New Concepts in Antiarrhythmic Therapy

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Arrhythmias are significant source of morbidity in the period surrounding surgery and anesthesia, and arrhythmia management strategies for perioperative patients are distinctive. The evidence linking arrhythmias to the length of hospital stay and cost of surgery has motivated new clinical investigation. At the same time, our understanding of the molecular targets for manipulating cardiac excitability has expanded the range of options for antiarrhythmic therapy. This summary will examine the clinical management of perioperative arrhythmias, using molecular targets as an organizing framework.

I. Molecular Targets and Drug Classification

Antiarrhythmic pharmacology focuses primarily on the cardiac ion channels and adrenergic receptors as therapeutic targets, and detailed discussion is provided in recent reviews[1]. For therapeutic purposes, it is useful to consider the ion channel targets in three general groups, based on the cation they conduct: sodium (Na), calcium (Ca), and potassium (K) channels. The target-based classification scheme provided (Table 1)[2] is not exhaustive, and highlights the agents available for use in the U.S. in intravenous (IV) form. Although the molecular targets are distinctive, many agents such as sotalol and amiodarone fall in more than one class.

Table 1. Antiarrhythmic agents used in the perioperative period.[3] *indicates unavailable or rarely used in IV form

Receptor Target	Class (ECG changes)	Drugs
Na and K channels	IA (QRS and QT prolonged)	procainamide, amiodarone *quinidine, *disopyramide
Na channels	IB (QRS prolonged)	lidocaine, phenytoin, *mexiletine, *tocainide
Beta receptors	II (PR prolonged)	esmolol, amiodarone, propranolol, atenolol, labetalol, *sotalol
K channels	III (QT prolonged)	bretylium, ibutilide, *sotalol, *dofetilide
Ca channels	IV (PR prolonged)	verapamil, diltiazem, amiodarone

In this chapter, the term supraventricular tachycardia (SVT) refers to all rhythms originating outside the ventricle. Recognizing that some practitioners reserve the term SVT for non-ventricular rhythms other than atrial fibrillation (AF) or flutter, we will refer to AF specifically when the therapy or concepts discussed are unique. *Pharmacologic arrhythmia management relies heavily upon the different ion channels responsible for impulse propagation in the atria and ventricles versus the SA and AV nodes.* In the atria and ventricles, impulse propagation is maintained mainly via Na current, and Na channel blockers (Table 1) slow conduction and prolong the QRS complex. In AV and SA nodal cells, Ca currents primarily support impulse conduction, and Ca channel blockers (Table 1) slow the atrial rate (by acting on the SA node), and also slow conduction through the AV node (prolonging the PR interval). The latter effect makes the AV node a more efficient "filter" for preventing rapid trains of atrial beats from passing into the ventricle, and forms the rationale for AV nodal blockade during SVT. Because Ca currents do *not* initiate impulse propagation in the atria and ventricles, Ca channel blockers (Table 1: verapamil, diltiazem) slow the ventricular *response* to atrial tachycardia, but usually *do not terminate* arrhythmias that are initiated in either the atrium or the ventricle.

IV adenosine activates K channels that hyperpolarize nodal tissue, causing a transient (~ 15 sec) 3rd degree AV nodal block. Adenosine has less effect in the atrium since atrial cells are already fully hyperpolarized. Hence, adenosine is a choice agent for terminating SVTs that involve the AV node in reentrant pathways, but only transiently slows the ventricular response for other SVTs due to reentry in atrial tissue, such as atrial flutter or atrial fibrillation (Table 2). Junctional tachycardias variably respond to adenosine.[4]

Table 2. The response of common SVTs to IV adenosine.[3]

SVT	Mechanism	Adenosine response
AV nodal reentry	Reentry within AV node	Termination
AV reciprocating tachycardias	Reentry involving AV node and accessory pathway (WPW)	Termination
Intraatrial reentry	reentry in the atrium	transiently slows ventricular response
Atrial flutter/fibrillation	reentry in the atrium	transiently slows ventricular response
Other atrial tachycardias	1. abnormal automaticity 2. cAMP-mediated triggered activity	1. transient suppression of the tachycardia 2. termination
AV junctional rhythms	Variable	Variable

Ventricular tachycardias (VTs) exhibit no response to adenosine since these rhythms originate in tissues distal to the AV conduction pathway. While adenosine has been used to discriminate wide-complex supraventricular rhythms from ventricular tachycardia, this is no longer recommended as a general practice.[5] It is increasingly recognized that adenosine, like other AV nodal blockers, has potent vasodilatory properties, and its use may cause hemodynamic collapse in patients with ventricular tachycardia and marginal hemodynamic stability. Rather, the decision to treat a wide complex rhythm as either SVT or VT should be based on history (usually VT in patients with coronary artery disease or structural heart disease) and inspection of the ECG (SVT if a P wave precedes each QRS complex). If in doubt, the most conservative approach is to consider the rhythm VT, and avoid the use of AV nodal blockers (especially long-acting agents) with vasodilatory properties.

Atrial and ventricular arrhythmias often arise from *reentry*, impulse loops induced by electrical inhomogeneities between adjacent regions of myocardium. Although Na or K channel block may interrupt reentry, by slowing conduction or increasing the refractory period respectively, clinical trials suggest that K channel blockade is a more effective strategy. At the same time, K channel blockade may also prolong the ECG QT interval and induce *triggered activity* in the ventricle, causing a polymorphic VT known as "Torsades de Pointes." Low serum K, slow heart rates, and pre-existing QT prolongation due to genetic factors may predispose patients to these drug-induced arrhythmias. Torsades occurs in 1-8% of patients who receive QT-prolonging drugs, and may be viewed as an "acquired" form of the rare congenital long-QT syndrome. With rapid advances in sequencing the human genome, ion channel mutations have been identified that only provoke arrhythmias when patients are exposed to K-channel blocking drugs.[6] These "silent" mutations provide a genetic rationale for the untoward response of patients to a myriad of drugs that prolong the QT interval, many of which are used routinely in anesthesiology and ICU medicine (Table 3). Technologies to identify these "acquired" long QT patients through efficient genetic screens are developing. At present, clinical awareness of the family history, recognition of potential triggering agents, and judicious use of QT interval monitoring are clinical practices that should be considered alongside steps taken to prevent complications from other inherited disorders (ie. malignant hyperthermia).

Table 3. QT-Prolonging drugs in general use

Antiarrhythmics	quinidine, procainamide, disopyramide, sotalol, amiodarone, ibutilide, dofetilide
Antipsychotics	haloperidol, risperidone
Antihistamines	terfenadine, astemizole
Antifungal	ketoconazole, fluconazole, itraconazole
Antibiotics	trimethoprim-sulfamethoxasole, pentamidine, erythromycin
Antidepressants	amitriptyline, imipramine, doxepin
Phenothiazines	chlorpromazine, thioridazine
Volatile anesthetics	isoflurane, enflurane
GI	cisapride, dolasetron, droperidol

II. Managing Perioperative SVT

Patients with narrow complex tachycardias who are dangerously hypotensive (e.g. loss of consciousness, cardiac ischemia, or a systolic BP < 80 mmHg) require immediate synchronous DC cardioversion in order to prevent irreversible complications of hypoperfusion (stroke, myocardial infarction). At the same time, attention should be focused on the many reversible causes of SVT, rather than on heart-directed pharmacologic therapies. SVT is among the anesthesiologist's most valuable warning signs, often foreshadowing life-threatening conditions that may be correctable. These include hypoxemia, hypoventilation, hypotension (absolute or relative hypovolemia due to bleeding, anaphylaxis), and cardiac ischemia. In addition, light anesthesia and electrolyte abnormalities may precipitate SVT. Drug therapy should be considered after these etiologies have been excluded.

In less urgent cases, adenosine may be administered as a 6 mg IV bolus (repeated with 12 mg if no response) instead of DC countershocks. Unfortunately, the rhythms most commonly seen in the perioperative period (Table 2: atrial fibrillation, intraatrial tachycardias) do not involve the AV node in a reentrant pathway, and AV nodal block by adenosine will therefore produce only transient slowing of the ventricular rate. *The vast majority of patients who develop intraoperative or postoperative SVT are hemodynamically stable and do not require cardioversion.* In these patients, ventricular rate control is the mainstay of therapy. Lengthening diastole serves to enhance left ventricular filling, thus enhancing stroke volume, and slowing the ventricular rate reduces myocardial oxygen consumption and lowers the risk of cardiac ischemia. Intraoperatively, rate control is readily achieved with one of a variety of AV nodal blockers (agents with class II or IV activity, Table 1). Among the IV beta blockers, esmolol has ultra-rapid elimination properties that render it titratable on a minute-to-minute basis, allowing meaningful dose adjustments during periods of surgery that provoke changes in hemodynamic status (ie. bleeding, abdominal traction). While esmolol is relatively β_1 selective and often well-tolerated by patients with reactive airways, the drug has obligatory negative inotropic effects that may be problematic for patients with left ventricular dysfunction. Both IV verapamil and IV diltiazem are Ca channel blockers that are less titratable than esmolol, but slow the ventricular rate within minutes. In addition, IV diltiazem has less negative inotropic action than verapamil or esmolol and is preferable in patients with heart failure. IV digoxin slows the ventricular response during SVT through its vagotonic effects, but should be supplemented with other IV agents due to its slow onset (~ 6 hours).

AV reciprocating SVTs (Table 2) arising from reentrant circuits that involve accessory pathways (congenital electrical connections between the atrium and ventricle that bypass the AV node) require distinctive management. During sinus rhythm, forward (antegrade) conduction through the accessory pathway may produce ventricular pre-excitation (known as Wolff-Parkinson-White Syndrome, or WPW), manifest on the ECG as a short PR interval (< 0.12 sec), a slurred QRS upstroke (delta wave) and a wide QRS complex. Episodes of AV reciprocating SVT usually do not provoke a marked deterioration in hemodynamic status. However, patients with SVT and WPW will sometimes

develop AF. In this case, the rapid rate of atrial excitation (> 300 impulses/min), normally transmitted to the ventricle after considerable "filtering" by the AV nodal system, may instead be transmitted to the ventricle via the accessory bundle at a rapid rate. The danger of inducing ventricular fibrillation in this scenario is exacerbated by AV nodal blocking agents (digoxin, Ca channel and beta blockers) because they reduce the accessory bundle refractory period. *Hence, WPW patients who experience SVT should not receive these AV nodal blockers.* Because of its short half-life, IV adenosine may be used to break SVT in WPW patients, as long as facilities for defibrillation are readily available should AF or VF occur. IV procainamide, which slows conduction over the accessory bundle, may be used to convert SVT in WPW in less urgent circumstances, or if AF occurs.

Most patients who develop SVT under anesthesia will remit spontaneously prior to or during emergence. Efforts to convert SVT to sinus rhythm in the operating room should therefore be aimed at those patients who cannot tolerate (or do not respond to) rate control therapy and are judged to be at high risk for ischemia or hemodynamic instability. Intraoperative elective DC cardioversion in an otherwise stable patient with SVT carries risks (ventricular fibrillation, asystole, stroke). Moreover, the underlying factors provoking SVT during or shortly after surgery are likely to persist beyond the time of cardioversion, inviting rapid recurrence. At the same time, most of the IV antiarrhythmic agents have limited efficacy when utilized alone for "chemical" cardioversion. However, bolus administration of an IV antiarrhythymic drug (IV procainamide or IV amiodarone) prior to administering DC countershocks may improve the chances of sustained cardioversion. Ibutilide, a rapid-acting class III antiarrhythmic (Table I), produces an impressive 30-45% rate of conversion of atrial fibrillation within 30 minutes (without DC countershocks), but unfortunately provokes polymorphic VT (Torsades) in up to 8% of patients, so its use in the surgical period has been limited.

III. Managing Perioperative Ventricular Arrhythmias

Ventricular arrhythmias may be subdivided according to their morphology, but are less distinctive than SVTs in their response to drug therapies. Nonsustained ventricular tachycardia (NSVT) is defined as three or more premature ventricular contractions (PVCs) that occur at a rate exceeding 100 beats/min, and last 30 sec or less without hemodynamic compromise. In patients with *preserved ventricular function*, NSVT does not predict more serious VT, and in the absence of hemodynamic instability does not require antiarrhythmic therapy. At the same time, new PVC's during the surgical period should not be ignored, and potential etiologies (hypoxemia, hypotension, cardiac ischemia, electrolyte disorders, or light anesthesia) should be rapidly evaluated and treated. In patients with poor ventricular function or severe LVH, the advent of NSVT may predict more serious arrhythmias. Prophylaxis with lidocaine is often used in this circumstance, although clinical trials evaluating this practice in high-risk patient groups are not available.

Therapy for most forms of sustained VT (either monomorphic or polymorphic) or ventricular fibrillation (VF) is similar, and is discussed below. The management of polymorphic VT with marked prolongation of the QT interval (Torsades de Pointes) is distinctive, and deserves separate discussion. Like all sustained ventricular arrhythmias that are accompanied by hemodynamic collapse, patients with Torsades de Pointes require asynchronous DC countershocks. Additional therapies are aimed at preventing recurrence of these arrhythmias, and include IV Mg^{2+} (2 – 4 g), K^{+} repletion, increasing the heart rate (atropine, isoproterenol, or temporary ventricular pacing), and rarely class IB antiarrhythmic drugs (lidocaine or phenytoin). If it is unclear whether an observed episode of polymorphic ventricular tachycardia is related to QT interval prolongation, Mg^{2+} and Na channel blockers may be administered empirically.

IV antiarrhythmic agents are commonly used as adjuncts to DC cardioversion during cardiopulmonary resuscitation. The IV antiarrhythmic agents most often used for this purpose include lidocaine, bretylium, procainamide, and amiodarone. Until recently, there was a paucity of prospective clinical data evaluating the efficacy of all antiarrhythmic agents during cardiac arrest. Of the available agents, IV amiodarone is the only agent studied in prospective, randomized clinical trials involving more than 1000 patients.[7] In hospitalized patients, IV amiodarone and IV bretylium are equally effective for suppressing VT refractory to procainamide or lidocaine, although significantly more patients treated with bretylium experienced hypotension (33% versus 21%) or congestive heart failure (5% versus

0%), leading to substantial between-group crossover from bretylium to amiodarone.[8] In addition, recent trials randomized, blinded trials have examined the efficacy of IV amiodarone in patients experiencing out-of-hospital cardiac arrest refractory to DC cardioversion.[9,10] In the Seattle study (ARREST), of the 504 patients enrolled, recipients of amiodarone were more likely to be resuscitated and admitted to the hospital than recipients of a placebo infusion (44% vs. 34%, p = 0.03). In the more recent Toronto study (ALIVE) comparing amiodarone to lidocaine, of 347 enrolled patients, survival to hospital admission was 22.8% in patients treated with amiodarone versus 12% in patients treated with lidocaine. Neither study revealed an effect on survival to discharge.

Should these findings influence our selection of antiarrhythmic therapy in surgical patients experiencing life-threatening VT and VF? Clearly, no drug has been evaluated prospectively for perioperative cardiac arrest, and survival-to-hospital discharge benefits have not been identified for any antiarrhythmic agent. At the same time, IV antiarrhythmic drugs are measures of last resort when patients remain pulseless following repeated DC countershocks. The motivation to use IV amiodarone in this setting is strengthened by the new evidence that the agent does produce at least a short-term survival benefit over placebo and lidocaine when administered during out-of-hospital cardiac arrest, [9,10] and is now recommended over lidocaine as a "IIB" agent in the revised American Heart Association guidelines.[5] While compelling, given the unique circumstances of the perioperative period, extrapolating the results of these studies to intraoperative cardiac arrest requires a degree of optimism, and antiarrhythmic trials that focus on perioperative patients are needed.

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