inotropy (contractility), dromotropy (electrical conduction), and lusitropy (relaxation). Therefore, β -blockers would enable a reduction in heart rate, contractility, conduction velocity, and relaxation rate. β -Blockers are used to treat hypertension, angina, myocardial infarction, arrhythmias, and heart failure, and have been proposed as protective strategy to prevent perioperative cardiac events in patients undergoing major surgery.⁸⁻¹⁰

Class III

Class III drugs are known as potassium channel blockers and comprise amiodarone. Class III drugs bind and block the potassium channels used for repolarization, thus slowing down the repolarization process. By delaying repolarization, APD and effective ERP would increase. Drugs that help increase ERP are effective in suppressing tachyarrhythmias caused by reentry mechanisms. Potassium channel blockers are used to treat supraventricular and ventricular arrhythmias, life-threatening arrhythmias, and atrial fibrillation and flutter.¹¹⁻¹³

Class IV

Class IV drugs are known as calcium channel blockers. These drugs bind to L-type calcium channels on vascular smooth muscle, cardiac myocytes, and cardiac nodal tissue. These channels regulate calcium entry into myocytes that stimulate smooth muscle and cardiac myocyte contractions. Calcium entry block enables calcium channel blockers to cause vasodilation, and decrease contractility, heart rate, and conduction velocity. Calcium channel blockers are administered for hypertension, angina, and arrhythmia therapies.¹⁴⁻¹⁶

LIDOCAINE, PROCAINAMIDE, AND BRETYLIUM

Procainamide and bretylium historically had an important clinical presence in ACLS and PALS (Pediatric Advanced Life Support), but today amiodarone is considered the drug of choice in cardiac arrest. Lidocaine continues to be an important drug, but is considered more as a local anesthetic than as an antiarrhythmic.

HISTORY OF AMIODARONE

Even though amiodarone was discovered in 1962, it was not put into use until 1967. Amiodarone was primarily used as an antianginal drug. In 1969, it was promoted to be used more specifically as an antiarrhythmic drug. The use of amiodarone as an antiarrhythmic to treat supraventricular and ventricular arrhythmias occurred primarily in France, South America, and the Scandinavian countries. By the mid-1980s, intravenous amiodarone was commonly used in Europe. In 1985, amiodarone gained approval by the US Food and Drug Administration (FDA). However, as harmful effects arose repeatedly, amiodarone was no longer viewed as an ideal antiarrhythmic.¹⁷ By the mid-1990s, amiodarone was being used as “reserve antiarrhythmic” when other antiarrhythmic agents failed. By the start of the millennium, amiodarone regained its position as the ideal antiarrhythmic in treating VT and VF, as suggested in the ACLS algorithm.¹⁸

AMIODARONE AS AN ANTIARRHYTHMIC

Amiodarone, also known as Pacerone or Cordarone, is an antiarrhythmic agent that acts by reducing heart rate when it is too fast, such as in VF, tachycardia, atrial fibrillation, and atrial flutter. Amiodarone is categorized in Vaughan Williams Class III, where its properties include inhibiting potassium channels, protracting action potential duration and ERP, and averting recurring arrhythmias. Even though amiodarone is classified as Class III, it does also have effects seen in Class I, II, and IV; however, the main mechanism of action is not yet known.

Acute arrhythmias are usually treated with a pump-infusion system to deliver constant intravenous dose of amiodarone, whereas patients with chronic arrhythmias and children may receive an oral administration as amiodarone hydrochloride.

Amiodarone molecule composition consists of 37.3% iodine in weight (Fig. 2). Due to this iodine composition, amiodarone is known to cause many adverse effects concerning thyroidal complications when administered chronically.

Amiodarone can be advantageous in stabilizing monomorphic and polymorphic VT, and other tachycardias. Metabolism of amiodarone is rather intricate. Intravenously, amiodarone's half-life is short just as the distribution is large, and the redistribution goes to the fat, liver, heart, and brain. Redistribution is slow, approximately a few hours or days, while amiodarone stays in the serum for about 12 to 24 hours. As

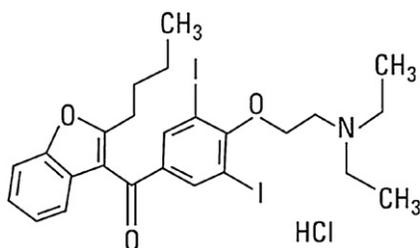


Fig. 2. Chemical structure of amiodarone.

amiodarone is metabolized via the liver, it evolves to become desethylamiodarone, a Vaughan Williams Class III antiarrhythmic.^{19–22}

ADVERSE EFFECTS OF AMIODARONE

Amiodarone has numerous side effects. Most individuals administered amiodarone on a chronic basis will experience at least one side effect.

The most serious reaction caused by amiodarone is interstitial lung disease. Risk factors include high cumulative dose, more than 400 mg per day, duration over 2 months, age, and preexisting pulmonary disease. Common practice is to avoid using the agent if possible in individuals with decreased lung function. The most specific test of pulmonary toxicity due to amiodarone is a dramatic reduction in gas exchange, measurable by a decreased diffusion capacity of carbon monoxide on pulmonary function testing.²³

Thyroxine and amiodarone have similar structures. Due to the iodine content of the agent, abnormalities in thyroid function are common. Both underactivity and overactivity of the thyroid may occur while on amiodarone treatment. Measurement of free thyroxine (FT₄) alone may be unreliable in detecting these problems, so thyroid-stimulating hormone (TSH) should also be checked every 6 months.^{23–25}

Corneal microdeposits (corneal verticillata, also called vortex keratopathy) are almost universally present (>90%) in individuals taking amiodarone for at least 6 months. These deposits typically do not cause any symptoms. Optic neuropathy occurs in 1% to 2% of people and is not dose dependent. Bilateral optic disk swelling and mild and reversible visual field defects can also occur.²⁶

Long-term administration of amiodarone is associated with a blue-gray discoloration of the skin, more commonly seen in individuals with lighter skin tones. The discoloration may revert on cessation of the drug. However, the skin color may not return completely to normal.²⁷

The most common adverse effect of intravenous amiodarone is hypotension.²⁸ This complication may possibly be associated with the infusion rate. Hypotension can be treated with vasopressor drugs, positive inotropic agents, and volume expansion therapies, or reduction of the infusion rate.

While amiodarone is known for its tachycardia treatments, it has proarrhythmic effects as well, such as bradycardia, asystole, and torsade de pointes. However, in clinical practice it might be difficult to differentiate between an insufficient dose of amiodarone and actual proarrhythmic effects. If the arrhythmias persist even with a higher dose and the patient is hemodynamically unstable, the drug should be ceased as soon as possible. QT interval analysis can help in reaching this decision. The problem is quite complex, as amiodarone can increase the QT interval while not inducing torsade de pointes, and can cause polymorphic VT while not stretching the QT interval.

AMIODARONE IN THE ACLS

Before its popularity evolved in the United States after its approval from the FDA, lidocaine was used to treat arrhythmias. Amiodarone and lidocaine are often used for CPR in cardiac arrest. Before amiodarone had been included in the ACLS algorithm, lidocaine was listed as the primary drug of choice to treat VF or VT (VF/VT). In 2000, as the guidelines in ACLS made some changes using an evidence-based approach, amiodarone was approved as the primary drug of choice in the ACLS tachycardia algorithm. After amiodarone's approval, some studies were also performed showing its effectiveness in preliminary resuscitation.¹⁰ The 2005 revision of the ACLS guidelines also mentions amiodarone as the preferred antiarrhythmic drug of choice based

on trials. ACLS guidelines now indicate that amiodarone must be the first antiarrhythmic administered to treat VF/VT; and only after attempts at using amiodarone are ineffective can lidocaine and procainamide be used.³

TRIALS REGARDING AMIODARONE IN SUSTAINED VENTRICULAR TACHYARRHYTHMIAS AND CARDIAC ARREST

Even though lidocaine had been used to treat VF/VT for many years, there was lack of evidence for its usefulness over other drugs. Compared with other antiarrhythmics, more controlled data can be found for amiodarone. Based on comparison trials wherein it was tested with other antiarrhythmics, amiodarone has been shown to enhance survival to hospital admission; however, a benefit in survival to hospital discharge has not yet been found.^{29–32}

Levine and colleagues²⁹ investigated the response to intravenous amiodarone in a prospective, double-blinded, randomized study of 273 patients with life-threatening ventricular arrhythmias causing systolic blood pressure to decrease to below 80 mm Hg with clinical signs and symptoms of shock. All patients included were refractory to lidocaine, procainamide, and bretylium, and were randomized to receive 1 of 3 doses of amiodarone: 525, 1050, or 2100 mg over 24 hours. The primary end point was to determine the proportion of patients who survived with no further episodes of hemodynamically instable VT. Secondary end points were survival during the first 24 hours, successful therapy, additional boluses of intravenous amiodarone, and proarrhythmic effect.

Of the 273 included patients, 110 (40%) survived within 24 hours without hypotensive ventricular tachyarrhythmia with amiodarone as a single antiarrhythmic. The number of supplemental doses of intravenous amiodarone was significantly greater in the 525-mg group than in the 2100-mg group ($P = .0043$). However, there was no clear dose-response correlation observed with respect to successful rate or mortality. This study concluded that amiodarone is a relatively safe therapy for hypotensive ventricular tachyarrhythmias.

In another randomized, double-blinded study,³⁰ amiodarone was compared with a placebo, polysorbate 80, a diluent for amiodarone, in 504 adults with nontraumatic prehospital cardiac arrest with VF or pulseless VT who had not been resuscitated after 3 precordial shocks. Of these patients, 246 were randomized to receive 300 mg of intravenous amiodarone (only a single dose) while 258 received placebo. The primary end point was admission to the hospital with a spontaneously perfusing rhythm. Secondary end points were adverse effects, the number of precordial shocks required after the study drug, the total duration of CPR, and the need for additional drugs. Eighty-eight percent of the patients had VF and 7% had pulseless VT. There was no significant difference between the two groups in the mean duration of the resuscitative efforts, the number of shocks, or the proportion of patients requiring additional antiarrhythmics. More patients receiving amiodarone had hypotension (59% vs 48%, $P = .04$) or bradycardia (41% vs 25%, $P = .004$). The patients in the amiodarone group were more likely to survive to be admitted to the hospital (44% vs 34%, $P = .03$). This trial showed that the administration of amiodarone resulted in a higher rate of survival to hospital admission in patients with prehospital cardiac arrest due to refractory ventricular tachyarrhythmias.

Another study³¹ compared amiodarone and lidocaine in adult patients with prehospital VF, resistant to 3 shocks, intravenous epinephrine, and a further shock. In total 347 patients were enrolled; 180 were randomized to receive amiodarone (5 mg/kg

estimated body weight) while 167 received lidocaine (1.5 mg/kg). The primary end point was survival to admission to the hospital. Secondary end points included survival to discharge from the hospital and adverse events. After treatment with amiodarone, 22.8% of patients survived to hospital admission, as compared with 12.0% of patients treated with lidocaine ($P = .009$). Among the 41 patients who survived to hospital admission after receiving amiodarone, 9 survived to hospital discharge (5% of the entire group), as compared with 5 of the 20 initial survivors in the lidocaine group (3% of the entire group) ($P = .34$). The investigators concluded that if an antiarrhythmic drug is to be considered in patients with shock-resistant VF, intravenous amiodarone should be the drug of choice, due to higher rates of survival to hospital admission in patients receiving amiodarone as compared with lidocaine.

Pollak and colleagues³² conducted a retrospective study in which charts of 347 patients who underwent cardiac resuscitation were studied to determine whether the use of amiodarone improved survival in the case of in-hospital cardiac arrest. The end points were survival of resuscitation effort to return of spontaneous circulation, and survival to discharge.

Pulseless VT or VF were present in 95 patients. Clinical uptake of amiodarone was limited; only 36 patients received amiodarone while 59 patients received other antiarrhythmics. In the 36 patients receiving amiodarone, survival of resuscitation was 67% vs 83% in the 59 patients receiving other drugs. Survival to discharge was 36.1% and 55.9% in the two groups, respectively. This study concluded that use of amiodarone was less than 50% and that no clinically observable survival benefit could be documented in in-hospital cardiac arrest. Possible explanations for the difference between this experience and that found in out-of-hospital resuscitation trials include differing patient populations and operator bias during resuscitation.

AMIODARONE IN CARDIAC SURGERY

Atrial fibrillation (AF) is an important and frequent complication after cardiac surgery, occurring in almost one-third of patients undergoing coronary artery bypass grafting and in up to 44% of patients undergoing a valvular procedure. Heart failure, hypotension, increased risk of stroke, need for anticoagulation, increased length of stay in the hospital, and long-term mortality are some of the various potential consequences of postoperative AF.

Postoperative AF was found to be significantly reduced in a double-blinded study³³ in which 124 patients were randomized to receive either oral amiodarone (64 patients) or placebo (60 patients) for a minimum of 7 days before elective cardiac surgery with cardiopulmonary bypass. Amiodarone dose was 600 mg/d for 7 days, then 200 mg/d until discharge from the hospital. The incidence of postoperative AF was 25% (16 patients) in the amiodarone group and 53% (25 patients) in the group receiving placebo ($P = .003$). Patients in the amiodarone group were hospitalized for significantly fewer days than those in placebo group (6.5 ± 2.6 vs 7.9 ± 4.3 days, $P = .04$), and total hospitalization costs were also significantly less in the amiodarone group ($P = .03$). No difference was found in the occurrence of postoperative complications between the two groups.

The safety of short-term amiodarone therapy with fentanyl-containing anesthesia was investigated in a randomized, double-blinded, placebo-controlled trial of cardiac surgical patients with fentanyl-isoflurane anesthesia.³⁴ There were 84 patients enrolled: 45 patients received amiodarone (3.4 g over 5 days or 2.2 g over 24 hours) while 39 received placebo. The primary end point was to compare the incidence of

hemodynamic instability, defined as: net increase in fluid balance during surgery of more than 2 L, use of more than 10 mg/kg/min dopamine, other vasopressive catecholamines, and need for a phosphodiesterase inhibitor or intra-aortic balloon pump. There were no significant differences between the two groups in any indicator for hemodynamic instability.

Although valvular surgery poses a greater risk for AF, most studies in cardiac surgery have been performed in patients undergoing coronary revascularization. In several of these protocols, the preoperative loading regimen was administered orally; however, this approach is currently impractical because most patients undergoing elective cardiac surgery are admitted the night before the procedure. Beaulieu and colleagues³⁵ randomized 120 patients to receive either amiodarone (intravenous loading dose after the induction of anesthesia followed by a 2-day perfusion) or placebo to compare the occurrence of postoperative AF. Postoperative AF occurred more frequently in patients who received amiodarone (59.3% vs 40.0% in the control group, $P = .035$). Four preoperative factors were found to be associated with a higher risk of postoperative AF: older age ($P = .0003$), recent myocardial infarction ($P = .026$), preoperative angina ($P = .0326$), and use of calcium channel blockers ($P = .0078$). This study showed that intravenous amiodarone administered in the perioperative period did not reduce the burden of postoperative AF in valvular surgery.

Amiodarone use during anesthesia for noncardiac procedures has not been described specifically, if not for patients requiring continuous antiarrhythmic therapy.

SUMMARY

Amiodarone is an antiarrhythmic drug that is useful to treat AF and perioperative tachyarrhythmias in cardiac surgery, and is the drug of choice for the treatment of out-of-hospital cardiac arrest as indicated in the ACLS protocol. Despite the promising results obtained in these settings, data about the use of amiodarone in noncardiac procedures are still lacking, and further studies are necessary to assess whether amiodarone can be advantageous.

REFERENCES

1. Rosamond W, Flegal K, Furie K, et al. Heart disease and stroke statistics—2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2008;117:25–146.
2. Lang E, Al Raisi M. Ventricular tachyarrhythmias (out of hospital cardiac arrests). *Clin Evid* 2006;15:295–300.
3. International Liaison Committee on Resuscitation. 2005 International Consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. Part 4: advanced life support. *Resuscitation* 2005;67(2/3):213–47. Available at: <http://www.cvphysiology.com/index.html>. Accessed May 21, 2011.
4. Klabunde R. *Cardiovascular physiology concepts*. Lippincott Williams & Wilkins; 2005.
5. Vaughan Williams EM. A classification of actions reassessed after a decade of new drugs. *J Cardiovasc Pharmacol* 1984;24:129–47.
6. Pallandi RT, Campbell TJ. Selective depression of conduction of premature action potentials in canine Purkinje fibres by class Ib antiarrhythmic drugs: comparison with Ia and Ic drugs. *Cardiovasc Res* 1988;22(3):171–8.
7. Man RY, Bril A. Effects of class I anti-arrhythmic drugs in infarcted tissue. *Clin Invest Med* 1991;14(5):466–75.

8. Zicha S, Tsuji Y, Shiroshita-Takeshita A, et al. Beta-blockers as antiarrhythmic agents. *Handb Exp Pharmacol* 2006;171:235–66.
9. Dorian P. Antiarrhythmic action of beta-blockers: potential mechanisms. *J Cardiovasc Pharmacol Ther* 2005;10(Suppl 1):S15–22.
10. Fleisher LA, Beckman JA, Brown KA, et al, American College of Cardiology Foundation/American Heart Association. Task Force on Practice Guidelines; American Society of Echocardiography; American Society of Nuclear Cardiology; Heart Rhythm Society; Society of Cardiovascular Anesthesiologists; Society for Cardiovascular Angiography and Interventions; Society for Vascular Medicine; Society for Vascular Surgery. ACCF/AHA focused update on perioperative beta blockade incorporated into the ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery. *J Am Coll Cardiol* 2009;54(22):e13–118.
11. Nattel S, Singh BN. Evolution, mechanisms, and classification of antiarrhythmic drugs: focus on class III actions. *Am J Cardiol* 1999;84(9A):11R–9R.
12. Khan MH. Oral class III antiarrhythmics: what is new? *Curr Opin Cardiol* 2004;19(1):47–51.
13. Woosley RL, Funck-Brentano C. Overview of the clinical pharmacology of antiarrhythmic drugs. *Am J Cardiol* 1988;61(2):61A–9A.
14. Weir MR. Calcium channel blockers: their pharmacologic and therapeutic role in hypertension. *Am J Cardiovasc Drugs* 2007;7(Suppl 1):5–15.
15. Holdgate A, Foo A. Adenosine versus intravenous calcium channel antagonists for the treatment of supraventricular tachycardia in adults. *Cochrane Database Syst Rev* 2006;4:CD005154.
16. Sica DA. Pharmacotherapy review: calcium channel blockers. *J Clin Hypertens (Greenwich)* 2006;8(1):53–6.
17. Singh BN, Venkatesh N, Nademanee K, et al. The historical development, cellular electrophysiology and pharmacology of amiodarone. *Prog Cardiovasc Dis* 1989;31(4):249–80.
18. de Latorre F, Nolan J, Robertson C, et al, European Resuscitation Council. European Resuscitation Council Guidelines 2000 for Adult Advanced Life Support. A statement from the Advanced Life Support Working Group(1) and approved by the Executive Committee of the European Resuscitation Council. *Resuscitation* 2001;48(3):211–21.
19. Ornato J. *Cardiopulmonary resuscitation*. Totowa (NJ): Humana Press Inc; 2005.
20. Zimetbaum P. Amiodarone for atrial fibrillation. *N Engl J Med* 2007;356:935–41.
21. London B. Amiodarone and atrial fibrillation. *J Cardiovasc Electrophysiol* 2007;18(12):1321–2.
22. Lafuente-Lafuente C, Alvarez JC, Leenhardt A, et al. Amiodarone concentrations in plasma and fat tissue during chronic treatment and related toxicity. *Br J Clin Pharmacol* 2009;67(5):511–9.
23. Vorperian VR, Havighurst TC, Miller S, et al. Adverse effects of low dose amiodarone: a meta-analysis. *J Am Coll Cardiol* 1997;30(3):791–8.
24. Eskes SA, Wiersinga WM. Amiodarone and thyroid. *Best Pract Res Clin Endocrinol Metab* 2009;23(6):735–51.
25. Cohen-Lehman J, Dahl P, Danzi S, et al. Effects of amiodarone therapy on thyroid function. *Nat Rev Endocrinol* 2010;6(1):34–41.
26. Greene HL, Graham EL, Werner JA, et al. Toxic and therapeutic effects of amiodarone in the treatment of cardiac arrhythmias. *J Am Coll Cardiol* 1983;2(6):1114–28.
27. Reid L, Khammo N, Clothier RH. An evaluation of the effects of photoactivation of bithionol, amiodarone and chlorpromazine on human keratinocytes in vitro. *Altern Lab Anim* 2007;35(5):471–85.

28. Aranki SF, Shaw DP, Adams DH, et al. Predictors of atrial fibrillation after coronary artery surgery. Current trends and impact on hospital resources. *Circulation* 1996;94(3):390–7.
29. Levine JH, Massumi A, Scheinman MM, et al. Intravenous Amiodarone Multi-center Trial Group. Intravenous amiodarone for recurrent sustained hypotensive ventricular tachyarrhythmias. *J Am Coll Cardiol* 1996;27(1):67–75.
30. Kudenchuk PJ, Cobb LA, Copass MK, et al. Amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation. *N Engl J Med* 1999; 341(12):871–8.
31. Dorian P, Cass D, Schwartz B, et al. Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation. *N Engl J Med* 2002;346(12):884–90.
32. Pollak PT, Wee V, Al-Hazmi A, et al. The use of amiodarone for in-hospital cardiac arrest at two tertiary care centres. *Can J Cardiol* 2006;22(3):199–202.
33. Daoud EG, Strickberger SA, Man KC, et al. Preoperative amiodarone as prophylaxis against atrial fibrillation after heart surgery. *N Engl J Med* 1997;337(25): 1785–91.
34. White CM, Dunn A, Tsikouris J, et al. An assessment of the safety of short-term amiodarone therapy in cardiac surgical patients with fentanyl-isoflurane anesthesia. *Anesth Analg* 1999;89(3):585–9.
35. Beaulieu Y, Denault AY, Couture P, et al. Perioperative intravenous amiodarone does not reduce the burden of atrial fibrillation in patients undergoing cardiac valvular surgery. *Anesthesiology* 2010;112(1):128–37.