Treatment of Cardiac Arrhythmias

2016 edition by

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Note to Instructors

The POPS exercises are divided into seven sections:

A. Introduction to the POPS System, introduction to and objectives of the clinical simulations, a pretest, and review topics
B-E. Four different color-coded sections with pretest answers and the clinical problem
F. Posttest
G. Posttest answers

For information on conducting the exercise, see the Instructor's Manual: Patient-Oriented Problem-Solving (POPS) System in Pharmacology.
Treatment of Cardiac Arrhythmias

**Introduction to the Patient-Oriented Problem-Solving (POPS) System**

This is a patient-oriented problem-solving activity. The purposes are

1. to help you learn how to apply your basic science knowledge to the solution of clinical problems;

2. to encourage you to better locate information necessary for solving problems by using sources (e.g., literature sources and peers) that will be available to you throughout your career; and

3. to encourage you to work with your fellow students and thus:
   a. increase your ability to evaluate your colleagues' opinions, thought processes, and clinical decisions;
   b. increase your communications skills; and
   c. increase your skills in interpersonal and interprofessional relations.

This activity consists of five phases:

First, you will review the attached set of objectives and complete the pretest on your own. In the second phase, you will use the pretest and the recommended review topics for further individual study before you meet with your group.

In the third phase, you will join three other students to review the pretest answers in an "open-book" discussion.

In the fourth phase, the group will solve patient-oriented problems. Information exchange and group interaction are keys to the success of this phase, which will allow you to teach your fellow students and, at the same time, learn from them.

Finally, you will take a posttest, individually, which will enable you to assess your progress.
Introduction

Normal initiation and conduction of electrical impulses are essential for the maintenance of optimal cardiac function. Disruptions in these processes can lead to the development of a wide range of cardiac irregularities. Supraventricular arrhythmias such as paroxysmal supraventricular tachycardia may lead only to periods of mild discomfort, while atrial fibrillation may be troublesome to the patient due to resulting rapid and irregular ventricular rate that if uncorrected may lead to thrombus formation and subsequent embolization. The occasional single ventricular extrasystole occurs with variable frequency in normal hearts; however, increased occurrence or several successive such beats may be a sign of cardiac disease. Ventricular arrhythmias are commonly associated with myocardial infarction and digitalis toxicity. Additionally, many drugs including some agents used in treating arrhythmias (class Ia, Ic, III) increase QT interval, which can cause potentially fatal torsade de pointes. The most serious ventricular arrhythmia, fibrillation, can cause cardiac arrest and death if not treated immediately. It is commonly preceded by sustained, rapid and often multifocal ventricular tachycardia.
Learning Objectives

When you have completed this exercise, you should be able to:

A. Demonstrate understanding of mechanisms responsible for the development of supraventricular arrhythmias and the basic physiologic processes and drug properties that will allow you to determine the best therapy by

1. explaining the cardiac effect of the carotid-sinus and aortic-arch reflexes.
2. explaining the effect of digitalis and pure alpha-adrenergic agonists on carotid-sinus activation.
3. explaining the basic mechanism of action and other actions of drugs that are useful in the treatment of reentrant supraventricular arrhythmias.

B. Demonstrate understanding of the major mechanisms of ventricular arrhythmias and the effective use of drug therapy by

1. explaining the arrhythmogenic phenomenon of reentry by citing the two types of myocardial conduction abnormalities that favor reentry and how drugs can be used to interrupt a reentrant path.
2. defining automaticity in a myocardial cell and explaining the mechanism of anti-arrhythmic drugs from electrophysiologic data.
3. identifying the major adverse effects of antiarrhythmic drugs that limit their use for ventricular arrhythmias.

When you have become familiar with the objectives, complete the pretest on the next page.
Pretest

Instructions: To facilitate later discussion and review, please mark these pretest pages with your answers to the following questions. If your instructor has provided a separate form, mark your answers both on that form (being sure to fill in the identification section) and on these pages.

Choose the one correct or most appropriate answer. If you do not know an answer, leave the space blank. Do not guess. Health professionals who think they know something, but do not, can do real harm. Those who know they don't know something can get help.

Don't be upset if you don't know all the answers. The purpose of the pretest and the objectives are to alert you to important concepts. The posttest will be similar in content to the pretest.

1. Which of the following statements is correct regarding automaticity?

A. Automaticity is a property of all normal cells in the heart.
B. Automaticity of Purkinje fiber cells is enhanced by most antiarrhythmic drugs.
C. Automaticity is absent in cells damaged by myocardial infarction.
D. Automaticity is defined as the gradual spontaneous depolarization of a cell toward threshold.
E. Automaticity occurs only in ventricular tissue.

2. A property of reentrant arrhythmias includes which of the following?

A. They require a site of unidirectional conduction block.
B. They require increases in automaticity.
C. They occur only in atrial tissue.
D. They are involved primarily in ventricular fibrillation.
E. They require AV nodal involvement.

3. Which of the following is a characteristic of the carotid-sinus reflex?

A. It modifies vagal and sympathetic tone on a beat-to-beat basis.
B. It modulates only parasympathetic tone on a beat-to-beat basis.
C. It modulates only sympathetic tone on a beat-to-beat basis.
D. It acts in the opposite direction to the reflex elicited in the aortic arch.
E. It involves only the peripheral nervous system.

4. Phenylephrine increases pressure in the carotid sinus by

A. activating only beta-adrenergic receptors.
B. being a partial agonist.
C. activating alpha1-adrenergic receptors.
D. causing release of norepinephrine from nerve endings.
E. activating alpha2-adrenergic receptors.
5. Which of the following antiarrhythmic drugs is not effective by the oral route?
   A. quinidine  
   B. flecainide  
   C. amiodarone  
   D. lidocaine  
   E. procainamide

6. Which of the following drugs is classified as a calcium-channel blocker?
   A. lidocaine  
   B. procainamide  
   C. disopyramide  
   D. verapamil  
   E. quinidine

7. Which of the following antiarrhythmic drugs is associated with the development of a syndrome that resembles systemic lupus erythematosus?
   A. verapamil  
   B. quinidine  
   C. propranolol  
   D. procainamide  
   E. disopyramide

8. Which of the following drugs may be contraindicated in a patient with bronchial asthma?
   A. propranolol  
   B. lidocaine  
   C. verapamil  
   D. procainamide  
   E. quinidine

9. In patients with supraventricular tachycardia, which of the following drugs would be least likely to depress myocardial contractility?
   A. verapamil  
   B. digoxin  
   C. propranolol  
   D. disopyramide  
   E. quinidine

10. The most frequent toxic effect associated with the use of lidocaine for the treatment of ventricular arrhythmias is
    A. AV heart block.  
    B. central nervous system (CNS) toxicity.  
    C. cardiac depression.  
    D. nausea and vomiting.  
    E. hepatotoxicity.
When you have completed the pretest, consult your study materials. Try to identify the correct answers and understand the concepts that make them correct. As a guideline for your studies, you may use the Learning Objectives. When your group meets, you will be responsible for explaining some of the answers. Please bring your materials to the group meeting.

To prepare for that meeting, which will be a problem-solving session, you should review the following topics:

1. Electrophysiologic basis of supraventricular and ventricular arrhythmias
2. Physiologic and pharmacologic mechanisms of treating cardiac arrhythmias
3. Consideration of drug efficacy, toxicity, and compliance in the treatment of arrhythmias
Note to Students

The fundamental purposes of all activities in the health-care professions are to help other people. Like all behavior, helping behavior becomes more effective and natural with practice. This exercise enables you to practice by helping your fellow students to learn basic science. Your skill at helping your fellow students should relate to your ability to help your patients in the future.

This is a Patient-Oriented Problem-Solving (POPS) exercise designed for four students. Before beginning this session, you should have (a) studied the objectives designed to prepare you for it, (b) taken the pretest, and (c) reviewed the topics listed at the end of the pretest. Now, each of you should take one of the four color-coded parts and follow the directions in it. If your group has only three students, one of you should take two parts. If your group has more than four students, two should take turns with a part.

Please begin by discussing the answers to the pretest.
Correct Answers to Pretest Questions

In the discussion to follow, you are given the correct answers to some of the 10 pretest questions, along with explanations. Other students in your group have been given the answers to other questions. This allocation of answers and explanations is designed to encourage all members of your group to actively exchange ideas and concepts. First, study the answers in your booklet and then EXPLAIN them to your group. Please don't simply read them to your classmates, and don't let your classmates read their answers to you. In explaining something to another person, most people gain and often transmit a better understanding of the subject. The pretest discussion and patient-oriented problem-solving parts of this activity are "open book"; be sure to refer to textbooks, notes, and other written resources whenever questions arise.

To help you review any questions that you may have missed, you probably will want to make notes on your pretest answer sheets. However, avoid "collecting pages" for 'later study and understanding." Learn the concepts now so that later you will only need to review them.

4. (C) is correct. Phenylephrine is equal in effectiveness to norepinephrine as an alpha1-adrenergic agonist. Phenylephrine does not cause release of norepinephrine and has no effect on alpha2-adrenergic receptors.

5. (D) is correct. Lidocaine is the only drug listed that is not effective by the oral route. It is subjected to significant first-pass hepatic metabolism, and the toxicity of its metabolites precludes administration of large doses. Propranolol also undergoes first-pass elimination, but its metabolites are not toxic, and effective blood levels can be obtained by increasing the dose.

9. (B) is correct. Digoxin produces a positive inotropic effect, while the other drugs can produce cardiac depression.

When your group has finished discussing all of the pretest questions, read "Instructions for the Clinical Problem" on the next page.
Instructions for the Clinical Problem

In the remainder of this exercise, you are to use your knowledge of the pharmacology of antiarrhythmic agents to make rational choices about the treatment of arrhythmias in specific patients. Each of the four members of your group has information about one episode to present. You must work together to solve the medical problems presented.

When the episode for which you are responsible comes up, read it to the group and lead a discussion of the questions included with the episode. Pose each question to a different member of the group. Use the Discussion Notes provided as a guide for the discussion. DO NOT SIMPLY READ THE NOTES to the group. Learning is facilitated by active processes such as thinking about the questions and their possible solutions. Do not leave a question until every member of the group is completely satisfied with the answer. During the discussion, members of the group may consult textbooks, notes, and any other reference material. This is a group effort. Work together and teach one another.

As the group member whose part contains Episode 1, you should begin the discussion.
Episode 1

Miss Patricia Ann Tarpon is a 26-year-old woman in good health. She is interested in exercise and music. She is distraught, pale, weak, and complains that, "My heart is racing and I can't stop it."

Physical examination indicates rapid shallow respirations, a regular pulse rate of 180 beats per minute, and a blood pressure of 130/80 mm Hg. After a few minutes of quiet conversation, her respiratory rate slows somewhat, but her pulse rate remains rapid. On several past occasions she has had the same feeling of having her heart race, often when she was excited. Several of these attacks only lasted a few seconds. She has learned that at other times she only had to take a deep breath and hold it, in order to feel better, but today, this has not helped. Her difficulty has lasted almost an hour, and she is worried that she has had a heart attack.

Her electrocardiogram (ECG) tracing shows supraventricular tachycardia with no evidence of the involvement of an accessory pathway (e.g., Wolff-Parkinson-White syndrome [WPW]). Based on this information and her history of the arrhythmia being intermittent and reversible by what is equivalent to a Valsalva maneuver, she is diagnosed as having paroxysmal supraventricular tachycardia.

How should Miss Tarpon be treated?

Use the following questions and the Discussion Notes to guide the discussion. Each member of the group should take the lead in answering at least one of the questions.

1.1 What is the most common mechanism of induction of paroxysmal supraventricular tachycardia?

1.2 Discuss the innervation at the AV node and how activation of these neural influences can be used to treat Miss Tarpon.

1.3 Name a few non-pharmacological methods that Miss Tarpon could use to help stop her arrhythmias. (She discovered one of them herself.)

1.4 Why is simultaneous massage of both sides of the carotid sinus not recommended?

1.5 What classes of drugs should be considered for Miss Tarpon, and what are their mechanisms of action?

1.6 What principles determine choice of agent among these classes of drugs and among the agents in each class?

Miss Tarpon is treated with intravenous adenosine. Miss Tarpon's rhythm is immediately restored to normal.
1.7 If adenosine had not converted the arrhythmia, what other options should be considered?

1.8 Which is the better choice: phenylephrine or epinephrine, and why?

Since her first visit, Miss Tarpon had been treated successfully for a period of 6 months using carotid-sinus massage and intravenous adenosine as required. However, over the past month Miss Tarpon has experienced an increasing number of attacks. This is making her very apprehensive, and her employer is becoming upset about her frequent and unexpected absences from work.

It is apparent that further treatment options should be considered to lessen the frequency of attacks. Drug treatment may be required for several years.

1.9 Since IV adenosine was effective in converting Miss Tarpon's arrhythmia, why not give her oral adenosine for maintenance therapy?

1.10 What other drugs should be considered to reduce these episodes? Which of these is the first choice and what is the rationale for this decision?

1.11 What other nondrug therapeutic measures should be considered?
Discussion Notes for Questions in Episode 1

1.1 Although other possibilities clearly exist (e.g., increased automaticity), we consider here only the common case of a reentrant circuit that exits on the atrial side. Remind your colleagues that reentry requires a site of unidirectional conduction block and an area of slowed conduction. Conduction of an impulse from the atria through the AV node normally follows two longitudinal pathways (alpha and beta) that join to form a final common path in the terminal area of the junction. The alpha-pathway conducts slowly and has a short refractory period, while the beta-path conducts rapidly but has a long refractory period. A premature atrial beat may find the beta-path refractory and thus conduct slowly through the alpha-path. If the impulse as it exits into the common path finds the beta-path recovered from its refractory period, it may conduct both in the antegrade direction into the ventricles and in the retrograde direction through the beta-path into the atria, thus establishing a reentrant circuit. Such a reentrant arrhythmia can lead to heart rates of 140 to 250 beats per minute. Remind your colleagues that reentrant supraventricular arrhythmias can also use accessory pathways such as the bundle of Kent, which may require different modalities of drug therapy. The therapeutic goal is to interrupt this circuit and restore normal sinus rhythm. This can best be done by slowing conduction or prolonging the refractory period of the reentrant pathway or both. These points are the key to understanding the treatment of all patients in this POPS activity and may require considerable discussion.

1.2 The AV node is one of the areas of the heart in which the cells are innervated by both the parasympathetic and the sympathetic nervous system. The two systems act in opposite directions; the vagus slows conduction and increases the refractory period. Physical maneuvers to elicit cardiovascular reflexes are preferable to drugs when one wishes to depress AV nodal conduction briefly, as is true in this case.

1.3 The methods that might help Miss Tarpon are those that stimulate the vagus nerve.

   a. Valsalva maneuver- bearing down while holding her breath.
   b. Forceful coughing.
   c. Gagging.
   d. Immersing her face in ice water.
   e. Carotid sinus massage can be done but this is not something that Miss Tarpon should do on her own.

1.4 Complications can arise from this procedure so it is best left to health care professionals. Also, while carotid-sinus massage is often effective in interrupting a reentrant pathway, in Miss Tarpon's case this maneuver has proven to be ineffective. It is clear, therefore, that drug therapy will be required.

1.5 a. Adenosine: This endogenous purine nucleoside blocks conduction through the AV node and is thus effective in both treating and diagnosing supraventricular arrhythmias. Adenosine reduces duration and amplitude of nodal cell action potential, which may account in part for its effects on AV nodal conduction.
b. **Non-dihydropyridine calcium-channel blocking drugs (e.g., verapamil and diltiazem):** Since conduction through the AV node is carried primarily by a calcium-dependent current, these drugs interrupt the reentrant pathway and revert the arrhythmia to a sinus rhythm. The dihydropyridine calcium-channel blockers (e.g., nifedipine) have less effect on heart calcium channels and are therefore not effective here.

c. **Drugs that reduce sympathetic tone:** beta-adrenergic-blocking drugs block sympathetic influences on the AV node and thus decrease conduction through the reentrant path.

d. **Drugs that enhance vagal tone:** In some cases, pharmacological enhancement of vagal tone might be effective. Digoxin enhances vagal activity at the AV node to decrease conduction and prolong the refractory period. Vasopressor drugs (e.g., phenylephrine) enhance vagal tone and reduce sympathetic tone at the AV node by raising pressure in the carotid sinus.

1.6 The drug chosen should have a minimum risk of side effects and a short duration of action. Intravenous (IV) adenosine or verapamil is quite effective in stopping paroxysmal supraventricular tachycardia and these drugs are now generally considered to be the drugs of choice when physical stimulation of the vagal reflexes is ineffective. Adenosine has the advantage of having a fast onset of action and short half-life (seconds) so that side effects (flushing, chest pain, and dyspnea) are fleeting. Bronchoconstriction in asthmatics, however, last longer and the drug should not be used in these patients. Verapamil is equally effective and has a longer half-life; this may be useful in patients whose arrhythmia recurs shortly after being terminated with adenosine. Adverse effects such as hypotension, complete AV block, and cardiac depression are of concern in patients with other cardiac disease or in those who are receiving concomitant beta-blocker therapy.

1.7 Unless there is underlying cardiac disease that would preclude their use, the calcium channel blockers IV verapamil or diltiazem should be used if adenosine proved ineffective. IV beta-blockers may also be effective in terminating PSVT some patients. However, the use of either calcium channel blockers or beta-blockers is associated with adverse effects associated with cardiodepression and should be used in those who are hemodynamically stable.

Other drugs to consider for acute treatment of PSVT in some patients include amiodarone, phenylephrine, or sodium channel blockers. These agents can be used in patients who fail to respond to recommended therapy above.

Digoxin is not as effective in termination of PSVT due to its relatively slower onset of action compared with other agents. In fact, caution should be used in WPW syndrome where both digoxin and verapamil may enhance conduction through an accessory path, such as the bundle of Kent, and lead to ventricular tachycardia or fibrillation. Patients with WPW most often respond to therapy with sodium-channel blockers, which prolong the refractory period of the anomalous pathway.
1.8 Phenylephrine does not activate beta-adrenergic receptors that would oppose the reflex vagal response to acute increases in blood pressure. Phenylephrine should be chosen because it has a shorter duration of action. Remember that stopping the reentry circuit just once will allow the sinus node to take over (until the conditions for reentry become just right again).

1.9 Since adenosine is metabolized so rapidly, it is best used in the acute management of arrhythmias.

1.10 Initial treatment for long-term management of Miss Tarpon should include consideration of oral verapamil, diltiazem or beta blockers. Caution should be used as calcium-channel blockers are potential cardiac depressants. Beta-blockers also may be effective, especially if the attack is precipitated by exercise or excitement (high sympathetic tone). Although beta-blockers may reduce myocardial contractility, Miss Tarpon is not showing any signs of heart failure. You must also be aware that beta-blockers may be unacceptable to Miss Tarpon because she enjoys exercise, and the decrease in maximum exercise tolerance that may result, might unduly affect her lifestyle.

Digoxin, which will be discussed in detail in Episode 2, increases vagal tone to the heart and is also a management option. Digoxin also has the advantage of being inexpensive and of having a long half-life so that you may be able to control Miss Tarpon's cardiac rhythm with maintenance doses given once a day. Digoxin may well be a suitable alternative prophylactic therapy for Miss Tarpon's condition.

1.11 Tell your colleagues that cardioversion or ablation of abnormal pathways can be effective in some patients who are resistant to or prefer ablation to long term drug therapy.

The group member whose part contains Episode 2 should now take over as discussion leader.
Note to Students

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Please begin by discussing the answers to the pretest.
Correct Answers to Pretest Questions

In the discussion to follow, you are given the correct answers to some of the 10 pretest questions, along with explanations. Other students in your group have been given the answers to other questions. This allocation of answers and explanations is designed to encourage all members of your group to actively exchange ideas and concepts. First, study the answers in your booklet and then EXPLAIN them to your group. Please don't simply read them to your classmates, and don't let your classmates read their answers to you. In explaining something to another person, most people gain and often transmit a better understanding of the subject. The pretest discussion and patient-oriented problem-solving parts of this activity are "open book"; be sure to refer to textbooks, notes, and other written resources whenever questions arise.

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2. (A) is correct. For reentry to occur, an area of unidirectional block is required (A). Conduction also must be slowed sufficiently so that when the impulse exits through the block in a retrograde direction, the cells will be out of their refractory periods and will therefore receive the reentrant impulse. (B) is not correct because while increased automaticity can precipitate arrhythmias, these are not responsible for reentrant rhythms. While reentry can lead to ventricular fibrillation (D), it is often responsible for single, extrasystoles, coupled beats, and runs of ventricular tachycardia. Atrial tachycardia and fibrillation also can be the result of a reentrant pathway.

7. (D) is correct. Long-term procainamide therapy often produces symptoms resembling systemic lupus erythematosus. Signs and symptoms are reversible upon cessation of therapy with the drug.

When your group has finished discussing the pretest, read “Instructions for the Clinical Problem” on the next page.
Instructions for the Clinical Problem

In the remainder of this exercise, you are to use your knowledge of the pharmacology of antiarrhythmic agents to make rational choices about the treatment of arrhythmias in specific patients. Each of the four members of your group has information about one episode to present. You must work together to solve the medical problems presented.

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The group member whose booklet contains Episode 1 should now begin the discussion.
Ms. Inita Rhythm is 55 years old and has been working in a textile plant for the past 30 years. During the past month, she has become fatigued easily; in the past week, she has experienced pounding in her chest and periods of dizziness. At age 12, Ms. Rhythm had rheumatic fever.

On physical examination, Ms. Rhythm has a blood pressure of 120/70 mm Hg and an irregular pulse rate of 125 beats per minute. Her neck veins are slightly distended. Cardiac examination reveals an irregular rhythm; there is an opening snap and a soft diastolic rumble at the apex. Chest x-ray examination reveals an enlarged right and left atrium and right ventricle with pulmonary venous congestion. The ECG shows atrial fibrillation with a ventricular rate of 125 beats per minute. Your impression is that this patient has rheumatic mitral stenosis with mild congestive heart failure. Your problem is to develop an appropriate therapeutic regimen for Ms. Rhythm's arrhythmia while she is being worked up for her underlying cardiac disease.

Use the following questions and the Discussion Notes at the end of your booklet, to lead a discussion of the best therapy for Ms. Rhythm. Each member of the group should take the lead in discussing at least one of the questions.

2.1 Inform your colleagues that successful long-term conversion of atrial fibrillation in patients with cardiac disease such as is manifested by Ms. Rhythm, is frequently unsuccessful and that two earlier attempts at cardioversion in this patient failed. What is the immediate therapeutic goal(s)?

2.2 What drugs would be most effective in controlling the ventricular rate?

You decide to treat Ms. Rhythm with carvedilol.

2.3 Under what conditions might administration of a beta-adrenergic-blocking drug be contraindicated?

2.4 Are there any other drugs that you could administer to reduce this patient's ventricular rate?

On a follow-up visit 10 days later, Ms. Rhythm's symptoms of congestive heart failure are somewhat improved. Her ventricular rate has been reduced to 100 beats per minute, but she still has some dizziness and palpitations. Her ventricular rate is still too high. You consider adding digoxin to Ms. Rhythm’s therapeutic regimen.

2.5 What is the mechanism by which digoxin enhances vagal activity on the AV node to increase the refractory period and decrease conduction?

Use the Discussion Notes on the next page and lead a discussion of the answers.
Discussion Notes for Questions in Episode 2

2.1 The immediate therapeutic goals are to
a. reduce the patient's ventricular rate to 60 to 80 beats per minute.
b. control the signs and symptoms of the congestive heart failure.

2.2 Beta-blockers, calcium-channel blockers and digoxin are the drugs to be considered. The major problem associated with atrial fibrillation is the shortened diastolic filling time that occurs, which can further reduce cardiac output in the presence of mitral valve obstruction. Each of the above drugs reduces the number of impulses conducted through the AV node into the ventricles and thereby effectively lowers the ventricular rate allowing for better filling. Since Ms. Rhythm is in mild congestive heart failure, current guidelines suggest the use of beta blockers as initial therapy (Circulation, 2012, 125:945-957, doi:10.1161/circulationaha.111.019935; Circulation, 2013, 128:e240-e327, doi:10.1161/cir.0b013e31829e8776; Circulation, 2014, 130:2071-2104, doi:10.1161/cir.0000000000000040). Digoxin can be useful as adjunctive therapy if the ventricular rate is not adequately controlled. The combined use of both beta-blockers and calcium-channel blockers have the potential to depress myocardial contractility; thus, care must be taken when these drugs are given to patients in heart failure.

2.3 Beta-blockers are contraindicated in asthmatics. Blocking beta2-adrenergic receptors in the bronchial smooth muscle may not only precipitate an attack, but limits the therapeutic choices since many bronchodilators are beta2-receptor agonists. One might argue that use of a cardioselective beta1-adrenergic blocker would be safe. However, the selectivity of these drugs is dose-dependent, and the literature cites many cases of asthmatic attacks following administration of beta1-blockers.

2.4 Combination therapy with beta blockers and digoxin or calcium-channel blockers and digoxin have been shown to be more effective in controlling heart rate in atrial fibrillation than either drug alone. Calcium channel blockers such as verapamil and diltiazem block the slow calcium channel, which is at least partially responsible for impulse conduction through the AV node. Beta-blockers slow AV conduction by reducing sympathetic influences on the node. Carvedilol in particular has been shown to increase LVEF and reduce mortality and hospitalizations in atrial fibrillation and heart failure, which could be of benefit in a patient with both conditions. In designing a treatment regimen, care must be taken to not suppress conduction to the point of producing complete AV block. Also remember that verapamil often leads to increased plasma levels of digoxin; thus, a lowering of the dose of digoxin is often required when the two drugs are administered concurrently. A concern with digoxin is its safety profile. Some studies have shown a correlation with digoxin use and an increased risk of mortality while others have shown a neutral effect. It is not clear whether the potential negative impact on mortality is due to digoxin itself or to the types of patient receiving digoxin. Further studies should serve to advance knowledge in this area.
2.5 Digoxin sensitizes the carotid-sinus baroreceptors and may also enhance vagal activity through a central effect. It may also sensitize the AV node to the effects of acetylcholine (ACh). These vagal effects of digoxin are most pronounced when the patient is at rest. During exercise, the sympathetic influences on the AV node can override the vagal effects of digoxin and tachycardia may return. The combination of beta blocker and digoxin could therefore be of benefit in such instances.

Digoxin can cause serious ventricular arrhythmias if drug levels are too high (toxic > 2.0 ng/mL). Keep in mind that digoxin has a low therapeutic index and its toxic effects are potentiated by the concomitant use of diuretics that cause hypokalemia and or hypomagnesemia.

The group member whose booklet contains Episode 3 should now take over as discussion leader.
Note to Students

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To help you review any questions that you may have missed, you probably will want to make notes on your pretest answer sheets. However, avoid “collecting pages” for “later study and understanding.” Learn the concepts now so that later you will only need to review them.

1. (D) is correct. (A) is not correct because only the specialized conducting cells (SA node, lower AV node, bundle of His, and Purkinje fibers) normally show automaticity. (B) and (C) are incorrect also because most antiarrhythmic drugs depress automaticity of Purkinje fiber cells (B), while damaged cells show enhanced automaticity (C).

3. (A) is correct. Central control of heart rate is accomplished by both parts of the autonomic nervous system, and the carotid-sinus reflex modulates the central control. Baroreceptors in the aortic arch serve the same function as those in the carotid sinus.

6. (D) is correct. Verapamil blocks the entry of calcium through the slow calcium channel (L-type). Since the slow action potentials of the AV node are mediated by this slow calcium current, verapamil can be effective in certain reentrant arrhythmias. Remember, however, that calcium entry is necessary for cardiac contraction.

When your group has finished discussing the pretest, read "Instructions for the Clinical Problem" on the next page.
Instructions for the Clinical Problem

In the remainder of this exercise, you are to use your knowledge of the pharmacology of antiarrhythmic agents to make rational choices about the treatment of arrhythmias in specific patients. Each of the four members of your group has information about one episode to present. You must work together to solve the medical problems presented.

When the episode for which you are responsible comes up, read it to the group and lead a discussion of the questions included with the episode. Pose each question to a different member of the group. Use the Discussion Notes provided as a guide for the discussion. DO NOT SIMPLY READ THE NOTES to the group. Learning is facilitated by active processes such as thinking about the questions and their possible solutions. Do not leave a question until every member of the group is completely satisfied with the answer. During the discussion, members of the group may consult textbooks, notes, and any other reference material. This is a group effort. Work together and teach one another.

The group member whose booklet contains Episode 1 should begin the discussion.
Episode 3

Mr. Lot A. Bucks, an executive at the local bank, has been admitted to the coronary care unit of the hospital after an apparent myocardial infarction (MI) on the golf course. On physical examination, his blood pressure is 130/70 mm Hg; there is no evidence of congestive heart failure. His pain, which was severe when he was admitted, has subsided since morphine was administered 50 minutes ago. Mr. Bucks' ECG, however, shows episodes of sustained ventricular tachycardia. The severity and frequency of these arrhythmias warrant immediate therapy.

Use the following questions and the Discussion Notes to guide the group discussion. Each member of the group should take the lead in answering at least one of the questions.

3.1 In terms of cellular electrophysiology, what are the two major causes of ventricular arrhythmias?

3.2 What options exist for treating Mr. Bucks' arrhythmia?

3.3 What factors should be considered in choosing a drug to manage this acute situation?

3.4 For pharmacological treatment at this time, which drugs would you consider?

3.5 What side effects should you watch for during administration of these drugs?

The Continuing Saga of Mr. Bucks

Mr. Bucks now has spent 2 weeks in the hospital and has reached his maximum level of recovery. Unfortunately, his ECG continues to show frequent ventricular extrasystoles whenever treatment is stopped. This puts him into that group of post-MI patients who are "at risk" of sudden death due to ventricular fibrillation.

3.6 Should continued antiarrhythmic drug therapy be recommended following his release from the hospital? If so, which agents should be considered?
Discussion Notes for Questions in Episode 3

3.1 a. Increased automaticity in latent pacemaker cells is a common cause of ventricular extrasystoles. Such arrhythmias can be generated by excess catecholamines, digitalis, or ischemia. All of these events increase the slope of phase 4 depolarization. Abnormal generation of impulses such as occurs with early and delayed after-potentials have been shown to initiate ectopic beats and rhythm.

b. As discussed earlier, reentrant arrhythmias result when conduction is blocked in one direction in a pathway while being conducted slowly in the opposite direction. The AV node is an area of normally slowed conduction and a common site of reentry. However, with ischemic heart disease, conduction in the myocardium can be sufficiently altered so that reentry into the Purkinje system can develop and lead to ventricular arrhythmias.

3.2 a. Arrhythmias may be precipitated or aggravated by pain, anxiety, or persistent ischemia. Removal of these complicating factors should be accomplished prior to or in conjunction with instituting antiarrhythmic drug therapy.

b. Pharmacological treatment with anti-arrhythmic agents can be administered to suppress the ventricular arrhythmias.

c. Electrical cardioversion, which depolarizes all cells simultaneously thereby interrupting aberrant rhythms, is also an option but is usually reserved for patients with life-threatening arrhythmias such as protracted ventricular tachycardia and fibrillation. Mr. Bucks may be a candidate for this procedure if medications are not effective and his condition deteriorates.

3.3 a. Efficacy
b. Ease and control of administration
c. Lack of side effects
d. Cost may also be a factor

3.4 The anti-arrhythmic medications to consider for Mr. Bucks include amiodarone, lidocaine and procainamide. In studies, amiodarone has been shown to be the most efficacious of these drugs and is the current recommended choice for treatment of sustained ventricular tachycardia (VT). Lidocaine may be considered for Mr. Bucks as it is effective in VT associated with acute myocardial infarction. Lidocaine is not effective orally because of significant first-pass hepatic metabolism; high doses can produce metabolites that can cause CNS toxicity. Both lidocaine and procainamide are considered second in line to amiodarone. Sotalol is an effective drug in suppressing ventricular tachycardia. However, some studies show increased mortality in post-MI patients and so it is not recommended in this situation. Sotalol is often used in chronic therapy to prevent ventricular arrhythmias.
3.5 The most common side effects associated with lidocaine are related to the CNS. Light-headedness occurs at therapeutic levels, and increasing doses can lead to involuntary muscle contractions and convulsions. At higher doses, cardiac abnormalities such as conduction defects, ventricular extrasystoles, and cardiac standstill may occur. Both amiodarone and procainamide are more proarrhythmic than lidocaine and can prolong the QT interval. The risk of developing torsade de pointes is less likely with amiodarone than with procainamide. This may lead to a real therapeutic dilemma. Is a resulting dysrhythmia due to the damage and the patient needs more drug, or is it due to the drug itself and hence the drug needs to be stopped? Monitoring of drug levels in blood is an option to maintain efficacy of the drug while reducing likelihood of adverse effects.

3.6 The continued presence of ventricular arrhythmias several days after myocardial infarction is associated with increased long-term mortality. CAST (The Cardiac Arrhythmia Suppression Trial) and other studies have shown that reducing ventricular premature beats with antiarrhythmic agents show little benefit or can actually increase mortality in postinfarction patients (New England J Med, 1991, 324(12):781-788, doi:10.1056/nejm199103213241201). The current recommendation is that antiarrhythmic drug therapy following myocardial infarction is generally reserved for documented life-threatening arrhythmias such as sustained ventricular tachycardia and torsade de pointes. At the present time the only class of medications with antiarrhythmic activity that has been shown to improve survival following myocardial infarction is the beta-blocking drugs. An appropriate therapeutic regimen for Mr. Bucks might, therefore, consist of a beta-blocker with a low dose of aspirin to inhibit platelet aggregation.

Amiodarone may be considered to suppress premature ventricular contractions if drug therapy beyond beta-blockers is necessary. However, it is generally not recommended because there is little mortality benefit associated with this drug in this setting but there is potential for serious adverse effects with long-term therapy. These effects include pulmonary fibrosis, photosensitivity, bluish skin, and hepatotoxicity. On the other hand, non-pharmacological therapy, Implantable Cardioverter Defibrillator (ICD), may be preferred and be of benefit in some patients at risk for life-threatening ventricular arrhythmias. These devices are used to stop an arrhythmia should one develop. Use of these devices is increasing because of the effectiveness in terminating ventricular arrhythmias.

The group member whose booklet contains Episode 4 should now take over as discussion leader.
Treatment of Cardiac Arrhythmias

2016 edition by

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Note to Students

The fundamental purposes of all activities in the health-care professions are to help other people. Like all behavior, helping behavior becomes more effective and natural with practice. This booklet enables you to practice by helping your fellow students to learn basic science. Your skill at helping your fellow students should relate to your ability to help your patients in the future.

This is a Patient-Oriented Problem-Solving (POPS) exercise designed for four students. Before beginning this session, you should have (a) studied the objectives designed to prepare you for it, (b) taken the pretest, and (c) reviewed the topics listed at the end of the pretest. Now, each of you should take one of the four color-coded parts and follow the directions in it. If your group has only three students, one of you should take two parts. If your group has more than four students, two should take turns with a part.

Please begin by discussing the answers to the pretest.
Correct Answers to Pretest Questions

In the discussion to follow, you are given the correct answers to some of the 10 pretest questions, along with explanations. Other students in your group have been given the answers to other questions. This allocation of answers and explanations is designed to encourage all members of your group to actively exchange ideas and concepts. First, study the answers in your booklet and then EXPLAIN them to your group. Please don't simply read them to your classmates, and don't let your classmates read their answers to you. In explaining something to another person, most people gain and often transmit a better understanding of the subject. The pretest discussion and patient-oriented problem-solving parts of this activity are "open book": be sure to refer to textbooks, notes, and other written resources whenever questions arise.

To help you review any questions that you may have missed, you probably will want to make notes on your pretest answer sheets. However, avoid “collecting pages” for “later study and understanding.” Learn the concepts now so that later you will only need to review them.

8. (A) is correct. By blocking beta2-adrenergic receptors in the lungs, propranolol can impede the treatment of asthma and may precipitate an attack.

10. (B) is correct. The most important toxicity associated with lidocaine administration involves the CNS. The effects are dose related and may include a feeling of dissociation, paresthesia, and agitation. At higher blood levels, muscle twitching, convulsions, and respiratory arrest can occur.

When your group has finished discussing the pretest, read "Instructions for the Clinical Problem" on the next page.
Treatment of Cardiac Arrhythmias

Instructions for the Clinical Problem

In the remainder of this exercise, you are to use your knowledge of the pharmacology of antiarrhythmic agents to make rational choices about the treatment of arrhythmias in specific patients. Each of the four members of your group has information about one episode to present. You must work together to solve the medical problems presented.

When the episode for which you are responsible comes up, read it to the group and lead a discussion of the questions included with the episode. Pose each question to a different member of the group. Use the Discussion Notes provided as a guide for the discussion. DO NOT SIMPLY READ THE NOTES to the group. Learning is facilitated by active processes such as thinking about the questions and their possible solutions. Do not leave a question until every member of the group is completely satisfied with the answer. During the discussion, members of the group may consult textbooks, notes, and any other reference material. This is a group effort. Work together and teach one another.

The group member whose booklet contains Episode 1 should begin the discussion.
**Episode 4**

Mr. Joe Cram, a second year medical student, comes to your office complaining of periods of light-headedness associated with a feeling that his heart beat is irregular. On several occasions he has had the distinct sensation that his heart has stopped momentarily. While these episodes have been occurring off and on over the past 2 months, the frequency of the attacks has increased significantly over the past 2 weeks while studying for National Board Exams. He is now extremely apprehensive and afraid that he may have significant heart disease; the potential consequences of which he is well aware of from his studies in pharmacology and pathology. On physical examination Mr. Cram has a blood pressure of 140/80 and an irregular pulse rate of approximately 90/min associated with what appears to be compensatory pauses. Auscultation reveals clear lungs and normal heart sounds. The ECG shows frequent (10 to 15/min), premature ventricular contractions (PVCs) of consistent configuration and occurrence in relation to the preceding normal beat.

**Use the following questions and the Discussion Notes to guide the group discussion. Each member of the group should take the lead in answering at least one of the questions.**

4.1 Ask your colleagues to develop a list of questions that could be asked while taking a history, which might provide some insight to the underlying etiology of Mr. Cram's arrhythmia.

Tell your colleagues that in response to the questions asked, Mr. Cram admits that he has fallen behind in studying for his board exams because he took off a week to participate in a friend's wedding. With the boards 2 days away, he is now in a state of panic and has been cramming for the past 2 weeks and as a result has only been sleeping 3 to 5 hours a day. He categorically denies taking any illicit drugs and indicates he has not had any alcohol since the wedding. He does admit to drinking 10 to 12 cups of coffee each day to keep awake and alert. He also indicates he has been taking pseudoephedrine orally to relieve nasal congestion that has developed with the onset of a cold.

4.2 What is an appropriate approach to manage Mr. Cram's arrhythmia?

Is drug therapy recommended and if so what drugs should be considered?

Mr. Cram, following your instructions, returns for his follow-up visit 2 weeks following board exams. He looks rested and tanned following a well-earned vacation at the beach. He feels good about his performance on his exam and is looking forward to finally getting started in his clinical training. He is now drinking decaffeinated coffee and has had no alcohol since his last visit. He is also taking no medication. He indicates, however, that while the number of attacks appears to have decreased, the frequency is still enough to cause him considerable discomfort and anxiety.
His physical examination is again unremarkable. The ECG does continue to show PVCs of the same configuration as before. You decide following a thorough exam that there is no evidence of significant underlying cardiac disease.

4.3 Would you now recommend drug therapy?

4.4 If so, what drugs would you consider as primary choices for treating Mr. Cram's arrhythmia?

4.5 What are the major side effects you should be concerned with?

You decide in consultation with your colleagues to put Mr. Cram on a beta-blocker. This decision is based on the beta-blocker's proven effectiveness in controlling anxiety induced PVCs and the relative lack of serious side effects associated with their use. On follow up 1 month later, Mr. Cram's rhythm is normal and he is tolerating the drug well.

Six months later you see Mr. Cram on the wards and ask how he is doing. He informs you that he is feeling well and enjoying his medical training. He admits, however, that he forgot to refill his prescription and has not taken his medication for about a month. He adds that he has not had any recurrence of his palpitations. You have him drop by for a Holter monitor; the results verify that Mr. Cram is in sinus rhythm with very infrequent PVCs.
Discussion Notes for Questions in Episode 4

4.1 a. Obviously Mr. Cram is under a great deal of stress and this alone can be a major contributor of PVCs in otherwise healthy individuals. You would want to explore this in more detail during the history. Remember that autonomic influences (both sympathetic and parasympathetic) are enhanced during periods of stress. Since these two systems work in opposition to each other on the conduction system, this can lead to incongruities in impulse initiation and conduction.

b. Is Mr. Cram taking any types of stimulants such as cocaine or amphetamines? Cocaine blocks the reuptake of the neurotransmitter norepinephrine into sympathetic nerve endings, and when injected or inhaled in sufficient quantities can produce marked cardiac stimulation and elevations in blood pressure, which can lead to the development of serious cardiac arrhythmias. Amphetamines and other similar drugs sometimes used (abused) for their CNS stimulant effects also produce marked cardiac effects.

c. How much coffee is Mr. Cram drinking each day? As you know, coffee, tea, and many soft drinks contain significant amounts of caffeine. Caffeine in addition to stimulating the central nervous system has significant cardiac stimulating properties as well as effects on other organ systems. Indeed high doses of caffeine are known to produce PVCs in otherwise healthy individuals.

d. What is Mr. Cram's current alcohol consumption? Alcohol is a peripheral vasodilator that can reflexly increase sympathetic tone. In addition, prolonged alcohol consumption can have deleterious effects on cardiac function.

e. Is Mr. Cram a cigarette smoker? As you are well aware, nicotine has marked effects on the autonomic nervous system, which may contribute to Mr. Cram's problems.

4.2 Following adequate discussion of the case, inform your colleagues that the type of arrhythmia exhibited by Mr. Cram is usually innocuous except for the anxiety that it may cause. It is quite possible that the combination of stress, fatigue, caffeine, and pseudoephedrine (a mild cardiac stimulant) may be primary contributors to Mr. Cram's problem. Remember that a first principle of therapeutics is to reserve drug therapy for those patients whose symptoms cannot be controlled by removing other etiological factors or underlying pathology. Since Mr. Cram's arrhythmia is not life threatening and there is good reason to believe that several possible contributing factors have been identified, an appropriate first step would be to have Mr. Cram:

a. remove caffeine from his diet,
b. stop taking pseudoephedrine,
c. get more rest, and
d. be re-examined after his board exam is completed and he has had time to relax.

4.3 Many clinicians would still elect not to treat this arrhythmia, but try to relieve his anxiety with stress management counseling or psychotherapy.
Treatment of Cardiac Arrhythmias

4.4 If drug therapy is elected, this type of ventricular arrhythmia often responds to beta-blockers. Sodium-channel blockers such as quinidine, procainamide, and disopyramide may also be effective but are associated with some serious adverse effects.

4.5 Side effects associated with the beta-blocker include bronchoconstriction in asthmatics, heart block and heart failure in patients with certain cardiac diseases, and lassitude. The sodium-channel blockers are associated with numerous side effects, some of which are severe. Quinidine may alter conduction resulting in potential lethal arrhythmias such as torsade de pointes, while its alpha-receptor-blocking properties may lead to hypotension. Quinidine, procainamide, and disopyramide all can cause significant gastrointestinal disturbances and anti-cholinergic effects of quinidine and disopyramide can pose problems as well. Other potential serious side effects include drug-induced lupus erythematosus (procainamide), thrombocytopenia and cinchonism (quinidine), and negative inotropism (disopyramide and quinidine). Equally serious side effects associated with the more recently introduced drugs would also tend to preclude their use in this case.

There are many drugs that are effective in suppressing cardiac arrhythmias. They are all, however, associated with significant and sometimes life-threatening side effects. Through experience, you should become knowledgeable about a few of these drugs and appropriate indications for their use. Since Mr. Cram's arrhythmia is thought to be due to anxiety-induced increased sympathetic activity and given the fact that he has been shown to be otherwise healthy, a short course of beta-blocker therapy may be most appropriate.

When you have finished discussing this episode, you have completed the clinical problem. Now, please have each group member individually answer the questions on the posttest.
Posttest

Instructions: To facilitate later discussion and review, please mark these posttest pages with your answers to the following questions. If your instructor has provided a separate answer form, mark your answers both on that form (being sure to fill in the identification section) and on these pages.

_____ 1. You have set up an experiment in which you are measuring the number of impulses arising from the carotid sinus. Following administration of digoxin, you would expect the number of impulses to
A. increase.
B. decrease.
C. remain the same.

_____ 2. Which of the following is an effect of massage of the carotid sinus?
A. occlusion of blood flow.
B. decreased activity of stretch receptors.
C. decreased sympathetic tone to the heart.
D. decreased vagal tone to the heart.
E. both (A) and (C).

In column A below, several drugs that are effective in treating reentrant supraventricular arrhythmias are listed. Match each drug with the mechanism in column B that is responsible for its therapeutic effect.

<table>
<thead>
<tr>
<th>COLUMN A</th>
<th>COLUMN B</th>
</tr>
</thead>
<tbody>
<tr>
<td>3. Propranolol</td>
<td>A. Blocks calcium-mediated action potentials</td>
</tr>
<tr>
<td>4. Verapamil</td>
<td>B. Inhibits sodium channels</td>
</tr>
<tr>
<td>5. Phenylephrine</td>
<td>C. Blocks sympathetic influences on the AV node</td>
</tr>
<tr>
<td>6. Procainamid</td>
<td>D. Increases pressure in the carotid sinus to reflexly increase vagal tone and reduce sympathetic tone</td>
</tr>
<tr>
<td></td>
<td>E. Sensitizes the carotid sinus and enhances vagal tone at the SA and AV nodes</td>
</tr>
</tbody>
</table>
Use the following information and diagrams to answer questions 7 and 8.

Depicted below are three Purkinje fibers. In each case, a stimulus can be initiated at each end (Stim 1 and Stim 2). An area of ischemia is present in the middle of each fiber. The arrows indicate the direction of conduction and whether the impulses are conducted through the ischemic zone.

7. Which one of the above fibers is most likely to show reentry?

8. Which fiber most typically shows the effects of antiarrhythmic therapy?
The graph below shows the elimination profile of lidocaine in a normal individual (A) and two additional curves (B, C). Use this data to answer questions 9 and 10.

9. In general, which of the above curves would represent a patient with congestive heart failure?

10. Given this data, how would you alter the dose of lidocaine in a patient with congestive heart failure?

A. The dose would not have to be altered.
B. The dose should be increased.
C. The dose should be decreased.

When you have finished the posttest, see the document with the correct answers or follow your instructor's directions.
Correct Answers to Posttest Questions

1. (A) is correct. Digoxin sensitizes the carotid sinus, and you would expect the number of impulses to be increased.

2. (E) is correct. Pressure on the carotid sinus does reduce flow through the carotid artery and thus should only be applied to one side. Also, while enhanced vagal activity is the most prominent response, sympathetic tone also decreases.

3. (C) is correct. Sympathetic influences acting through beta-adrenergic receptors in the AV node enhance conduction. Propranolol, a beta-adrenergic antagonist, slows conduction through the AV node.

4. (A) is correct. Conduction through the AV node is mediated primarily by slow-action potentials mediated by the influx of calcium. Verapamil blocks the calcium channel and thus slows conduction.

5. (D) is correct. Phenylephrine, an alpha-adrenergic agonist, raises blood pressure in the carotid sinus to increase vagal tone and slow conduction in the AV node.

6. (B) is correct. Procainamide primarily inhibits the voltage-gated sodium channels that regulate phase 0 of the action potential in non-nodal cardiac myocytes, resulting in a reduction of conduction velocity.

7. For reentry to occur, an area of decreased conduction (ischemic zone) with a unidirectional block is required. Therefore, (B) is correct.

8. Reentry can be interrupted either by removing the unidirectional block as in fiber A or by imposing a bidirectional block as in fiber C. Most antiarrhythmic drugs depress conduction in ischemic areas and thereby convert a unidirectional block to a bidirectional block. Answer (C) is therefore correct.

9. Patients with heart failure tend to have reduced hepatic and renal blood flow. Consequently, elimination of the drug would be prolonged. In the case of lidocaine, hepatic elimination is most important. Curve B is the correct answer.

10. Since the elimination is going to be prolonged, the dose of the drug may have to be reduced. Answer (C) is correct.