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A 55-year-old man comes to the emergency department with recurrent episodes of retrosternal chest pain. The episodes occur during physical activity, usually when he climbs stairs or walks uphill. The patient has no known medical problems and does not use tobacco, alcohol, or illicit drugs. He is given a sublingual tablet and reports rapid relief of the pain. This drug most likely improved this patient's symptoms by causing which of the following hemodynamic changes?

☐

A. Decrease in arteriolar resistance

☐

B. Decrease in heart rate

☐

C. Decrease in left ventricular end-diastolic volume

☐

D. Increase in coronary blood flow

☐

E. Increase in coronary perfusion pressure

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A 55-year-old man comes to the emergency department with recurrent episodes of retrosternal chest pain. The episodes occur during physical activity, usually when he climbs stairs or walks uphill. The patient has no known medical problems and does not use tobacco, alcohol, or illicit drugs. He is given a sublingual tablet and reports rapid relief of the pain. This drug most likely improved this patient's symptoms by causing which of the following hemodynamic changes?

- ☐ A. Decrease in arteriolar resistance [17%]
- ☐ B. Decrease in heart rate [1%]
- ☒ C. Decrease in left ventricular end-diastolic volume [48%]
- ☐ D. Increase in coronary blood flow [29%]
- ☐ E. Increase in coronary perfusion pressure [2%]

Omitted

Correct answer
C



48%
Answered correctly



30 Seconds
Time Spent



09/21/2018
Last Updated

Explanation

Mechanisms of action of antianginal therapy

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Mechanisms of action of antianginal therapy

↑ Coronary vasodilation

- Nondihydropyridines
- Dihydropyridines
- Nitrates (mild)

↓ Heart rate

- Beta blockers
- Nondihydropyridines
 - Verapamil
 - Diltiazem

Venodilation (↓ preload)

- Nitrates

Arterial dilation (↓ afterload)

- Dihydropyridines
 - Amlodipine
 - Nifedipine

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This patient has a classic presentation of **chronic stable angina**, which is characterized by chest pain that occurs with activity and is relieved with rest or sublingual nitroglycerin. **Nitrates** exert their effect by direct vascular smooth muscle relaxation that results in:

- Vasodilation of the peripheral veins and arteries, predominantly **venodilation**
- Decreased left ventricular wall stress due to **reduced preload** (decreased left ventricular end-diastolic volume and pressure)
- Modest reduction in afterload due to systemic arterial vasodilation
- Mild coronary artery dilation and reduction of coronary vasospasm

This results in **decreased myocardial oxygen demand**, leading to improved exercise tolerance and relief of angina symptoms.

(Choices A and D) Nitrates dilate the large epicardial arteries more than the smaller resistance vessels (eg, arterioles). Furthermore, coronary arterioles in an area of flow-limited stenosis are typically dilated maximally to maintain resting blood flow, limiting the ability of nitrates to significantly increase blood flow in stenotic coronary arteries.

(Choice B) Nitrates do not directly affect cardiac chronotropy and/or inotropy but can increase the heart rate as a reflex response to reduced blood pressure. Beta blockers and nondihydropyridine calcium channel blockers may exert their antianginal effect in part via a decrease in the heart rate (negative chronotropic effect).

(Choice E) Coronary perfusion pressure is the pressure gradient that drives coronary perfusion during diastole and is equal to the difference between the end-diastolic aortic pressure and the left ventricular end-diastolic pressure. Nitrates may slightly reduce coronary perfusion pressure as they lower systemic arterial pressure; however, the overall hemodynamic effects of nitrates are beneficial during angina as they lead to decreased myocardial oxygen demand.

Educational objective:

Sublingual nitroglycerin is used for rapid symptom relief in patients with stable angina. The primary anti-ischemic effect of nitrates is mediated by venodilation with a decrease in left ventricular end-diastolic volume and wall stress, resulting in decreased myocardial oxygen demand and relief of angina symptoms.

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A 53-year-old man comes to the emergency department with shortness of breath and chest tightness. The patient was playing in a poker tournament when his symptoms first began. He has a history of hypertension and is not compliant with his medications. His last medical follow-up was a year ago. Blood pressure is 195/115 mm Hg and pulse is 90/min and regular. Lung examination reveals bibasilar crackles. Nitroglycerin infusion is started and results in significant symptomatic improvement. Repeat blood pressure is 165/90 mm Hg. Which of the following intracellular events is most likely responsible for the beneficial effects of this patient's treatment?

- ☐ A. Actin phosphorylation
- ☐ B. Calcium release from sarcoplasmic reticulum
- ☐ C. Enhanced cyclic mononucleotide degradation
- ☐ D. Inositol triphosphate accumulation
- ☐ E. Myosin dephosphorylation
- ☐ F. Tyrosine kinase activation

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A 53-year-old man comes to the emergency department with shortness of breath and chest tightness. The patient was playing in a poker tournament when his symptoms first began. He has a history of hypertension and is not compliant with his medications. His last medical follow-up was a year ago. Blood pressure is 195/115 mm Hg and pulse is 90/min and regular. Lung examination reveals bibasilar crackles. Nitroglycerin infusion is started and results in significant symptomatic improvement. Repeat blood pressure is 165/90 mm Hg. Which of the following intracellular events is most likely responsible for the beneficial effects of this patient's treatment?

☐

A. Actin phosphorylation [3%]

☐

B. Calcium release from sarcoplasmic reticulum [8%]

☐

C. Enhanced cyclic mononucleotide degradation [22%]

☐

D. Inositol triphosphate accumulation [11%]

☒

E. Myosin dephosphorylation [49%]

☐

F. Tyrosine kinase activation [4%]

Omitted

Correct answer
E

49%

Answered correctly

5 Seconds

Time Spent

12/28/2018

Last Updated

Explanation

This patient's clinical presentation is consistent with acute pulmonary edema due to severely elevated blood pressure (**hypertensive emergency**). In such cases, intravenous vasodilators (nitroglycerine, sodium nitroprusside) are often used to improve the acute heart failure by

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This patient's clinical presentation is consistent with acute pulmonary edema due to severely elevated blood pressure (**hypertensive emergency**). In such cases, intravenous vasodilators (nitroglycerine, sodium nitroprusside) are often used to improve the acute heart failure by reducing preload and afterload.

Nitrates are metabolized within vascular smooth muscle cells to nitric oxide, which activates guanylate cyclase and promotes the conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (**cGMP**). Increased levels of cGMP lead to **decreased intracellular calcium** (reduces the activity of myosin light-chain kinase) and activation of myosin light chain phosphatase. This promotes **myosin light-chain dephosphorylation** and vascular smooth muscle **relaxation**.

(Choice A) Actin phosphorylation has no role in smooth or skeletal muscle relaxation. In smooth muscle, a stimulus to contract leads to increased intracellular calcium, which leads to myosin phosphorylation. Once myosin is phosphorylated, it is able to bind directly to actin and cause muscle contraction.

(Choice B) Calcium release from sarcoplasmic reticulum would lead to increased contraction of the cardiac myocytes. It is not involved in the mechanism of action of nitrates on vascular smooth muscle cells.

(Choice C) Nitrates do not cause an increase in cyclic mononucleotide degradation. On the contrary, they activate guanylate cyclase and promote conversion of GTP to cGMP, which ultimately leads to smooth muscle relaxation.

(Choice D) Inositol triphosphate binds to its receptor on the endoplasmic reticulum and leads to the release of Ca^{2+} into the cytoplasm. In vascular smooth muscle cells, this increased concentration of cytoplasmic Ca^{2+} results in increased smooth muscle contraction.

(Choice F) Tyrosine kinases play a role in a wide variety of intracellular processes and pathways. The effects of insulin and insulin-like growth factor occur via activation of receptor tyrosine kinases, which in turn cause phosphorylation of tyrosine residues on intracellular proteins important for signal transduction.

Educational objective:

Nitrates (via conversion to nitric oxide) activate guanylate cyclase and increase intracellular levels of cyclic guanosine monophosphate (cGMP). Increased levels of cGMP lead to myosin light-chain dephosphorylation, resulting in vascular smooth muscle relaxation.

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(reduces the activity of myosin light-chain kinase) and activation of myosin light chain phosphatase. This promotes **myosin light-chain dephosphorylation** and vascular smooth muscle **relaxation**.

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Nitrates (via conversion to nitric oxide) activate guanylate cyclase and increase intracellular levels of cyclic guanosine monophosphate (cGMP). Increased levels of cGMP lead to myosin light-chain dephosphorylation, resulting in vascular smooth muscle relaxation.

References

- Identification of the enzymatic mechanism of nitroglycerin bioactivation.

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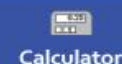


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Item 3 of 40

Question Id: 142



A 60-year-old Caucasian male is diagnosed with exertional angina. His treatment regimen includes metoprolol, isosorbide dinitrate and aspirin. He takes isosorbide dinitrate early in the morning and again in the afternoon, but he does not take an evening dose. Such a pattern of drug administration is intended to decrease which of the following?

- ☐ A. Pharmacokinetic drug interaction
- ☐ B. Pharmacodynamic drug antagonism
- ☐ C. Effect potentiation
- ☐ D. Tolerance development
- ☐ E. Withdrawal symptoms
- ☐ F. Drug noncompliance

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A 60-year-old Caucasian male is diagnosed with exertional angina. His treatment regimen includes metoprolol, isosorbide dinitrate and aspirin. He takes isosorbide dinitrate early in the morning and again in the afternoon, but he does not take an evening dose. Such a pattern of drug administration is intended to decrease which of the following?

☐

A. Pharmacokinetic drug interaction [4%]

☐

B. Pharmacodynamic drug antagonism [3%]

☐

C. Effect potentiation [18%]

☒

D. Tolerance development [65%]

☐

E. Withdrawal symptoms [3%]

☐

F. Drug noncompliance [4%]

Omitted

Correct answer
D

65%

Answered correctly

4 Seconds

Time Spent

12/22/2018

Last Updated

Explanation

Around-the-clock nitrate administration (in any form) rapidly results in development of tolerance to nitrates. This is why a nitrate-free interval must be provided every day in patients that are using daily long acting nitrates. The mechanism by which this occurs has not been fully demonstrated, but it is theorized that it is due to a decreased vascular sensitivity to nitrates and an increased sensitivity to endogenous vasoconstricting agents. Usually the nitrate-free period is timed to occur during the night when the patient is sleeping and cardiac work is the least.

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(Choice A) A pharmacokinetic drug interaction refers to how drugs that are used together in a patient affect the absorption and elimination of each other. An example of this is the ability of rifampin to increase the metabolism and elimination of warfarin by inducing cytochrome P-450. This is not the reason for providing a nitrate-free interval.

(Choice B) Pharmacodynamic drug antagonism refers to the ability of a drug, as part of its mechanism of action, to antagonize, or prevent, the effect of another drug or endogenous substance. An example of this is the effect that labetalol has on alpha-1 and beta adrenergic receptors – it prevents the binding of catecholamines to these receptors.

(Choice C) Effect potentiation refers to one drug's ability to increase the pharmacologic effect of another agent. The drugs mentioned in this question stem do not potentiate the effects of each other, and this is not the reason for providing a nitrate-free period. Beta-adrenergic blockers are often prescribed along with nitrates to prevent reflex tachycardia as well as to provide decreased cardiac work by a mechanism different from that of nitrates.

(Choice E) Withdrawal symptoms occur when a patient forms a physiologic dependence on a drug or medication and that drug or medication is then discontinued. This is common in patients using alcohol, opiates, benzodiazepines, stimulants and some antidepressants. This is not the reason for providing a nitrate-free period in patients taking nitrates.

(Choice F) Drug noncompliance is a problem where patients do not take the medications prescribed to them properly or at all. It is frequent among patients who do not understand their disease, can not afford medications, or simply can not remember to take them. The latter becomes much more frequent when patients are taking multiple medications with many times-per-day dosing schedules. This is also not the reason for providing a nitrate-free period every day in patients taking long-term nitrates.

Educational Objective:

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but it is theorized that it is due to a decreased vascular sensitivity to nitrates and an increased sensitivity to endogenous vasoconstricting agents.

Usually the nitrate-free period is timed to occur during the night when the patient is sleeping and cardiac work is the least.

(Choice A) A pharmacokinetic drug interaction refers to how drugs that are used together in a patient affect the absorption and elimination of each other. An example of this is the ability of rifampin to increase the metabolism and elimination of warfarin by inducing cytochrome P-450. This is not the reason for providing a nitrate-free interval.

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Educational Objective:

Patients taking daily maintenance nitrates need to have a nitrate-free period every day to avoid tolerance to the drug.

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Question Id: 901



A new antiarrhythmic medication (drug A) is tested in a series of experiments that measure the flow of ions responsible for producing an action potential in cardiac muscle cells. Ion flow is measured before and after the drug is administered, and the results are shown in the chart below (each colored line represents a different type of ion).

Drug A has an antiarrhythmic effect most similar to which of the following drugs?

- ☐ A. Adenosine
- ☐ B. Digoxin
- ☐ C. Dofetilide
- ☐ D. Esmolol
- ☐ E. Flecainide
- ☐ F. Lidocaine
- ☐ G. Quinidine
- ☐ H. Verapamil

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Exhibit Display

Recorded action potential

Into cell

Ion flow before drug A

Out of cell

Into cell

Ion flow after drug A

Out of cell

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Zoom In

Zoom Out

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Item 4 of 40

Question Id: 901



A new antiarrhythmic medication (drug A) is tested in a series of experiments that measure the flow of ions responsible for producing an action potential in cardiac muscle cells. Ion flow is measured before and after the drug is administered, and the results are shown in the chart below (each colored line represents a different type of ion).

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- ☐ D. Esmolol
- ☐ E. Flecainide
- ☐ F. Lidocaine
- ☐ G. Quinidine
- ☐ H. Verapamil

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A new antiarrhythmic medication (drug A) is tested in a series of experiments that measure the flow of ions responsible for producing an action potential in cardiac muscle cells. Ion flow is measured before and after the drug is administered, and the results are shown in the chart below (each colored line represents a different type of ion).

Drug A has an antiarrhythmic effect most similar to which of the following drugs?

☐

A. Adenosine [8%]

☐

B. Digoxin [5%]

☒

C. Dofetilide [59%]

☐

D. Esmolol [4%]

☐

E. Flecainide [5%]

☐

F. Lidocaine [3%]

☐

G. Quinidine [7%]

☐

H. Verapamil [5%]

Omitted

Correct answer
C

59%

Answered correctly

4 Seconds

Time Spent

10/30/2018

Last Updated

Explanation

Block Time Remaining: 00:00:52

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Cardiac action potentials

Pacemaker action potential

Non-pacemaker action potential

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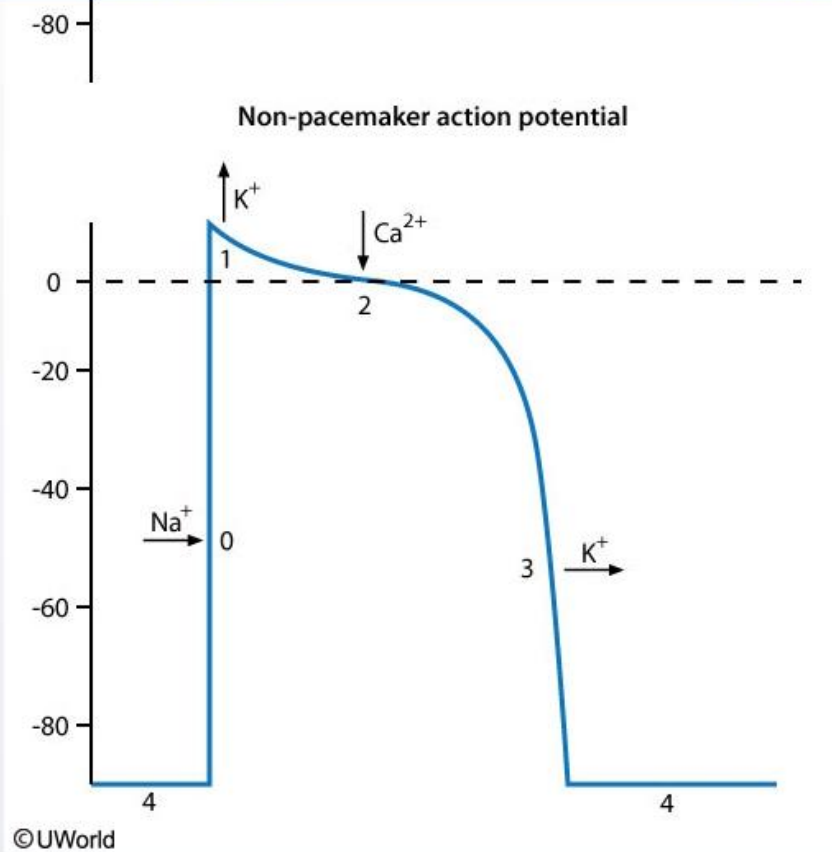
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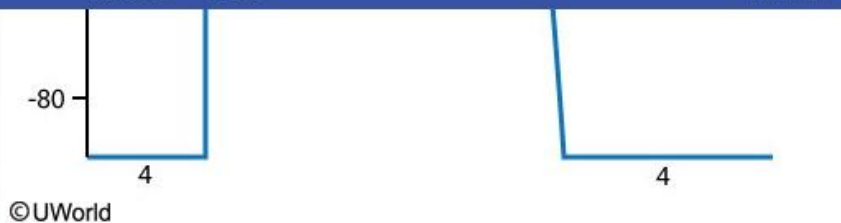
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The recorded action potential shows the typical profile of **non-pacemaker** cardiac cells, which includes the following phases:

- Phase 0 (rapid depolarization)** – occurs when the resting membrane potential reaches threshold; is characterized by rapid sodium entry into the cell due to activation and opening of voltage-dependent sodium channels.



The recorded action potential shows the typical profile of **non-pacemaker** cardiac cells, which includes the following phases:

- Phase 0 (rapid depolarization)** – occurs when the resting membrane potential reaches threshold; is characterized by rapid sodium entry into the cell due to activation and opening of voltage-dependent sodium channels.
- Phase 1 (early repolarization)** – caused primarily by activation of transient outward potassium currents along with a rapid decline in inward sodium current.
- Phase 2 (plateau phase)** – stable membrane potential due to a balance of late inward calcium current (L-type channels) and outward potassium current.
- Phase 3 (late repolarization)** – characterized by the opening of additional potassium channels (delayed-rectifier potassium currents) and continued efflux of potassium ions from the cell; this is in conjunction with the decay of inward calcium current.
- Phase 4 (resting)** – normal resting membrane potential is between -80 mV and -95 mV, and it is generated by outward potassium flow through potassium leak channels open at rest. The $\text{Na}^+\text{-K}^+\text{-ATPase}$ pump allows the potassium and sodium gradients to be maintained across the membrane.

The ion flow graph after drug A administration shows a **decrease in outward potassium flow** from the myocyte during phase 3 repolarization of the myocardial action potential. Class III **antiarrhythmic drugs** (eg, amiodarone, sotalol, **dofetilide**) predominantly block potassium channels and inhibit the outward potassium currents during phase 3 of the cardiac action potential, thereby prolonging repolarization and total action potential duration.

(Choice A) Adenosine stimulates A1 receptors on the surface of cardiac cells, activating potassium channels and increasing potassium conductance, which causes the membrane potential to remain negative for a longer period. This results in transient slowing of the sinus rate and increased atrioventricular (AV) nodal conduction delay.

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the myocardial action potential. Class III **antiarrhythmic drugs** (eg, amiodarone, sotalol, **dofetilide**) predominantly block potassium channels and inhibit the outward potassium currents during phase 3 of the cardiac action potential, thereby prolonging repolarization and total action potential duration.

(Choice A) Adenosine stimulates A1 receptors on the surface of cardiac cells, activating potassium channels and increasing potassium conductance, which causes the membrane potential to remain negative for a longer period. This results in transient slowing of the sinus rate and increased atrioventricular (AV) nodal conduction delay.

(Choice B) Digoxin inhibits the Na⁺-K⁺-ATPase pump in myocardial cells, resulting in an increase in intracellular sodium, which leads in turn to a rise in intracellular calcium concentration. Digoxin does not affect potassium channels and has minimal effect on potassium efflux from myocardial cells during the action potential.

(Choice D) Esmolol is a rapid-acting, short-duration beta blocker (class II antiarrhythmic) that slows the rate of discharge of sinus or ectopic pacemakers and increases the refractory period of the AV node. It has no effect on potassium efflux from myocardial cells.

(Choices E, F, and G) Class IA (procainamide, quinidine), IB (lidocaine), and IC (flecainide) antiarrhythmic drugs inhibit sodium-dependent (phase 0) depolarization and slow conduction. Class IA and IC agents also have some potassium-blocking activity and can cause prolongation of the action potential (seen mostly with class IA agents). However, all class I drugs have prominent sodium channel-blocking activity, which would blunt the blue tracing in the above graph.

(Choice H) Calcium channel blockers (eg, verapamil, diltiazem) inhibit the L-type calcium channels during phase 2 of the myocardial action potential and phase 0 of the pacemaker action potential. They slow the sinus rate, prolong conduction through the AV node, and depress myocardial contractility.

Educational objective:

Class III antiarrhythmic drugs (eg, amiodarone, sotalol, dofetilide) predominantly block potassium channels and inhibit the outward potassium currents during phase 3 of the cardiac action potential, thereby prolonging repolarization and total action potential duration.

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Exhibit Display

Antiarrhythmic drugs – Vaughan Williams classification		
Class	Drugs	Predominant actions
IA	Sodium channel blockers - Disopyramide - Procainamide - Quinidine	- Slows AP conduction velocity - Prolongs APD
	IB - Lidocaine - Mexiletine - Phenytoin	- No effect on AP conduction velocity - Shortens APD
	IC - Flecainide - Propafenone	- Slows AP conduction velocity - Minimal effect on APD
II	Beta receptor blockers - Atenolol - Metoprolol - Esmolol - Carvedilol	- Slows sinus node discharge rate - Slows AV nodal conduction & prolongs refractoriness
III	Potassium channel blockers - Amiodarone - Dronedarone - Dofetilide - Sotalol (also class II)	- No effect on AP conduction velocity - Prolongs APD
IV	Non-dihydropyridine calcium channel blockers - Verapamil - Diltiazem	- Slows sinus node discharge rate - Slows AV nodal conduction & prolongs refractoriness

AP = action potential, APD = action potential duration, AV = atrioventricular.

Zoom In

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rise in intracellular calcium concentration. Digoxin does not affect potassium channels and has minimal effect on potassium efflux from myocardial

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Question Id: 145



A 62-year-old man comes to the office for follow-up of hypertension. He was diagnosed with hypertension 10 years ago and has been treated with a number of different medications. However, the patient has had to discontinue several medications due to side effects such as dizziness, palpitations, and headaches. Currently he takes ramipril and chlorthalidone and is tolerating them well. Blood pressure is 160/92 mm Hg and was 158/89 mm Hg at his most recent prior visit. ECG shows sinus bradycardia (55/min) with PR interval prolongation (280 msec). Which of the following medications would be most effective for lowering this patient's blood pressure without worsening his ECG abnormalities?

- ☐ A. Diltiazem
- ☐ B. Metoprolol
- ☐ C. Nifedipine
- ☐ D. Sotalol
- ☐ E. Verapamil

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A 62-year-old man comes to the office for follow-up of hypertension. He was diagnosed with hypertension 10 years ago and has been treated with a number of different medications. However, the patient has had to discontinue several medications due to side effects such as dizziness, palpitations, and headaches. Currently he takes ramipril and chlorthalidone and is tolerating them well. Blood pressure is 160/92 mm Hg and was 158/89 mm Hg at his most recent prior visit. ECG shows sinus bradycardia (55/min) with PR interval prolongation (280 msec). Which of the following medications would be most effective for lowering this patient's blood pressure without worsening his ECG abnormalities?

☐

A. Diltiazem [5%]

☐

B. Metoprolol [9%]

☒

C. Nifedipine [71%]

☐

D. Sotalol [7%]

☐

E. Verapamil [6%]

Omitted

Correct answer
C

71%

Answered correctly

3 Seconds

Time Spent

08/22/2018

Last Updated

Explanation

Calcium channel blockers are frequently used in the treatment of several cardiovascular disorders, including hypertension, angina pectoris, and certain cardiac arrhythmias. They inhibit the L-type calcium channel on vascular smooth muscle and cardiac cells and are divided into 2 major categories based on their predominant actions:

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Explanation

Calcium channel blockers are frequently used in the treatment of several cardiovascular disorders, including hypertension, angina pectoris, and certain cardiac arrhythmias. They inhibit the L-type calcium channel on vascular smooth muscle and cardiac cells and are divided into 2 major categories based on their predominant actions:

1. **Dihydropyridines** (nifedipine, amlodipine, felodipine) primarily affect **arterial smooth muscle**, causing vasodilation with little or no effect on cardiac conduction or contractility.
2. **Nondihydropyridines** (verapamil, diltiazem) affect the **myocardium**, slowing heart rate (negative chronotropic effect) and reducing contractility (negative inotropic effect).

This patient's ECG shows sinus bradycardia (rate <60/min) with first-degree atrioventricular (AV) block (PR interval >200 msec). Of the choices above, nifedipine is the most appropriate agent to manage hypertension as it has minimal effect on cardiac conduction. Dihydropyridines can cause reflex tachycardia in response to peripheral vasodilation and are therefore useful in hypertensive patients with resting bradycardia.

(Choices A and E) Verapamil is a nondihydropyridine calcium channel blocker with a significant depressive effect on cardiac conduction. Diltiazem has combined effects and acts at both the myocardium and peripheral arterial beds. These medications can worsen bradycardia and AV block and should not be used in patients with underlying conduction abnormalities.

(Choices B and D) Metoprolol is a cardioselective beta blocker with negative chronotropic and dromotropic (decreased AV conduction) effects. Sotalol is a class III antiarrhythmic drug with significant beta-blocking properties. These drugs can worsen bradycardia and AV conduction defects and would not be recommended for this patient.

Educational objective:

Calcium channel blockers inhibit the L-type calcium channel on vascular smooth muscle and cardiac cells. Dihydropyridines (eg, nifedipine, amlodipine) primarily affect peripheral arteries and cause vasodilation. Nondihydropyridines (eg, verapamil, diltiazem) affect the myocardium and can cause bradycardia and slowed atrioventricular conduction.

References

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A 53-year-old man comes to the physician for a follow-up visit after an acute myocardial infarction. His medications include metoprolol and low-dose aspirin. He used to smoke 2 packs of cigarettes daily but quit after his myocardial infarction. The patient's father has hypertension and his mother has type 2 diabetes mellitus. He currently weighs 100 kg (220 lb) and is 178 cm (70 in) tall. Examination shows an obese male with no other abnormalities. His total serum cholesterol level is 155 mg/dL, with an HDL level of 27 mg/dL and a triglyceride level of 92 mg/dL. Which of the following lipid-lowering agents would be most effective for preventing future cardiovascular events in this patient?

☐

A. Absorption inhibitor

☐

B. Cationic exchange resin

☐

C. Enzyme inhibitor

☐

D. Essential fatty acids

☐

E. Pharmacologic vitamin

☐

F. Transcription factor ligand

Submit

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A 53-year-old man comes to the physician for a follow-up visit after an acute myocardial infarction. His medications include metoprolol and low-dose aspirin. He used to smoke 2 packs of cigarettes daily but quit after his myocardial infarction. The patient's father has hypertension and his mother has type 2 diabetes mellitus. He currently weighs 100 kg (220 lb) and is 178 cm (70 in) tall. Examination shows an obese male with no other abnormalities. His total serum cholesterol level is 155 mg/dL, with an HDL level of 27 mg/dL and a triglyceride level of 92 mg/dL. Which of the following lipid-lowering agents would be most effective for preventing future cardiovascular events in this patient?

☐ A. Absorption inhibitor [4%]

☐ B. Cationic exchange resin [2%]

☒ C. Enzyme inhibitor [55%]

☐ D. Essential fatty acids [5%]

☐ E. Pharmacologic vitamin [28%]

☐ F. Transcription factor ligand [4%]

Omitted

Correct answer C

55%

Answered correctly

2 Seconds

Time Spent

01/18/2019

Last Updated

Explanation

Patients with **low high-density lipoprotein (HDL) levels** (men <40 mg/dL, women <50 mg/dL) are at **increased risk for cardiovascular disease**. HDL is involved in reverse cholesterol transport; it helps to remove cholesterol from peripheral tissues and transports it to the liver for

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Explanation

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Patients with **low high-density lipoprotein (HDL) levels** (men <40 mg/dL, women <50 mg/dL) are at **increased risk for cardiovascular disease**. HDL is involved in reverse cholesterol transport; it helps to remove cholesterol from peripheral tissues and transports it to the liver for metabolism. This is accomplished through 2 different pathways. In the direct pathway, HDL delivers cholesterol esters directly to the liver via a scavenger receptor (SCARB1) on the hepatocyte cell membrane. In the indirect pathway, the cholesterol in HDL is transferred to low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) by the cholesteryl ester transfer protein.

Nonpharmacologic measures such as exercise, weight loss, and smoking cessation help to raise HDL levels and have significant cardiovascular benefits. In contrast, use of medications to raise HDL levels does **not** improve cardiovascular outcomes. Pharmacologic treatment of patients with low HDL levels should focus on lowering LDL cholesterol with **HMG-CoA reductase inhibitors** (statins), as these are the most effective lipid-lowering drugs for preventing cardiovascular events. Statins are indicated for secondary prevention in all patients with known atherosclerotic cardiovascular disease, **regardless** of baseline lipid levels.

(Choice A) Ezetimibe inhibits cholesterol absorption from the gastrointestinal tract, but evidence for reduction in cardiovascular events is mixed, and benefits over statin monotherapy are likely minimal. It may be considered for patients who cannot take statins due to significant hepatotoxicity or myopathy, or who have very high LDL levels despite statin therapy.

(Choice B) Cationic exchange resins (eg, cholestyramine) decrease LDL cholesterol by interfering with the enterohepatic circulation of bile acids. Bile acid binding resins can significantly increase triglyceride levels in patients with pre-existing hypertriglyceridemia. In addition, cationic exchange resins have not been proven to prevent cardiac events.

(Choice D) Omega-3 essential fatty acids are sometimes used for hyperlipidemia treatment. They cause a decrease in serum triglycerides and a slight increase in HDL concentration but do not appear to significantly reduce cardiovascular events.

(Choice E) Niacin (vitamin B₃) given in pharmacologic doses is the most effective agent for raising HDL levels, but does not reduce the risk of cardiovascular events and is associated with adverse effects (eg, flushing, hyperglycemia). It is primarily used for patients who have failed other lipid-lowering drugs.

(Choice F) Fibrates activate peroxisomal proliferator-activated receptor alpha, a transcription factor that increases lipoprotein lipase activity.

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with low HDL levels should focus on lowering LDL cholesterol with **HMG-CoA reductase inhibitors** (statins), as these are the most effective lipid-lowering drugs for preventing cardiovascular events. Statins are indicated for secondary prevention in all patients with known atherosclerotic cardiovascular disease, **regardless** of baseline lipid levels.

(Choice A)

Ezetimibe inhibits cholesterol absorption from the gastrointestinal tract, but evidence for reduction in cardiovascular events is mixed, and benefits over statin monotherapy are likely minimal. It may be considered for patients who cannot take statins due to significant hepatotoxicity or myopathy, or who have very high LDL levels despite statin therapy.

(Choice B)

Cationic exchange resins (eg, cholestyramine) decrease LDL cholesterol by interfering with the enterohepatic circulation of bile acids. Bile acid binding resins can significantly increase triglyceride levels in patients with pre-existing hypertriglyceridemia. In addition, cationic exchange resins have not been proven to prevent cardiac events.

(Choice D)

Omega-3 essential fatty acids are sometimes used for hyperlipidemia treatment. They cause a decrease in serum triglycerides and a slight increase in HDL concentration but do not appear to significantly reduce cardiovascular events.

(Choice E)

Niacin (vitamin B₃) given in pharmacologic doses is the most effective agent for raising HDL levels, but does not reduce the risk of cardiovascular events and is associated with adverse effects (eg, flushing, hyperglycemia). It is primarily used for patients who have failed other lipid-lowering drugs.

(Choice F)

Fibrates activate peroxisomal proliferator-activated receptor alpha, a transcription factor that increases lipoprotein lipase activity. Fibrates decrease triglyceride levels and raise HDL levels. However, fibrates are inferior to statins for reducing cardiovascular events and are primarily used to prevent pancreatitis in patients with very high triglyceride levels.

Educational objective:

Although low HDL concentration is associated with increased cardiovascular risk, the use of medications to raise HDL levels does not improve cardiovascular outcomes. HMG-CoA reductase inhibitors (statins) lower total cholesterol and LDL levels. Statins are the most effective lipid-lowering drugs for primary and secondary prevention of cardiovascular events, regardless of baseline lipid levels.

References

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Question Id: 1364



An experiment is conducted to assess the effects of drug A on the hemodynamic actions of epinephrine. Two groups of healthy volunteers are selected. The first group receives only low-dose epinephrine, and its effects on diastolic blood pressure and heart rate are monitored and shown below (epinephrine group). The second group is pretreated with drug A and then infused with low-dose epinephrine to produce a new set of curves (epinephrine + drug A group).

Which of the following medications is most likely to be drug A?

- ☐ A. Atropine
- ☐ B. Isoproterenol
- ☐ C. Phentolamine
- ☐ D. Phenylephrine
- ☐ E. Propranolol

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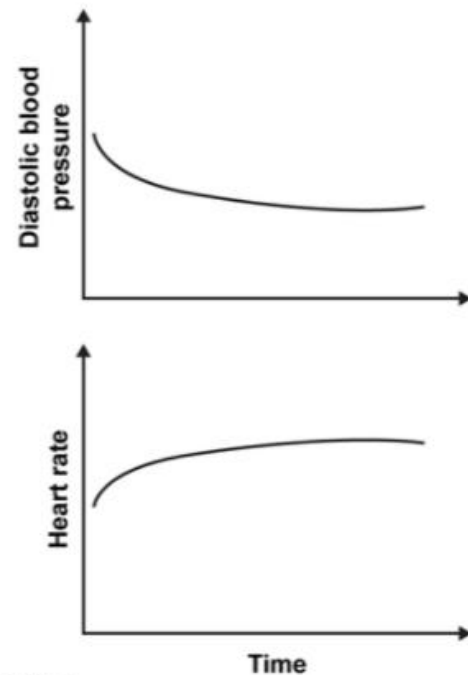
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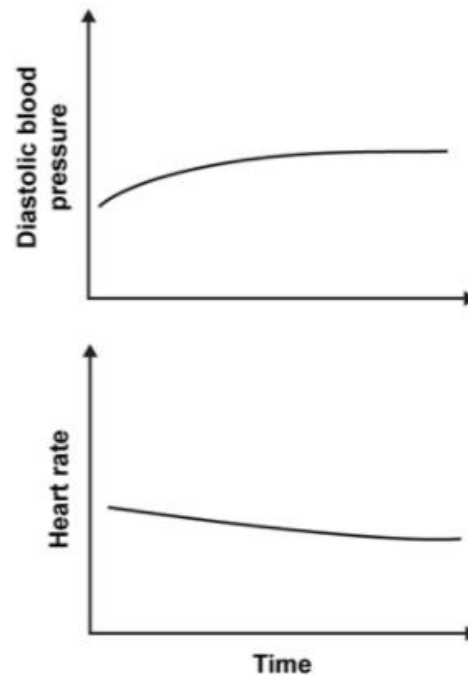
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Epinephrine group



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Epinephrine + Drug A group



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Question Id: 1364



An experiment is conducted to assess the effects of drug A on the hemodynamic actions of epinephrine. Two groups of healthy volunteers are selected. The first group receives only low-dose epinephrine, and its effects on diastolic blood pressure and heart rate are monitored and shown below (epinephrine group). The second group is pretreated with drug A and then infused with low-dose epinephrine to produce a new set of curves (epinephrine + drug A group).

Which of the following medications is most likely to be drug A?

- ☐ A. Atropine
- ☐ B. Isoproterenol
- ☐ C. Phentolamine
- ☐ D. Phenylephrine
- ☐ E. Propranolol

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An experiment is conducted to assess the effects of drug A on the hemodynamic actions of epinephrine. Two groups of healthy volunteers are selected. The first group receives only low-dose epinephrine, and its effects on diastolic blood pressure and heart rate are monitored and shown below (epinephrine group). The second group is pretreated with drug A and then infused with low-dose epinephrine to produce a new set of curves (epinephrine + drug A group).

Which of the following medications is most likely to be drug A?

☐

A. Atropine [3%]

☐

B. Isoproterenol [15%]

☐

C. Phentolamine [11%]

☐

D. Phenylephrine [14%]

☒

E. Propranolol [55%]

Omitted

Correct answer
E

55%

Answered correctly

3 Seconds

Time Spent

12/11/2018

Last Updated

Explanation

Hemodynamic actions of epinephrine		
	Effect	Involved receptors

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2/7/2019

Explanation

Hemodynamic actions of epinephrine		
	Effect	Involved receptors
Heart rate & contractility	↑	β_1
Systolic blood pressure	↑↑	$\beta_1 + \alpha_1$
Diastolic blood pressure	↓ (low-dose)	$\beta_2 > \alpha_1$
	↑ (high-dose)	$\alpha_1 > \beta_2$

The hemodynamic actions of **epinephrine** occur secondary to agonistic effects at α_1 , β_1 , and β_2 adrenoreceptors (relative strength: $\beta_1 = \beta_2 > \alpha_1$). Stimulation of β_1 receptors in the heart increases cardiac rate and contractility, which increases systolic blood pressure due to the rise in cardiac output. Stimulation of β_2 receptors in the skeletal muscle vasculature produces vasodilation and decreased diastolic blood pressure, while activation of α_1 receptors on vascular smooth muscle in the skin and viscera increases peripheral resistance and raises diastolic blood pressure. At **low doses**, β_2 -mediated **vasodilation predominates**, whereas at high doses α_1 -induced vasoconstriction becomes more pronounced.

In this experiment, low-dose epinephrine by itself caused **increased heart rate** (β_1 response) and **decreased diastolic blood pressure** (β_2 response). However, after pretreatment with drug A, the heart rate *fails* to increase and there is a marked *rise* in diastolic blood pressure. These effects are best explained by pretreatment with a **nonselective beta antagonist** such as propranolol. When administered alone, propranolol produces peripheral vasoconstriction (β_2 antagonism) without significantly increasing blood pressure (due to concomitant β_1 blockade). However, in combination with epinephrine, propranolol will counteract epinephrine's β_2 -mediated vasodilation and β_1 -mediated heart rate increase while leaving the α_1 effect (vasoconstriction) intact. This will increase diastolic blood pressure and cause a slight reflexive reduction in heart rate.

(Choice A) Atropine is a competitive antagonist of cholinergic muscarinic receptors in the heart (M_2). Atropine increases the heart rate by

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In this experiment, low-dose epinephrine by itself caused **increased heart rate** (β_1 response) and **decreased diastolic blood pressure** (β_2 response). However, after pretreatment with drug A, the heart rate *fails* to increase and there is a marked *rise* in diastolic blood pressure. These effects are best explained by pretreatment with a **nonselective beta antagonist** such as propranolol. When administered alone, propranolol produces peripheral vasoconstriction (β_2 antagonism) without significantly increasing blood pressure (due to concomitant β_1 blockade). However, in combination with epinephrine, propranolol will counteract epinephrine's β_2 -mediated vasodilation and β_1 -mediated heart rate increase while leaving the α_1 effect (vasoconstriction) intact. This will increase diastolic blood pressure and cause a slight reflexive reduction in heart rate.

(Choice A) Atropine is a competitive antagonist of cholinergic muscarinic receptors in the heart (M_2). Atropine increases the heart rate by blocking parasympathetic vagal influence; after pretreatment with atropine, epinephrine-mediated tachycardia would increase.

(Choice B) Isoproterenol is a nonselective β -adrenergic agonist that stimulates both β_2 receptors on vascular smooth muscle (leading to vasodilatation) and cardiac β_1 receptors (leading to increases in cardiac rate and contractility). A combination of isoproterenol and epinephrine would further decrease diastolic blood pressure and exacerbate the tachycardia.

(Choice C) Phentolamine is a nonspecific α_1 and α_2 blocker with no beta-blocking effects that cause a profound fall in diastolic blood pressure and reflex tachycardia. If this were drug A, blood pressure would have decreased further in the pretreatment group and the rise in heart rate would have been exacerbated.

(Choice D) Phenylephrine is a selective α -adrenergic agonist. Administration by itself may cause elevated systolic and diastolic blood pressures, which may be associated with reflex bradycardia. However, after pretreatment, epinephrine would still produce an *initial rise* in heart rate due to unopposed β_1 stimulation.

Educational objective:

Epinephrine increases systolic blood pressure ($\alpha_1 + \beta_1$) and heart rate (β_1), and either increases or decreases diastolic blood pressure depending on the dose (either α_1 or β_2 predominates). Pretreatment with propranolol eliminates the β effects of epinephrine (vasodilatation and tachycardia), leaving only the α effect (vasoconstriction).

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A 68-year-old man comes to the office due to several weeks of progressive exertional dyspnea and lower extremity edema. Medical history is significant for non-Hodgkin lymphoma, which is in remission after chemotherapy 8 years ago. Blood pressure is 126/76 mm Hg and pulse is 88/min. Auscultation reveals bibasilar lung crackles and 1+ bilateral lower extremity edema. Echocardiogram shows biventricular dilation and a left ventricular ejection fraction of 35%. Stress myocardial perfusion scan is negative for inducible ischemia. After initial stabilization, long-term use of which of the following medications will most likely improve survival in this patient?

☐ A. Amiodarone

☐ B. Amlodipine

☐ C. Carvedilol

☐ D. Digoxin

☐ E. Diltiazem

☐ F. Flecainide

☐ G. Furosemide

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Text Zoom

A 68-year-old man comes to the office due to several weeks of progressive exertional dyspnea and lower extremity edema. Medical history is significant for non-Hodgkin lymphoma, which is in remission after chemotherapy 8 years ago. Blood pressure is 126/76 mm Hg and pulse is 88/min. Auscultation reveals bibasilar lung crackles and 1+ bilateral lower extremity edema. Echocardiogram shows biventricular dilation and a left ventricular ejection fraction of 35%. Stress myocardial perfusion scan is negative for inducible ischemia. After initial stabilization, long-term use of which of the following medications will most likely improve survival in this patient?

☐

A. Amiodarone [2%]

☐

B. Amlodipine [4%]

☒

C. Carvedilol [53%]

☐

D. Digoxin [19%]

☐

E. Diltiazem [3%]

☐

F. Flecainide [0%]

☐

G. Furosemide [16%]

Omitted

Correct answer
C

53%

Answered correctly

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09/23/2018

Last Updated

Explanation

This patient's clinical presentation is consistent with **decompensated systolic heart failure** (HF) due to nonischemic cardiomyopathy, likely as a

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Explanation

This patient's clinical presentation is consistent with **decompensated systolic heart failure** (HF) due to nonischemic cardiomyopathy, likely as a result of chemotherapy for non-Hodgkin lymphoma. **After initial stabilization**, long-term use of **beta blockers** (eg, carvedilol, metoprolol) has been shown to improve survival in patients with HF due to left ventricular systolic dysfunction.

Beta blockade decreases myocardial work and oxygen demand by slowing the ventricular rate and reducing contractility. It also lowers peripheral resistance (afterload) by decreasing circulating levels of vasoconstricting hormones (eg, renin, endothelin). These effects are cardioprotective and help reduce cardiomyocyte death and limit deleterious cardiac remodeling. Beta blockers should not be initiated in patients with unstable (decompensated) HF, as they can further impair cardiac output; they should be introduced slowly after the patient has been stabilized.

Other drugs that improve long-term survival in patients with systolic HF include **ACE inhibitors**, **angiotensin II receptor blockers**, and **aldosterone antagonists** (eg, spironolactone, eplerenone).

(Choice A) Amiodarone is a class III antiarrhythmic agent used for management of supraventricular and ventricular arrhythmias.

(Choices B and E) Calcium channel blockers (eg, amlodipine, diltiazem) do not provide any benefit or improve survival in patients with HF due to left ventricular systolic dysfunction.

(Choice D) Digoxin is used as an adjunctive therapy in patients with HF due to systolic dysfunction. It improves symptoms and reduces the rate of hospitalization, but has not been shown to improve overall survival.

(Choice F) Flecainide is a class IC antiarrhythmic drug that is occasionally used for management of supraventricular arrhythmias in patients with a structurally normal heart. It has no role in the management of patients with HF.

(Choice G) Diuretics (eg, furosemide) are used as first-line agents for rapid symptom control in patients with acute congestive HF. They have not been shown to improve long-term survival.

Educational objective:

Drugs that have been shown to improve long-term survival in patients with heart failure due to left ventricular systolic dysfunction include beta

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(Choice G) Diuretics (eg, furosemide) are used as first-line agents for rapid symptom control in patients with acute congestive HF. They have not been shown to improve long-term survival.

Educational objective:

Drugs that have been shown to improve long-term survival in patients with heart failure due to left ventricular systolic dysfunction include beta blockers, ACE inhibitors, angiotensin II receptor blockers, and aldosterone antagonists.

References

- 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines.

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A 45-year-old man is brought to a rural emergency department due to severe chest pain, sweating, and nausea. The symptoms began suddenly an hour ago. He has no significant medical history. His father died at age 50 after experiencing sudden-onset chest pain. The patient smokes a pack of cigarettes daily. He does not take any medications and has no known drug allergies. Examination shows normal heart sounds and breath sounds. ECG shows sinus tachycardia with ST segment elevation in leads II, III, and aVF. Medical management for the patient's acute condition is initiated. After initial treatment, the chest pain decreases in intensity and a reperfusion complex ventricular arrhythmia emerges. The arrhythmia is asymptomatic and resolves spontaneously. Which of the following drugs is most likely responsible for rapid reperfusion in this patient?

☐ A. Alteplase

☐ B. Apixaban

☐ C. Argatroban

☐ D. Aspirin

☐ E. Heparin

☐ F. Prasugrel

☐ G. Rosuvastatin

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A 45-year-old man is brought to a rural emergency department due to severe chest pain, sweating, and nausea. The symptoms began suddenly an hour ago. He has no significant medical history. His father died at age 50 after experiencing sudden-onset chest pain. The patient smokes a pack of cigarettes daily. He does not take any medications and has no known drug allergies. Examination shows normal heart sounds and breath sounds. ECG shows sinus tachycardia with ST segment elevation in leads II, III, and aVF. Medical management for the patient's acute condition is initiated. After initial treatment, the chest pain decreases in intensity and a reperfusion complex ventricular arrhythmia emerges. The arrhythmia is asymptomatic and resolves spontaneously. Which of the following drugs is most likely responsible for rapid reperfusion in this patient?

✓

☒ A. Alteplase [71%]

☐ B. Apixaban [1%]

☐ C. Argatroban [2%]

☐ D. Aspirin [9%]

☐ E. Heparin [11%]

☐ F. Prasugrel [2%]

☐ G. Rosuvastatin [0%]

Omitted

Correct answer

A

71%

Answered correctly

2 Seconds

Time Spent

08/21/2018

Last Updated

Explanation

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Explanation

This patient had an **ST-elevation myocardial infarction** (STEMI) and, following medical treatment, experienced symptomatic improvement and reperfusion-related arrhythmia; this is most likely the result of **fibrinolytic (thrombolytic) therapy**. Fibrinolytic agents (eg, **alteplase**) are indicated in patients with acute STEMI who cannot receive percutaneous coronary intervention in a timely manner. Administration of these agents leads to breakdown of fibrin clot and often restoration of myocardial perfusion; some patients develop a self-limiting reperfusion-related arrhythmia (most commonly an accelerated idioventricular rhythm).

In the **fibrinolytic pathway**, tissue plasminogen activator (tPA) is released by the endothelium and cleaves plasminogen to form plasmin. Plasmin then acts to both degrade individual fibrinogen molecules and break down fibrin clot that has already formed. The breakdown of fibrin clot leads to elevated levels of fibrin split products (eg, d-dimer) in the blood.

Pharmacologic fibrinolytic agents that are used clinically include streptokinase and recombinant forms of tPA (eg, alteplase, tenecteplase). All of these agents inherently increase bleeding risk and are contraindicated in patients with increased risk of bleeding complications (eg, recent hemorrhagic stroke).

(Choices B and C) Apixaban is a direct factor Xa inhibitor used in the treatment and prevention of venous thromboembolism, and argatroban is a direct thrombin inhibitor used to treat heparin-induced thrombocytopenia. Both of these drugs are anticoagulants; neither causes fibrinolysis or is typically used in the treatment of STEMI.

(Choices D and F) Aspirin inhibits cyclooxygenase to reduce thromboxane levels, and P2Y12 receptor blockers (eg, clopidogrel, prasugrel) prevent the binding of adenosine diphosphate to platelets; both actions lead to irreversible **inhibition of platelet aggregation**. These drugs are used together in acute STEMI to prevent the development of additional platelet thrombus; however, they do not cause lysis of existing thrombus.

(Choice E) Heparin potentiates the activity of antithrombin III to inhibit thrombin and factor Xa and exert an anticoagulation effect. Heparin is used in acute STEMI to prevent further progression of clot formation, but it does not cause thrombolysis.

(Choice G) Statins (eg, rosuvastatin) are used for acute STEMI as they may stabilize atherosclerotic plaques, reduce vascular inflammation, and promote long-term regression of atherosclerosis. However, they do not cause thrombolysis.

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Pharmacologic fibrinolytic agents that are used clinically include streptokinase and recombinant forms of tPA (eg, alteplase, tenecteplase). All of these agents inherently increase bleeding risk and are contraindicated in patients with increased risk of bleeding complications (eg, recent hemorrhagic stroke).

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(Choice G) Statins (eg, rosuvastatin) are used for acute STEMI as they may stabilize atherosclerotic plaques, reduce vascular inflammation, and promote long-term regression of atherosclerosis. However, they do not cause thrombolysis.

Educational objective:

In the fibrinolytic pathway, tissue plasminogen activator (tPA) converts plasminogen to plasmin, which then breaks down fibrin clot. The administration of a tPA analogue (eg, alteplase, tenecteplase, streptokinase) triggers fibrinolysis and can restore myocardial perfusion in patients with ST-elevation myocardial infarction who cannot undergo timely percutaneous coronary intervention.

References

- 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines.

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A 60-year-old man comes to the hospital with chest pain. He has had intermittent, squeezing substernal pain over the last 3 days that is now sustained. The patient has no associated palpitations, lightheadedness, or shortness of breath. Medical history is notable for moderate chronic obstructive pulmonary disease with a recent admission for an exacerbation. Blood pressure is 145/90 mm Hg and pulse is 93/min. Oxygen saturation by pulse oximetry is 98% on room air. Physical examination shows no heart murmurs, and lungs are clear to auscultation. ECG shows sinus rhythm with 2-mm anterior ST segment elevation. Cardiac troponin I levels are elevated. Which of the following is the most appropriate treatment for this patient?

☐ A. Ibutilide

☐ B. Metoprolol

☐ C. Nadolol

☐ D. Propranolol

☐ E. Sotalol

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☐

A. Ibutilide [8%]

☒

B. Metoprolol [68%]

☐

C. Nadolol [3%]

☐

D. Propranolol [11%]

☐

E. Sotalol [7%]

Omitted

Correct answer
B

68%

Answered correctly

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01/09/2019

Last Updated

Explanation

Effects of adrenergic blockade			
Receptor	Target organ	Effect	Potential adverse effects

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Effects of adrenergic blockade			
Receptor	Target organ	Effect	Potential adverse effects
B1-adrenergic blockade	Heart	↓ Heart rate ↓ Contractility ↓ O ₂ consumption	Worsening of heart failure Bradycardia/heart block
	Kidney	↓ Renin release	
B2-adrenergic blockade	Muscle vasculature	Vasospasm	Exacerbation of peripheral artery disease
	Lungs	Bronchoconstriction	Worsening of obstructive lung disease
	Liver	↓ Glycogenolysis & gluconeogenesis	May cause hypoglycemia in diabetic patients
	Most tissues	↓ Potassium entry into cells	Hyperkalemia

This patient's clinical presentation—chest discomfort, ST elevation on ECG, elevated troponin I level—is consistent with **acute myocardial infarction** (AMI). Beta blockers are used in AMI to reduce myocardial oxygen demand by lowering heart rate, cardiac contractility, and afterload. They have been shown to reduce short-term morbidity (eg, recurrent symptoms or reinfarction), minimize infarct size, and improve long-term survival.

Contraindications to beta blockers include bradycardia or heart block, hypotension, and overt heart failure (eg, pulmonary edema). Also, **non-cardioselective beta blockers** (eg, propranolol, nadolol) can **trigger bronchospasm** in patients with underlying obstructive lung disease (asthma, **chronic obstructive pulmonary disease** [COPD]) due to beta-2 receptor blockade and should be avoided (**Choices C and D**).

Cardioselective beta blockers with predominant action on beta-1 receptors (eg, **metoprolol**, atenolol, bisoprolol, nebivolol) are **safe** in patients with stable obstructive lung disease and are the beta blocker of choice in these patients. Combined beta and alpha receptor blockers (eg,

This patient's clinical presentation—chest discomfort, ST elevation on ECG, elevated troponin I level—is consistent with **acute myocardial infarction** (AMI). Beta blockers are used in AMI to reduce myocardial oxygen demand by lowering heart rate, cardiac contractility, and afterload. They have been shown to reduce short-term morbidity (eg, recurrent symptoms or reinfarction), minimize infarct size, and improve long-term survival.

Cardioselective beta blockers with predominant action on beta-1 receptors (eg, **metoprolol**, atenolol, bisoprolol, nebivolol) are **safe** in patients with stable obstructive lung disease and are the beta blocker of choice in these patients. Combined beta and alpha receptor blockers (eg, carvedilol, labetalol) are also well tolerated and have been used safely in patients with COPD.

(Choice E) Sotalol is a class III antiarrhythmic drug with beta blocker properties and is primarily used for the treatment of atrial and ventricular arrhythmias. It would not be indicated in a patient with a recent myocardial infarction who is in sinus rhythm.

Beta blockers are used in acute myocardial infarction to reduce morbidity and mortality by decreasing cardiac output and myocardial oxygen demand. Non-cardioselective beta blockers (eg, propranolol, nadolol) can trigger bronchospasm in patients with underlying asthma or chronic obstructive pulmonary disease. Cardioselective beta blockers (eg, metoprolol) predominantly affect beta-1 receptors and are preferred in such patients.

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A 24-year-old man comes to the emergency department due to the sudden onset of palpitations. The patient says it feels like "my heart is racing." He had an episode similar to this a year ago that resolved spontaneously. Blood pressure is 126/74 mm Hg and pulse is 164/min. Rapid intravenous administration of a medication to this patient results in instantaneous resolution of the arrhythmia but is accompanied by short-lived flushing, burning in the chest, and shortness of breath. Which of the following medications was used to treat this patient's condition?

☐ A. Adenosine

☐ B. Amiodarone

☐ C. Digoxin

☐ D. Ibutilide

☐ E. Lidocaine

☐ F. Verapamil

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✓

☒ A. Adenosine [75%]

☐ B. Amiodarone [6%]

☐ C. Digoxin [4%]

☐ D. Ibutilide [1%]

☐ E. Lidocaine [6%]

☐ F. Verapamil [5%]

Omitted

Correct answer
A

75%

Answered correctly

3 Seconds

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02/02/2019

Last Updated

Explanation

Pharmacotherapy for supraventricular arrhythmias	
Medication	Short-term adverse effects

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Pharmacotherapy for supraventricular arrhythmias	
Medication	Short-term adverse effects
Flecainide/propafenone (class IC)	Ventricular arrhythmias*
Metoprolol (class II)	Bradycardia & advanced AV block
Amiodarone (class III)	- Bradycardia - Hepatic toxicity, thyroid dysfunction
Ibutilide/dofetilide/sotalol (class III)	Torsades de pointes
Verapamil/diltiazem (class IV)	- Bradycardia & advanced AV block - Decreased ventricular contractility - Constipation (verapamil)
Adenosine	- Flushing & hypotension - Bronchospasm - High-grade AV block
Digoxin	- Bradycardia & other arrhythmias - Nausea & vomiting ± visual disturbances

AV = atrioventricular.

*Especially with ischemic or structural heart disease.

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	High-grade AV block
Digoxin	- Bradycardia & other arrhythmias - Nausea & vomiting ± visual disturbances

AV = atrioventricular.

*Especially with ischemic or structural heart disease.

This patient is exhibiting symptoms consistent with **paroxysmal supraventricular tachycardia (PSVT)**. As the name implies, PSVT comes on suddenly and the focus of automaticity lies above the ventricles (ie, atria or atrioventricular node). When due to development of a **reentrant circuit**, the tachyarrhythmia may be terminated by the administration of **adenosine**.

Adenosine is a coronary arteriole vasodilator, but it also affects cardiac conduction. As an anti-arrhythmic, it acts by hyperpolarizing the nodal pacemaker and conducting cells to briefly **block conduction through the atrioventricular node**. Its effects are rapid-onset and short-lived (half-life <10 seconds); by temporarily blocking signal conduction from the atria to the ventricles, administration of the drug will often terminate the reentrant circuit and lead to conversion of PSVT to normal sinus rhythm.

The most frequent **adverse effects** associated with adenosine are flushing, chest burning (due to bronchospasm), hypotension, and high-grade atrioventricular block.

(Choice B) Amiodarone (class III anti-arrhythmic) is one of the broadest-spectrum anti-arrhythmic drugs available, and can be used to treat both supraventricular (eg, PSVT, atrial fibrillation) and ventricular arrhythmias. It has a wide range of adverse effects, including photodermatitis, blue/gray skin discoloration, pulmonary fibrosis, liver toxicity, and hyper- or hypothyroidism.

(Choice C) Digoxin slows conduction through the atrioventricular node and is useful in treating supraventricular tachycardia, especially atrial fibrillation. It causes a well-characterized toxicity in overdose; symptoms include fatigue, yellow-tinted vision, nausea/vomiting, diarrhea, and confusion.

(Choice D) Ibutilide (class III anti-arrhythmic) is used in the treatment of atrial fibrillation and flutter. Its principal adverse effect is QTc prolongation leading to torsades de pointes.

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atrioventricular block.

(Choice B) Amiodarone (class III anti-arrhythmic) is one of the broadest-spectrum anti-arrhythmic drugs available, and can be used to treat both supraventricular (eg, PSVT, atrial fibrillation) and ventricular arrhythmias. It has a wide range of adverse effects, including photodermatitis, blue/gray skin discoloration, pulmonary fibrosis, liver toxicity, and hyper- or hypothyroidism.

(Choice C) Digoxin slows conduction through the atrioventricular node and is useful in treating supraventricular tachycardia, especially atrial fibrillation. It causes a well-characterized toxicity in overdose; symptoms include fatigue, yellow-tinted vision, nausea/vomiting, diarrhea, and confusion.

(Choice D) Ibutilide (class III anti-arrhythmic) is used in the treatment of atrial fibrillation and flutter. Its principal adverse effect is QTc prolongation leading to torsades de pointes.

(Choice E) Lidocaine (class IB anti-arrhythmic) is sometimes used for ventricular arrhythmias but has little utility for supraventricular arrhythmias. Lidocaine toxicity most commonly causes neurologic symptoms or arrhythmias.

(Choice F) Verapamil (class IV anti-arrhythmic) is the most cardioselective of the calcium channel blockers, and is often used in the treatment of supraventricular tachycardia. Common adverse reactions noted with verapamil are bradycardia and constipation. Because verapamil decreases cardiac contractility, it can also exacerbate systolic heart failure.

Educational objective:

Adenosine causes hyperpolarization of the nodal pacemaker to briefly block conduction through the atrioventricular node, and it is effective in the initial treatment of paroxysmal supraventricular tachycardia. Common adverse effects include flushing, chest burning (due to bronchospasm), hypotension, and high-grade atrioventricular block.

References

- Diagnosis and management of common types of supraventricular tachycardia.

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A 77-year-old man comes to the office after he was found to have high blood pressure during a health fair. The patient denies any medical problems and feels proud that he has not needed to see a doctor for many years. His blood pressure is 170/70 mm Hg and pulse is 74/min. Other physical examination findings are normal. The patient is started on a medication to treat his hypertension. During his follow-up visit 3 weeks later, he reports bilateral leg swelling. He has no chest pain, shortness of breath, or abdominal symptoms. His blood pressure is 135/65 mm Hg and pulse is 80/min. Cardiopulmonary examination is normal, but there is bilateral, symmetrical, 2+ pitting lower extremity edema. Laboratory studies show serum creatinine of 0.8 mg/dL, and urinalysis is negative for proteinuria. Which of the following was most likely prescribed to treat this patient's hypertension?

☐

A. Amlodipine

☐

B. Eplerenone

☐

C. Hydrochlorothiazide

☐

D. Ramipril

☐

E. Torsemide

☐

F. Valsartan

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✓

☒

A. Amlodipine [46%]

☐

B. Eplerenone [4%]

☐

C. Hydrochlorothiazide [15%]

☐

D. Ramipril [22%]

☐

E. Torsemide [6%]

☐

F. Valsartan [5%]

Omitted

Correct answer
A

46%

Answered correctly

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Time Spent

01/21/2019

Last Updated

Explanation

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A

Explanation

Dihydropyridine calcium channel blockers (eg, amlodipine, nifedipine) are effective antihypertensive agents commonly used as monotherapy or in combination with other agents for treatment of hypertension. The major side effects associated with use of calcium channel blockers include headache, flushing, dizziness, and **peripheral edema**. Development of peripheral edema is related to preferential dilation of precapillary vessels (arteriolar dilation), which leads to increased capillary hydrostatic pressure and fluid extravasation into the interstitium. Renin-angiotensin system blockers (eg, ACE inhibitors or angiotensin II receptor blockers [ARBs]) cause postcapillary venodilation and can normalize the increased capillary hydrostatic pressure, reducing the risk of peripheral edema in patients taking calcium channel blockers.

(Choice B) Eplerenone is an aldosterone antagonist and functions similarly to spironolactone as a potassium-sparing diuretic. The most frequent side effects of eplerenone are hyperkalemia, increased creatinine, and gynecomastia (~1% versus 10% with spironolactone).

(Choices C and E) The most common side effects of thiazide (eg, hydrochlorothiazide) and loop diuretics (eg, furosemide) are electrolyte abnormalities such as hypokalemia, hyponatremia, and hypomagnesemia. They do not cause peripheral edema.

(Choices D and F) The potential side effects of ACE inhibitors (eg, ramipril) and ARBs (eg, valsartan) include cough, hypotension, hyperkalemia, and angioedema. The risk of cough and angioedema is much lower with ARBs. These medications do not cause peripheral edema.

Educational objective:

Amlodipine is a dihydropyridine calcium channel blocker commonly used as monotherapy or in combination with other agents for treatment of hypertension. Major side effects include headache, flushing, dizziness, and peripheral edema.

References

- Vasodilatory edema: a common side effect of antihypertensive therapy.

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Physiologists conduct a series of experiments on hypophysectomized animals to investigate the effects of cortisol on vascular reactivity. Their initial tests show that administration of cortisol alone does not elicit a vascular response. Next, the researchers measure vascular reactivity to an infusion of norepinephrine both with and without pretreatment with cortisol. The results of their experiments are shown in the graph below.

Which of the following pharmacologic principles best describes the response to cortisol in this experiment?

☐ A. Additive effect

☐ B. Altered metabolism

☐ C. Permissiveness

☐ D. Synergistic effect

☐ E. Tachyphylaxis

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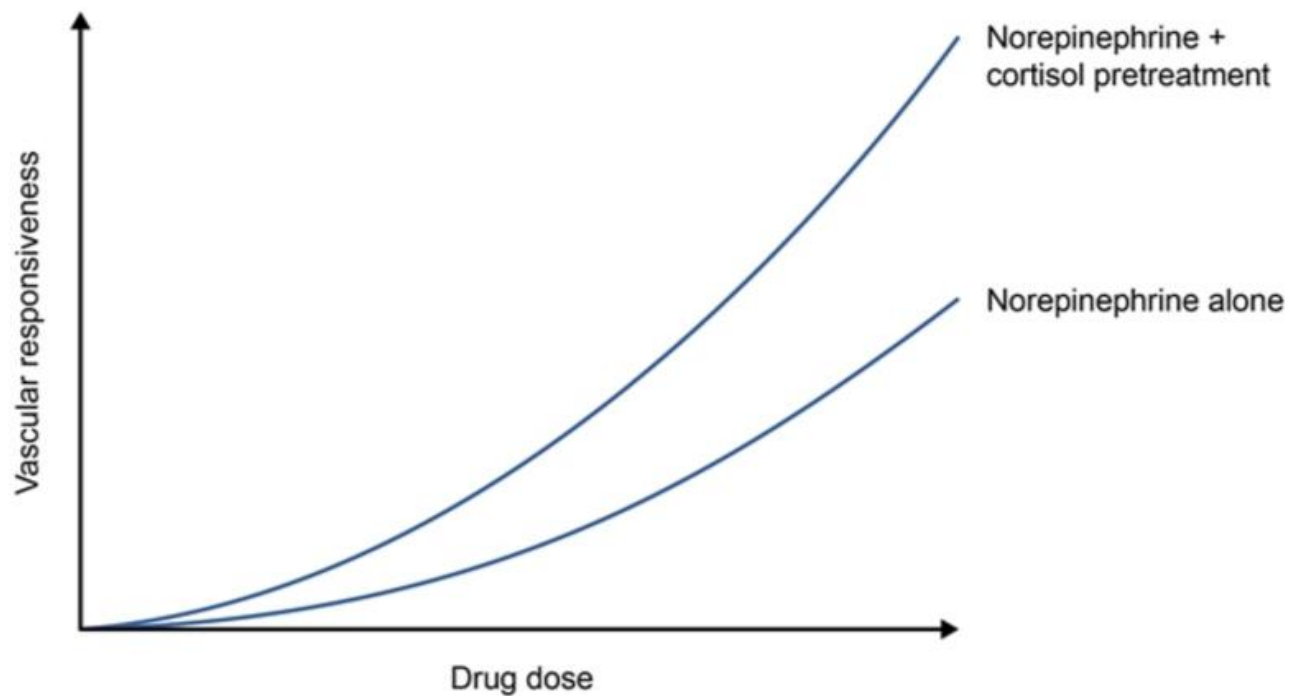


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Exhibit Display



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☐ A. Additive effect [16%]

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Which of the following pharmacologic principles best describes the response to cortisol in this experiment?

☐ A. Additive effect

☐ B. Altered metabolism

☐ C. Permissiveness

☐ D. Synergistic effect

☐ E. Tachyphylaxis

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Physiologists conduct a series of experiments on hypophysectomized animals to investigate the effects of cortisol on vascular reactivity. Their initial tests show that administration of cortisol alone does not elicit a vascular response. Next, the researchers measure vascular reactivity to an infusion of norepinephrine both with and without pretreatment with cortisol. The results of their experiments are shown in the graph below.

Which of the following pharmacologic principles best describes the response to cortisol in this experiment?

☐ A. Additive effect [16%]

☐ B. Altered metabolism [2%]

☒ C. Permissiveness [36%]

☐ D. Synergistic effect [44%]

☐ E. Tachyphylaxis [0%]

Omitted

Correct answer
C

36%

Answered correctly

3 Seconds

Time Spent

11/14/2018

Last Updated

Explanation

Although cortisol has no direct vasoactive properties, it augments the vasoconstrictive effects of catecholamines and angiotensin II. The above graph shows that administration of norepinephrine produced a limited degree of vasoconstriction that was markedly increased following pretreatment with cortisol. This effect is termed **permissiveness** and occurs when one hormone allows another to exert its maximal effect. Cortisol exerts its potentiating effect in part through upregulation of alpha-1 adrenergic receptors on vascular smooth muscle cells. In adrenal

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Although cortisol has no direct vasoactive properties, it augments the vasoconstrictive effects of catecholamines and angiotensin II. The above graph shows that administration of norepinephrine produced a limited degree of vasoconstriction that was markedly increased following pretreatment with cortisol. This effect is termed **permissiveness** and occurs when one hormone allows another to exert its maximal effect. Cortisol exerts its potentiating effect in part through upregulation of alpha-1 adrenergic receptors on vascular smooth muscle cells. In adrenal insufficiency, low glucocorticoid levels can contribute to hypotensive crisis by decreasing vascular responsiveness to angiotensin II and norepinephrine.

(Choices A and D) The combination of 2 drugs with similar actions can have a **synergistic or additive** effect. When the combined effect of 2 drugs is equal to the sum of their individual effects, it is termed an additive response. When the combined effect exceeds the sum of the individual drug effects, the interaction is called synergistic. In this case, cortisol's influence on vascular responsiveness is best described as permissive rather than synergistic as cortisol has no intrinsic vasoconstrictive effects.

(Choice B) Alterations in metabolism can change a drug's pharmacokinetic and pharmacodynamic properties. For example, certain drugs (eg, amiodarone, fluconazole) can inhibit the P450 cytochrome oxidase system, decreasing the metabolism of other drugs metabolized through this pathway, which can lead to additive or synergistic responses.

(Choice E) Tachyphylaxis describes decreased drug responsiveness in a short period following one or more doses (ie, rapidly developing tolerance). Drug response over time is not shown in the graph and cannot be assessed.

Educational objective:

Cortisol exerts a permissive effect on many hormones to help improve the response to a variety of stressors. For example, cortisol increases vascular and bronchial smooth muscle reactivity to catecholamines and increases glucose release by the liver in response to glucagon.

References

- Glucocorticoids and vascular reactivity.

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A 64-year-old man comes to the office due to exertional chest pain over the last 6 months. He is a lifelong 1 pack per day cigarette smoker and has a history of type 2 diabetes mellitus and peripheral artery disease. The patient undergoes treadmill exercise stress testing and develops substernal chest pain on moderate exertion accompanied by ECG changes that resolve immediately upon rest. He refuses invasive cardiac testing. The patient is started on low-dose aspirin therapy for secondary prevention of cardiovascular disease but experiences shortness of breath and wheezing with the medication. Which of the following is the best alternate therapy for this patient?

☐ A. Apixaban

☐ B. Cilostazol

☐ C. Clopidogrel

☐ D. Enoxaparin

☐ E. Eptifibatide

☐ F. Naproxen

☐ G. Warfarin

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A 64-year-old man comes to the office due to exertional chest pain over the last 6 months. He is a lifelong 1 pack per day cigarette smoker and has a history of type 2 diabetes mellitus and peripheral artery disease. The patient undergoes treadmill exercise stress testing and develops substernal chest pain on moderate exertion accompanied by ECG changes that resolve immediately upon rest. He refuses invasive cardiac testing. The patient is started on low-dose aspirin therapy for secondary prevention of cardiovascular disease but experiences shortness of breath and wheezing with the medication. Which of the following is the best alternate therapy for this patient?

☐ A. Apixaban [2%]

☐ B. Cilostazol [6%]

☒ C. Clopidogrel [70%]

☐ D. Enoxaparin [5%]

☐ E. Eptifibatide [1%]

☐ F. Naproxen [5%]

☐ G. Warfarin [7%]

Omitted

Correct answer
C

70%

Answered correctly

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Last Updated

Explanation

This patient's clinical history is consistent with stable angina (**angina pectoris**) due to underlying coronary heart disease (CHD). Patients with

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This patient's clinical history is consistent with stable angina (**angina pectoris**) due to underlying coronary heart disease (CHD). Patients with stable angina should be started on aspirin to decrease the risk of adverse cardiovascular events. Aspirin impairs prostaglandin synthesis by irreversibly inhibiting cyclooxygenase (COX). Inhibition of COX-1 in platelets prevents synthesis of thromboxane A₂, a potent stimulator of platelet aggregation and vasoconstriction. This helps reduce the risk of occlusive thrombus formation and subsequent myocardial infarction.

Some patients are unable to tolerate aspirin due to exacerbation of preexisting respiratory symptoms (eg, rhinitis, asthma) or development of allergic reactions (eg, urticaria, angioedema, anaphylaxis). In these patients, alternate antiplatelet agents should be used for prevention of cardiovascular events. **Clopidogrel** irreversibly **blocks** the P2Y₁₂ component of **ADP receptors** on the platelet surface and prevents platelet aggregation. Clopidogrel is as **effective as aspirin** for **prevention of cardiovascular events** and should be used in patients with aspirin allergy.

(Choices A and G) Apixaban is a direct factor Xa inhibitor that prevents platelet activation and fibrin clot formation. Warfarin inhibits an enzyme required for synthesis of active vitamin K, resulting in decreased synthesis of vitamin K-dependent clotting factors (II, VII, IX, and X). Both apixaban and warfarin are typically used for prevention and/or treatment of thromboembolic events, not coronary artery disease.

(Choice B) Cilostazol is a phosphodiesterase inhibitor that is occasionally used in patients with symptomatic peripheral vascular disease (ie, claudication).

(Choice D) Low molecular weight heparins (LMWHs; enoxaparin, dalteparin) are indirect thrombin inhibitors that bind with antithrombin and convert it from a slow to a rapid inactivator of thrombin and factor Xa. They are used in patients with acute coronary syndrome (unstable angina or myocardial infarction) but have no role in the management of patients with stable angina.

(Choice E) Eptifibatide is a platelet glycoprotein IIb/IIIa inhibitor that inhibits the final common pathway of platelet aggregation. Eptifibatide is occasionally used in some patients with acute coronary syndrome, but it is not used for patients with stable CHD.

(Choice F) Naproxen is a nonsteroidal anti-inflammatory drug (NSAID) that is used for pain management in patients with osteoarthritis. Use of both nonselective and selective COX-2 NSAIDs increases the risk of adverse cardiovascular events.

Educational objective:

Clopidogrel irreversibly blocks the P2Y₁₂ component of ADP receptors on the platelet surface and prevents platelet aggregation. Clopidogrel is as

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cardiovascular events. **Clopidogrel** irreversibly **blocks** the P2Y₁₂ component of **ADP receptors** on the platelet surface and prevents platelet aggregation. Clopidogrel is as **effective as aspirin** for **prevention of cardiovascular events** and should be used in patients with aspirin allergy.

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(Choice E) Eptifibatide is a platelet glycoprotein IIb/IIIa inhibitor that inhibits the final common pathway of platelet aggregation. Eptifibatide is occasionally used in some patients with acute coronary syndrome, but it is not used for patients with stable CHD.

(Choice F) Naproxen is a nonsteroidal anti-inflammatory drug (NSAID) that is used for pain management in patients with osteoarthritis. Use of both nonselective and selective COX-2 NSAIDs increases the risk of adverse cardiovascular events.

Educational objective:

Clopidogrel irreversibly blocks the P2Y₁₂ component of ADP receptors on the platelet surface and prevents platelet aggregation. Clopidogrel is as effective as aspirin in the prevention of cardiovascular events in patients with coronary heart disease.

References

- Collaborative meta-analysis of randomized trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high-risk patients.

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A 36-year-old man comes to the office after he was found to have an abnormal lipid panel during employee wellness testing at his company. He has no prior medical problems and takes no medications. The patient is a software technician and has a sedentary lifestyle. He eats mostly fast foods, rarely exercises, and drinks 2-3 cans of beer daily. His BMI is 31 kg/m². Physical examination is unremarkable. Results of laboratory studies performed in the office are as follows:

Total cholesterol	290 mg/dL
High-density lipoprotein	45 mg/dL
Low-density lipoprotein	110 mg/dL
Triglycerides	675 mg/dL

Lifestyle modification with a balanced diet, regular exercise, and reduced alcohol intake is advised. He is also started on fenofibrate therapy. This medication is most likely to help the patient by which of the following mechanisms?

☐ A. Blocking intestinal cholesterol absorption

☐ B. Decreasing hepatic cholesterol synthesis

☐ C. Increasing fecal loss of cholesterol derivatives

☐ D. Inhibiting LDL receptor degradation

☐ E. Reducing hepatic VLDL production

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A 36-year-old man comes to the office after he was found to have an abnormal lipid panel during employee wellness testing at his company. He has no prior medical problems and takes no medications. The patient is a software technician and has a sedentary lifestyle. He eats mostly fast foods, rarely exercises, and drinks 2-3 cans of beer daily. His BMI is 31 kg/m². Physical examination is unremarkable. Results of laboratory studies performed in the office are as follows:

Total cholesterol	290 mg/dL
High-density lipoprotein	45 mg/dL
Low-density lipoprotein	110 mg/dL
Triglycerides	675 mg/dL

Lifestyle modification with a balanced diet, regular exercise, and reduced alcohol intake is advised. He is also started on fenofibrate therapy. This medication is most likely to help the patient by which of the following mechanisms?

☐ A. Blocking intestinal cholesterol absorption [14%]

☐ B. Decreasing hepatic cholesterol synthesis [8%]

☐ C. Increasing fecal loss of cholesterol derivatives [16%]

☐ D. Inhibiting LDL receptor degradation [15%]

☒ E. Reducing hepatic VLDL production [45%]

Omitted

Correct answer

45%

Answered correctly

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Explanation

This patient has a moderately elevated (>500 mg/dL) triglyceride level, which is associated with an increased risk of cardiovascular disease. Lifestyle modifications (increased aerobic exercise, decreased alcohol and total caloric intake) can decrease triglycerides, but moderate (or worse) hypertriglyceridemia usually requires pharmacologic therapy.

Lipoprotein lipase (LPL) hydrolyzes triglycerides in chylomicrons and VLDL to release free fatty acids, which can be used for energy or converted back to triglycerides for storage in adipose tissue. It also facilitates the transfer of triglycerides from these lipoproteins to HDL.

Fibrates (eg, gemfibrozil, fenofibrate) activate **peroxisome proliferator-activated receptor alpha** (PPAR- α), which leads to **decreased hepatic VLDL** production and increased LPL activity. They are able to decrease triglyceride levels by 25%-50% and increase HDL by 5%-20%. Fish oil supplements containing high concentrations of **omega-3 fatty acids** also decrease **VLDL production**, and inhibit synthesis of apolipoprotein B as well. These supplements lower triglycerides and can be used as an alternate treatment for patients with moderate hypertriglyceridemia.

(Choices A, C, and D) Ezetimibe selectively blocks intestinal cholesterol absorption. Bile acid-binding resins (eg, cholestyramine) increase fecal loss of cholesterol derivatives by binding bile acids in the intestine and disrupting enterohepatic bile acid circulation. Proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors are monoclonal antibodies that reduce LDL receptor degradation in the liver. These drugs are used primarily in patients with elevated cholesterol levels but have minimal effect on triglyceride levels.

(Choice B) Statins (eg, atorvastatin) decrease hepatic cholesterol synthesis by inhibiting HMG-CoA reductase. Statins have a modest effect on triglyceride levels and are recommended for patients with mild to moderate hypertriglyceridemia.

Educational objective:

Fibrates lower triglyceride levels by activating peroxisome proliferator-activated receptor alpha, which leads to decreased hepatic VLDL production and increased lipoprotein lipase activity. Fish oil supplements containing high concentrations of omega-3 fatty acids lower triglycerides by decreasing production of VLDL and apolipoprotein B.

References

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A

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A 45-year-old man who was recently started on medication for paroxysmal atrial fibrillation undergoes stress ECG testing. The patient exercises on a treadmill for 9 minutes and reaches 98% of age-predicted maximal heart rate without chest pain or ST-segment changes. His pre-test resting QRS complex duration is 95 msec (normal: 80-120 msec) and corrected QT (QTc) interval duration is 410 msec (normal ≤ 440 msec). ECG findings recorded at his maximally achieved heart rate show a QRS complex duration of 125 msec and QTc interval duration of 400 msec. Based on the patient's test results, which of the following medications is most likely being used to treat his atrial fibrillation?

☐

A. Atenolol

☐

B. Digoxin

☐

C. Dofetilide

☐

D. Flecainide

☐

E. Verapamil

Submit

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☐

A. Atenolol [10%]

☐

B. Digoxin [10%]

☐

C. Dofetilide [18%]

☒

D. Flecainide [44%]

☐

E. Verapamil [15%]

Omitted

Correct answer D

44%

Answered correctly

3 Seconds

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Last Updated

Explanation

The **QRS complex duration** is typically slightly **reduced during exercise** in response to the increase in cardiac conduction velocity that accompanies faster heart rates. However, this patient's QRS duration is normal at rest and prolonged at near-maximal heart rate. This suggests that the drug used to treat his atrial fibrillation lengthens the QRS duration in a rate-dependent manner, which is consistent with a drug exhibiting

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The **QRS complex duration** is typically slightly **reduced during exercise** in response to the increase in cardiac conduction velocity that accompanies faster heart rates. However, this patient's QRS duration is normal at rest and prolonged at near-maximal heart rate. This suggests that the drug used to treat his atrial fibrillation lengthens the QRS duration in a rate-dependent manner, which is consistent with a drug exhibiting strong use-dependence such as flecainide.

Flecainide is a **class 1C antiarrhythmic** that is typically used to treat supraventricular tachycardias such as those caused by atrial fibrillation. Class 1C antiarrhythmics bind to the fast sodium channels responsible for **phase 0 depolarization** of cardiac myocytes, blocking the inward sodium current. This **prolongs the QRS duration** with little effect on total action potential or QT interval duration. Class 1C drugs are the slowest of the class 1 agents to dissociate from the sodium channel, and do so primarily during diastole. This results in a phenomenon known as **use-dependence**, in which their sodium-blocking effects intensify as the heart rate increases due to less time for the medication to dissociate from the receptor.

(Choice A) Selective β_1 blockers such as atenolol do not significantly affect QRS duration. However, their use during exercise ECG testing can limit the maximal heart rate that is achieved.

(Choice B) Digoxin can cause false-positive ST-segment depression during exercise ECG testing as well as lower the maximal achievable heart rate. It does not significantly affect QRS duration.

(Choice C) Dofetilide is a class III antiarrhythmic drug that blocks the outward potassium current during repolarization. As a result, it increases the QT interval duration but does not affect QRS duration. Class III agents demonstrate reverse use-dependence (the slower the heart rate, the more the QT interval is prolonged).

(Choice E) Verapamil (a class IV antiarrhythmic) is a calcium channel blocker that slows sinoatrial and atrioventricular nodal conduction. It also increases coronary blood flow and reduces myocardial oxygen demand, which can mask ischemia during stress testing. Verapamil does not affect QRS duration.

Educational objective:

Class 1C antiarrhythmics such as flecainide are potent sodium channel blockers that have increased effect at faster heart rates (use-

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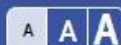
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that the drug used to treat his atrial fibrillation lengthens the QRS duration in a rate-dependent manner, which is consistent with a drug exhibiting strong use-dependence such as flecainide.

Flecainide is a **class 1C antiarrhythmic** that is typically used to treat supraventricular tachycardias such as those caused by atrial fibrillation. Class 1C antiarrhythmics bind to the fast sodium channels responsible for **phase 0 depolarization** of cardiac myocytes, blocking the inward sodium current. This **prolongs the QRS duration** with little effect on total action potential or QT interval duration. Class 1C drugs are the slowest of the class 1 agents to dissociate from the sodium channel, and do so primarily during diastole. This results in a phenomenon known as **use-dependence**, in which their sodium-blocking effects intensify as the heart rate increases due to less time for the medication to dissociate from the receptor.

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(Choice E) Verapamil (a class IV antiarrhythmic) is a calcium channel blocker that slows sinoatrial and atrioventricular nodal conduction. It also increases coronary blood flow and reduces myocardial oxygen demand, which can mask ischemia during stress testing. Verapamil does not affect QRS duration.

Educational objective:

Class 1C antiarrhythmics such as flecainide are potent sodium channel blockers that have increased effect at faster heart rates (use-dependence). This makes them more effective at treating tachyarrhythmias, but can also cause prolonged QRS duration (a proarrhythmic effect) at higher heart rates.

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that the drug used to treat his atrial fibrillation lengthens the QRS duration in a rate-dependent manner, which is consistent with a drug exhibiting

Exhibit Display

Class I (sodium channel-blocking) antiarrhythmics			
	Specific agents	Inhibition of phase 0 depolarization	Effect on length of action potential
Class IA	Quinidine, procainamide, disopyramide	Intermediate	Prolonged
Class IB	Lidocaine, mexiletine	Weak	Shortened
Class IC	Flecainide, propafenone	Strong	No change

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that the drug used to treat his atrial fibrillation lengthens the QRS duration in a rate-dependent manner, which is consistent with a drug exhibiting

Exhibit Display

Cardiac action potentials

Pacemaker action potential

Non-pacemaker action potential

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A 43-year-old woman comes to the office due to occasional chest discomfort over the last year. She describes the pain as a mid-line pressure or squeezing sensation that lasts 10-15 minutes and is sometimes accompanied by diaphoresis. The patient has no history of hypertension or diabetes mellitus but is an active smoker. Exercise stress testing shows good exercise capacity with no ischemic signs or symptoms. Ambulatory ECG monitoring shows transient ST-segment elevations in leads I, aVL, and V1-V4 during an episode of chest pain at night. Which of the following would most likely provoke this patient's chest pain?

☐

A. Amlodipine

☐

B. Aspirin

☐

C. Dihydroergotamine

☐

D. Morphine

☐

E. Nitroglycerin

☐

F. Phentolamine

Submit

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☐

A. Amlodipine [12%]

☐

B. Aspirin [2%]

☒

C. Dihydroergotamine [48%]

☐

D. Morphine [4%]

☐

E. Nitroglycerin [7%]

☐

F. Phentolamine [23%]

Omitted

Correct answer C

48%

Answered correctly

3 Seconds

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Last Updated

Explanation

This patient with spontaneous episodes of **rest and nighttime** angina associated with **transient ST elevation** on ambulatory ECG monitoring, likely has vasospastic or **variant (Prinzmetal) angina**. Variant angina is caused by transient, sudden, and significant reduction in the luminal

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This patient with spontaneous episodes of **rest and nighttime** angina associated with **transient ST elevation** on ambulatory ECG monitoring, likely has vasospastic or **variant (Prinzmetal) angina**. Variant angina is caused by transient, sudden, and significant reduction in the luminal diameter of an epicardial coronary artery due to spasm, leading to brief myocardial ischemia. **Coronary vasospasm** can occur in normal coronary vessels and at the site of atherosclerotic plaques.

Dihydroergotamine is an ergot alkaloid commonly used to treat acute migraine headache. This drug may induce vasospastic angina as it constricts vascular smooth muscle via stimulation of both alpha-adrenergic (partial agonist) and serotonergic receptors. Other possible triggers include cigarette smoking, cocaine/amphetamines, and triptans.

(Choice A) Amlodipine is a calcium channel blocker that causes coronary and peripheral vasodilation. Calcium channel blockers are often used to treat and prevent attacks in patients with vasospastic angina.

(Choice B) Conventional doses of aspirin result in inhibition of platelet thromboxane A₂ synthesis but do not significantly impair endothelial PGI₂ production as endothelial cells continue synthesizing new prostaglandin G/H synthase. Therefore, conventional aspirin doses do not provoke vasoconstriction, including coronary vasospasm.

(Choice D) Morphine does not provoke coronary vasospasm; rather, it acts as a vasodilator, increasing venous capacitance, reducing systemic vascular resistance, and potentially causing central nervous system sympatholytic effects on the cardiovascular system. It is used occasionally to manage severe pain during acute myocardial infarction.

(Choice E) Nitrates cause systemic vasodilation (predominantly venodilation) with a decrease in left ventricular volume and stress. Nitroglycerin is typically used to treat episodes of vasospastic angina.

(Choice F) Phentolamine is nonselective α blocker and acts as a vasodilator. Although reflex tachycardia is a known side effect of nonselective α blockers, studies have shown that vasospastic angina does not occur with phentolamine due to the underlying mechanism of angina being coronary vasospasm and not coronary artery disease.

Educational objective:

Prinzmetal (variant) angina is characterized by episodic, transient attacks of coronary vasospasm (at rest and at night), producing temporary

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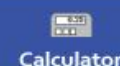
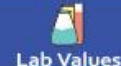
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Dihydroergotamine is an ergot alkaloid commonly used to treat acute migraine headache. This drug may induce vasospastic angina as it constricts vascular smooth muscle via stimulation of both alpha-adrenergic (partial agonist) and serotonergic receptors. Other possible triggers include cigarette smoking, cocaine/amphetamines, and triptans.

(Choice A) Amlodipine is a calcium channel blocker that causes coronary and peripheral vasodilation. Calcium channel blockers are often used to treat and prevent attacks in patients with vasospastic angina.

(Choice B) Conventional doses of aspirin result in inhibition of platelet thromboxane A_2 synthesis but do not significantly impair endothelial PGI_2 production as endothelial cells continue synthesizing new prostaglandin G/H synthase. Therefore, conventional aspirin doses do not provoke vasoconstriction, including coronary vasospasm.

(Choice D) Morphine does not provoke coronary vasospasm; rather, it acts as a vasodilator, increasing venous capacitance, reducing systemic vascular resistance, and potentially causing central nervous system sympatholytic effects on the cardiovascular system. It is used occasionally to manage severe pain during acute myocardial infarction.

(Choice E) Nitrates cause systemic vasodilation (predominantly venodilation) with a decrease in left ventricular volume and stress. Nitroglycerin is typically used to treat episodes of vasospastic angina.

(Choice F) Phentolamine is nonselective α blocker and acts as a vasodilator. Although reflex tachycardia is a known side effect of nonselective α blockers, studies have shown that vasospastic angina does not occur with phentolamine due to the underlying mechanism of angina being coronary vasospasm and not coronary artery disease.

Educational objective:

Prinzmetal (variant) angina is characterized by episodic, transient attacks of coronary vasospasm (at rest and at night), producing temporary transmural myocardial ischemia with ST-segment elevation. Possible triggers are cigarette smoking, cocaine/amphetamines, and dihydroergotamine/triptans. Treatment includes tobacco/drug cessation and vasodilator therapy (eg, nitrates, calcium channel blockers).

References

- [International standardization of diagnostic criteria for vasospastic angina.](#)

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TUTOR



An 85-year-old man is transferred to the hospital from a nursing home due to fever and confusion. On arrival, the patient is admitted directly to the intensive care unit with a presumptive diagnosis of septic shock. Antibiotic therapy is initiated. The patient is unable to provide any history, but his caretakers state that he has had nonspecific symptoms, including fever, for the past few days. The patient has a history of cardiovascular disease, diverticulitis, and dementia. Blood pressure is 60/40 mm Hg despite aggressive intravenous hydration. Intravenous norepinephrine is administered in response to the patient's hypotension. Which of the following cellular changes is most likely to occur in direct response to the medication?

- ☐ A. cAMP decrease in bronchial smooth muscle cells
- ☐ B. cAMP increase in cardiac muscle cells
- ☐ C. cAMP increase in vascular smooth muscle cells
- ☐ D. DAG decrease in vascular smooth muscle cells
- ☐ E. IP_3 increase in cardiac muscle cells

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An 85-year-old man is transferred to the hospital from a nursing home due to fever and confusion. On arrival, the patient is admitted directly to the intensive care unit with a presumptive diagnosis of septic shock. Antibiotic therapy is initiated. The patient is unable to provide any history, but his caretakers state that he has had nonspecific symptoms, including fever, for the past few days. The patient has a history of cardiovascular disease, diverticulitis, and dementia. Blood pressure is 60/40 mm Hg despite aggressive intravenous hydration. Intravenous norepinephrine is administered in response to the patient's hypotension. Which of the following cellular changes is most likely to occur in direct response to the medication?

☐ A. cAMP decrease in bronchial smooth muscle cells [2%]

☒ B. cAMP increase in cardiac muscle cells [38%]

☐ C. cAMP increase in vascular smooth muscle cells [35%]

☐ D. DAG decrease in vascular smooth muscle cells [9%]

☐ E. IP₃ increase in cardiac muscle cells [13%]

Omitted

Correct answer
B

38%
Answered correctly

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Explanation

Receptor stimulated	Change in second	Primary effects
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Explanation

Receptor stimulated	Change in second messenger	Primary effects
Alpha-1	↑IP ₃	- Peripheral vasoconstriction - Urethral constriction - Pupillary dilation (via radial muscle contraction)
Alpha-2	↓cAMP	- Central nervous system sympatholytic ↓Insulin release by pancreatic beta cells ↓Intestinal motility
Beta-1	↑cAMP	↑Cardiac contractility & heart rate ↑Renin release by JG cells of kidney
Beta-2	↑cAMP	- Peripheral vasodilation - Bronchodilation ↑Glucagon release by pancreatic alpha cells

JG = juxtaglomerular.

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		kidney
Beta-2	↑cAMP	- Peripheral vasodilation - Bronchodilation ↑Glucagon release by pancreatic alpha cells

JG = juxtaglomerular.

Stimulation of adrenoceptors leads to a change in concentration of a second messenger (eg, cAMP), which mediates the effects on the target organ. **Norepinephrine**, an adrenergic agonist, is the preferred pharmacologic treatment for **septic shock** as it predominately stimulates α_1 , α_2 , and β_1 receptors, with little influence on β_2 receptors. This leads to the following clinical effects:

1. Stimulation of **α_1 adrenoceptors** leads to **vasoconstriction** in the skin and viscera, resulting in increased systolic and diastolic blood pressure with decreased renal and hepatic blood flow. α_1 -mediated vasoconstriction occurs via the **IP_3 -second messenger pathway**.
2. Stimulation of **β_1 adrenoceptors** within the heart increases **cAMP** concentrations through **G_s -mediated receptor coupling**, which leads to increased **cardiac contractility**, **conduction**, and **heart rate**. However, the direct effect of norepinephrine on heart rate is counteracted by an indirect, baroreceptor-mediated reflex bradycardia that occurs following the increase in peripheral resistance. The combined result of these effects is often an unchanged or even decreased heart rate.
3. Stimulation of α_2 adrenoceptors causes a decrease in cAMP in pancreatic β cells and in the intestines, resulting in decreased insulin secretion and reduced intestinal motility. Central α_2 adrenoceptors are not stimulated by intravenous administration of norepinephrine as the molecule does not cross the blood-brain barrier.

(Choice A) Stimulation of β_2 adrenoceptors in bronchial smooth muscle cells leads to increased, rather than decreased, cAMP synthesis, resulting in bronchodilation. Regardless, norepinephrine does not significantly stimulate β_2 adrenoceptors.

(Choices C and D) Norepinephrine-mediated stimulation of α_1 adrenoceptors increases, rather than decreases, IP_3 (increased calcium release) and DAG concentrations in vascular smooth muscle cells. cAMP is increased after β_2 adrenoceptors are stimulated; however, because

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to increased **cardiac contractility, conduction, and heart rate**. However, the direct effect of norepinephrine on heart rate is counteracted by an indirect, baroreceptor-mediated reflex bradycardia that occurs following the increase in peripheral resistance. The combined result of these effects is often an unchanged or even decreased heart rate.

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(Choice A) Stimulation of β_2 adrenoreceptors in bronchial smooth muscle cells leads to increased, rather than decreased, cAMP synthesis, resulting in bronchodilation. Regardless, norepinephrine does not significantly stimulate β_2 adrenoreceptors.

(Choices C and D) Norepinephrine-mediated stimulation of α_1 adrenoreceptors increases, rather than decreases, IP_3 (increased calcium release) and DAG concentrations in vascular smooth muscle cells. cAMP is increased after β_2 adrenoreceptors are stimulated; however, because norepinephrine does not significantly stimulate β_2 adrenoreceptors, cAMP concentrations in vascular smooth muscle are not increased.

(Choice E) A significant elevation in IP_3 concentration does not occur in cardiac muscle cells following norepinephrine administration. The cardiac effects of norepinephrine are primarily mediated by β_1 adrenoreceptors that are linked to a cAMP, rather than IP_3 , signal transduction pathway.

Educational objective:

Norepinephrine stimulates cardiac β_1 adrenoreceptors, which increases cAMP concentration within cardiac myocytes and leads to increased contractility, conduction, and heart rate. Peripheral vasoconstriction occurs via stimulation of α_1 adrenoreceptors in vascular smooth muscle cells and activation of an IP_3 signaling pathway.

References

- Early administration of norepinephrine increases cardiac preload and cardiac output in septic patients with life-threatening hypotension.

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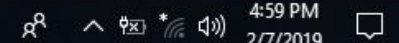
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Exhibit Display

Phosphatidylinositol 2nd messenger system

Diagram illustrating the Phosphatidylinositol 2nd messenger system. The system involves a hormone binding to a receptor, activating a G protein (GDP-bound), which then activates Phospholipase C. Phospholipase C cleaves a phospholipid into Diacylglycerol (DAG) and Inositol trisphosphate (IP₃). IP₃ binds to a calcium channel, releasing Ca²⁺ from the endoplasmic reticulum. The combination of Ca²⁺ and DAG activates Protein Kinase C, leading to the phosphorylation of various proteins.

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The diagram illustrates a cellular signaling pathway. On the left, a cross-section of the endoplasmic reticulum (ER) membrane is shown, with several Ca^{2+} ions (represented as grey spheres) inside the ER lumen. A purple protein channel is embedded in the membrane. A green sphere labeled IP_3 is shown binding to this channel. An arrow points from the IP_3 to the channel, and another arrow points from the channel to the cytosol, where Ca^{2+} ions are released. In the cytosol, a large teal protein labeled Ca^{2+} is shown. An arrow points from the Ca^{2+} ion to a box labeled "Protein kinase C activation". From this box, an arrow points down to a box labeled "Phosphorylated proteins", and another arrow points down to a box labeled "Physiologic effects (eg, smooth muscle contraction)".

Labels in the diagram include: G protein, IP_3 , Ca^{2+} , Protein kinase C activation, Phosphorylated proteins, Physiologic effects (eg, smooth muscle contraction), Endoplasmic reticulum, and Cytosol.

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Exhibit Display

G protein activation of adenylate cyclase

The diagram illustrates the G protein activation of adenylate cyclase in five steps:

- 1**: A bound ligand (purple) binds to the extracellular domain of a G protein-coupled receptor (blue) embedded in a lipid bilayer.
- 2**: The activated receptor facilitates the exchange of GDP (red) for GTP (orange) on the α subunit (red) of the G protein (consisting of α , β , and γ subunits).
- 3**: The GTP-bound α subunit dissociates from the $\beta\gamma$ complex and binds to the intracellular domain of adenylate cyclase (green).
- 4**: Activated adenylate cyclase converts ATP (blue) into cAMP (blue).
- 5**: cAMP leads to the activation of Protein kinase A, which then produces physiologic effects.

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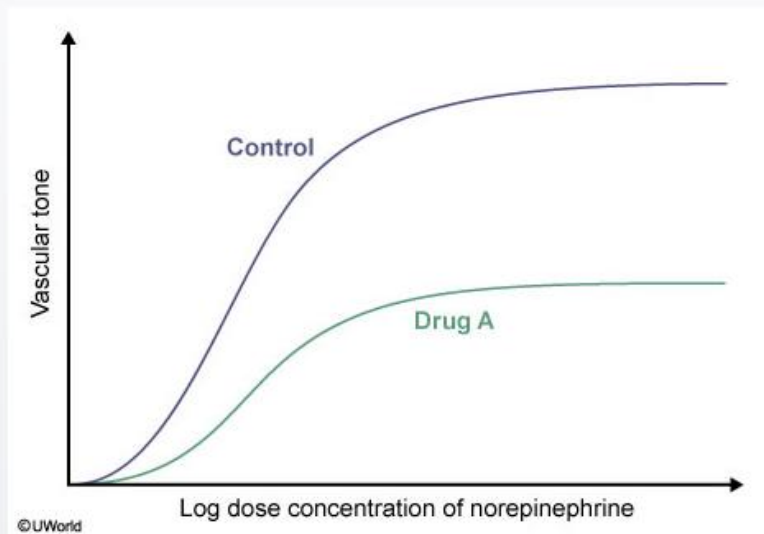
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In an experiment investigating vasoconstriction of the arterial wall, two samples of isolated porcine arterial vessels are studied. Vascular tone is measured in the control vessel during infusion of increasing doses of norepinephrine. The other vessel is pretreated with experimental drug A prior to infusion of norepinephrine. A graph of the study results is depicted below.



Drug A is most similar to which of the following agents?

- ☐ A. Atropine
- ☐ B. Labetalol
- ☐ C. Phenoxybenzamine
- ☐ D. Phentolamine

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Drug A is most similar to which of the following agents?

☐ A. Atropine

☐ B. Labetalol

☐ C. Phenoxybenzamine

☐ D. Phentolamine

☐ E. Propranolol

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Drug A is most similar to which of the following agents?

☐ A. Atropine [5%]

☐ B. Labetalol [11%]

☒ C. Phenoxybenzamine [48%]

☐ D. Phentolamine [24%]

☐ E. Propranolol [9%]

Omitted

Correct answer

48%

Answered correctly

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C

Explanation

Biological effect

Log dose concentration

Maximum effect

Control

Decreased Vmax

Noncompetitive inhibitor or irreversible inhibitor

Biological effect

Log dose concentration

Maximum effect

Control

Reversible competitive inhibitor

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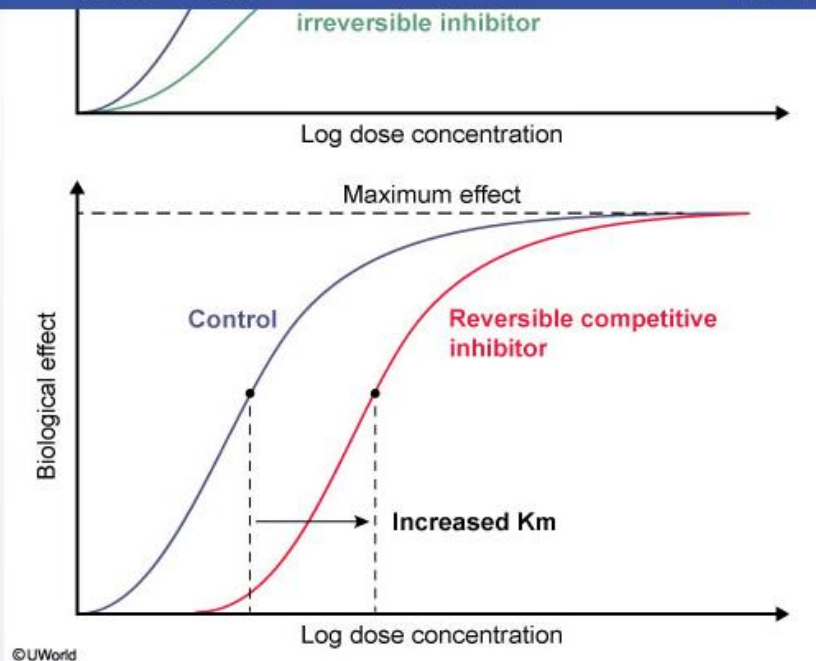
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Alpha-1 adrenergic receptors mediate arterial vasoconstriction whereas β_2 receptors mediate vasodilation. **Norepinephrine** is an agonist at α_1 and β_1 receptors but has significantly less action at β_2 receptors; it is therefore a potent vasoconstrictor. This experiment is testing the efficacy of drug A at blocking the **α_1 -mediated vasoconstriction** caused by norepinephrine administration.

The results show that pretreatment with drug A results in **decreased maximal effect** (V_{max}) of norepinephrine without a significant change in the affinity (K_m) of norepinephrine for α_1 receptors. This suggests that drug A is acting as either a **noncompetitive antagonist** or an **irreversible antagonist** of α_1 adrenergic receptors. **Phenoxybenzamine** is an irreversible α_1 and α_2 receptor antagonist that would produce results similar to those observed. It is primarily used in the treatment of pheochromocytoma, in which a tumor of the adrenal medulla overproduces norepinephrine, causing systemic arterial vasoconstriction.

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Log dose concentration

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Alpha-1 adrenergic receptors mediate arterial vasoconstriction whereas β_2 receptors mediate vasodilation. **Norepinephrine** is an agonist at α_1 and β_1 receptors but has significantly less action at β_2 receptors; it is therefore a potent vasoconstrictor. This experiment is testing the efficacy of drug A at blocking the **α_1 -mediated vasoconstriction** caused by norepinephrine administration.

The results show that pretreatment with drug A results in **decreased maximal effect** (V_{max}) of norepinephrine without a significant change in the affinity (K_m) of norepinephrine for α_1 receptors. This suggests that drug A is acting as either a **noncompetitive** antagonist or an **irreversible antagonist** of α_1 adrenergic receptors. **Phenoxybenzamine** is an irreversible α_1 and α_2 receptor antagonist that would produce results similar to those observed. It is primarily used in the treatment of pheochromocytoma, in which a tumor of the adrenal medulla overproduces norepinephrine, causing systemic arterial vasoconstriction.

(Choice A) Atropine is a competitive muscarinic acetylcholine receptor antagonist. Pretreatment with atropine would not alter norepinephrine's effects on vascular tone.

(Choices B and D) Labetalol is a reversible, competitive antagonist of α_1 and β adrenergic receptors with partial β_2 agonist activity that is used to treat hypertension. Phentolamine is a reversible, competitive α -adrenergic antagonist used in the management of catecholamine-induced hypertensive crises (eg, pheochromocytoma, monoamine oxidase inhibitor toxicity, cocaine intoxication). High doses of norepinephrine can overcome the α -adrenergic inhibition of these drugs.

(Choice E) Propranolol is a nonspecific β -adrenergic antagonist. Pretreatment with a β antagonist would potentiate the vasoconstrictive effects of norepinephrine due to unopposed α -adrenergic stimulation.

Educational objective:

Phenoxybenzamine is an irreversible α_1 and α_2 adrenergic antagonist that effectively reduces the arterial vasoconstriction induced by norepinephrine. Because phenoxybenzamine is an irreversible antagonist, even very high concentrations of norepinephrine, such as those seen in pheochromocytoma, cannot overcome its effects.

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A 60-year-old man with known coronary artery disease comes to the office due to exertional chest tightness for the last 6 months. The symptoms occur when he walks more than 3 blocks, especially in cold weather. The patient underwent coronary artery bypass graft surgery 3 years ago for progressive angina. Past medical history also includes asthma, benign prostate hyperplasia, and peripheral artery disease. The physician discusses adding isosorbide dinitrate to his current therapy but the patient is concerned about adverse effects. Which of the following is most likely to occur in this patient with the add-on therapy?

A. Atrioventricular conduction delay

B. Cold extremities

C. Constipation

D. Joint pains

E. Nocturnal wheezing

F. Throbbing headaches

G. Urinary retention

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☐

A. Atrioventricular conduction delay [4%]

☐

B. Cold extremities [11%]

☐

C. Constipation [3%]

☐

D. Joint pains [1%]

☐

E. Nocturnal wheezing [4%]

☒

F. Throbbing headaches [67%]

☐

G. Urinary retention [6%]

Omitted

Correct answer
F

67%

Answered correctly

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Explanation

Nitrates are frequently used for symptomatic relief in patients with chronic stable angina. The anti-ischemic effect of nitrates is mediated by

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Explanation

Nitrates are frequently used for symptomatic relief in patients with chronic stable angina. The anti-ischemic effect of nitrates is mediated by systemic vasodilation (predominantly venodilation) with a decrease in left ventricular end-diastolic volume and wall stress, resulting in decreased myocardial oxygen demand and relief of angina symptoms.

The main adverse effects seen with nitrate therapy include **headaches**, **cutaneous flushing**, lightheadedness, **hypotension**, and reflex tachycardia. Nitrates must be avoided in patients with hypertrophic cardiomyopathy (due to increased outflow tract obstruction), right ventricular infarction (due to reduction in preload, impairing cardiac output), and those on phosphodiesterase inhibitors (synergism increases the risk of severe hypotension).

(Choice A) Atrioventricular conduction delay is a potential adverse effect of several drugs used for management of chronic stable angina. These include calcium channel blockers (eg, verapamil, diltiazem) and beta blockers (eg, metoprolol, propranolol).

(Choice B) Cold extremities due to Raynaud phenomenon are associated with medications such as amphetamines, ergotamine, and chemotherapeutic agents.

(Choice C) Constipation is a common side effect of opioid analgesics, iron supplements, calcium channel blockers such as verapamil, and anticholinergic medications such as atropine.

(Choice D) Thiazide diuretics can lead to hyperuricemia and precipitate an acute gout attack.

(Choice E) Nocturnal wheezing can be a symptom of asthma or gastroesophageal reflux disease. In addition, the use of beta blockers in patients with underlying bronchospastic disease can cause increased bronchoconstriction and lead to wheezing.

(Choice G) Urinary retention is typically associated with medications that exhibit anticholinergic properties such as tricyclic antidepressants (eg, amitriptyline) and antihistamines (eg, diphenhydramine).

Educational objective:

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myocardial oxygen demand and relief of angina symptoms.

The main adverse effects seen with nitrate therapy include **headaches, cutaneous flushing**, lightheadedness, **hypotension**, and reflex tachycardia. Nitrates must be avoided in patients with hypertrophic cardiomyopathy (due to increased outflow tract obstruction), right ventricular infarction (due to reduction in preload, impairing cardiac output), and those on phosphodiesterase inhibitors (synergism increases the risk of severe hypotension).

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(Choice E) Nocturnal wheezing can be a symptom of asthma or gastroesophageal reflux disease. In addition, the use of beta blockers in patients with underlying bronchospastic disease can cause increased bronchoconstriction and lead to wheezing.

(Choice G) Urinary retention is typically associated with medications that exhibit anticholinergic properties such as tricyclic antidepressants (eg, amitriptyline) and antihistamines (eg, diphenhydramine).

Educational objective:
The main adverse effects seen with nitrate therapy include headaches and cutaneous flushing along with lightheadedness and hypotension due to systemic vasodilation.

References
• Mechanisms of action of nitrates

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An 82-year-old man is brought to the emergency department with fatigue and palpitations. The patient was playing chess at the park when his symptoms developed suddenly. He immediately called an ambulance as he has never experienced symptoms like this before. Past medical history is significant for asthma, gout, and hypertension. Blood pressure is 110/70 mm Hg, pulse is 130/min, and rhythm is irregularly irregular. The lungs are clear on auscultation. Intravenous digoxin is administered. Two hours later, the patient appears comfortable; his pulse is 82/min and still irregularly irregular. Which of the following best explains the heart rate lowering effects of the medication?

☐ A. Decreased action potential duration

☐ B. Decreased atrial refractoriness

☐ C. Delayed after-depolarizations

☐ D. Increased parasympathetic tone

☐ E. Increased ventricular contractility

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An 82-year-old man is brought to the emergency department with fatigue and palpitations. The patient was playing chess at the park when his symptoms developed suddenly. He immediately called an ambulance as he has never experienced symptoms like this before. Past medical history is significant for asthma, gout, and hypertension. Blood pressure is 110/70 mm Hg, pulse is 130/min, and rhythm is irregularly irregular. The lungs are clear on auscultation. Intravenous digoxin is administered. Two hours later, the patient appears comfortable; his pulse is 82/min and still irregularly irregular. Which of the following best explains the heart rate lowering effects of the medication?

☐ A. Decreased action potential duration [6%]

☐ B. Decreased atrial refractoriness [5%]

☐ C. Delayed after-depolarizations [16%]

☒ D. Increased parasympathetic tone [48%]

☐ E. Increased ventricular contractility [22%]

Omitted

Correct answer
D

48%

Answered correctly

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12/15/2018

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Explanation

This patient developed **atrial fibrillation with rapid ventricular response** (AF with RVR) and was treated with digoxin for ventricular **rate control**. Although calcium channel blockers and beta blockers are preferred for rate control, digoxin is sometimes used. **Digoxin** slows the ventricular rate during AF primarily by **increasing parasympathetic tone**, which leads to inhibition of atrioventricular (AV) nodal conduction.

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Explanation

This patient developed **atrial fibrillation with rapid ventricular response** (AF with RVR) and was treated with digoxin for ventricular **rate control**. Although calcium channel blockers and beta blockers are preferred for rate control, digoxin is sometimes used. **Digoxin** slows the ventricular rate during AF primarily by **increasing parasympathetic tone**, which leads to inhibition of atrioventricular (AV) nodal conduction.

Several mechanisms may explain the parasympathomimetic effects of digoxin. Inhibition of the sodium-potassium ATPase pump in vagal afferent fibers sensitizes arterial baroreceptors (eg, carotid, aortic) and cardiac receptors, augmenting afferent input from the cardiovascular system to the brain. Digoxin also enhances efferent parasympathetic ganglionic transmission, leading to increased vagal output.

Slowed AV conduction is useful in AF and flutter with RVR (heart rate $\geq 100/\text{min}$) because the focus of increased automaticity in these conditions is located in the atria and the rapidity of the ventricular response depends on the refractory period of the AV node. When AV node conduction is slowed, the atria will continue to fibrillate/flutter, but the ventricles will contract at a more normal rate. RVR is serious as inadequate diastolic filling time can lead to poor cardiac output and backup of blood in the lungs (heart failure).

(Choices A and B) Decreased action potential duration leads to a decreased refractory period and would allow the cardiac pacemaker cells (or ectopic foci) to fire with greater frequency. Decreased atrial refractoriness would give the atria the ability to depolarize at a higher rate and increase the risk of reentry circuit formation. These states predispose to AF.

(Choice C) Delayed after-depolarizations are abnormal depolarizations of cardiac myocytes that occur after repolarization has completed. They can occur in states of hyperexcitability (eg, very high intracellular calcium, high catecholamine stimulation states). Digoxin toxicity can cause delayed after-depolarizations via its mechanism of increasing intracellular calcium, leading to ventricular tachycardia and death.

(Choice E) Digoxin can improve systolic heart failure symptoms (eg, dyspnea, orthopnea) by increasing ventricular contractility. Digoxin inhibits the sodium-potassium ATPase pump, which results in increased intracellular sodium. This leads to increased intracellular calcium, which enhances excitation-contraction coupling and allows maximal cross-linking of actin and myosin for greater contractility. In contrast, the chronotropic effects of digoxin result indirectly from the increase in vagal tone.

Educational objective:

Digoxin is used for ventricular rate control in atrial fibrillation as it decreases atrioventricular nodal conduction by increasing parasympathetic vagal

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brain. Digoxin also enhances efferent parasympathetic ganglionic transmission, leading to increased vagal output.

Slowed AV conduction

 is useful in AF and flutter with RVR (heart rate $\geq 100/\text{min}$) because the focus of increased automaticity in these conditions is located in the atria and the rapidity of the ventricular response depends on the refractory period of the AV node. When AV node conduction is slowed, the atria will continue to fibrillate/flutter, but the ventricles will contract at a more normal rate. RVR is serious as inadequate diastolic filling time can lead to poor cardiac output and backup of blood in the lungs (heart failure).

(Choices A and B)

 Decreased action potential duration leads to a decreased refractory period and would allow the cardiac pacemaker cells (or ectopic foci) to fire with greater frequency. Decreased atrial refractoriness would give the atria the ability to depolarize at a higher rate and increase the risk of reentry circuit formation. These states predispose to AF.

(Choice C)

 Delayed after-depolarizations are abnormal depolarizations of cardiac myocytes that occur after repolarization has completed. They can occur in states of hyperexcitability (eg, very high intracellular calcium, high catecholamine stimulation states). Digoxin toxicity can cause delayed after-depolarizations via its mechanism of increasing intracellular calcium, leading to ventricular tachycardia and death.

(Choice E)

 Digoxin can improve systolic heart failure symptoms (eg, dyspnea, orthopnea) by increasing ventricular contractility. Digoxin inhibits the sodium-potassium ATPase pump, which results in increased intracellular sodium. This leads to increased intracellular calcium, which enhances excitation-contraction coupling and allows maximal cross-linking of actin and myosin for greater contractility. In contrast, the chronotropic effects of digoxin result indirectly from the increase in vagal tone.

Educational objective:

Digoxin is used for ventricular rate control in atrial fibrillation as it decreases atrioventricular nodal conduction by increasing parasympathetic vagal tone. Digoxin is also used in heart failure due to its positive inotropic effect. These effects are accomplished via inhibition of the sodium-potassium ATPase pump.

References

Endocardial stimulation of efferent parasympathetic nerves to the atrioventricular node in humans: optimal stimulation sites and the effects of digoxin.

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A 25-year-old man comes to the office due to shortness of breath. He states that even moderate exertion forces him to stop to catch his breath. The patient has no family history of sudden cardiac death. He does not use tobacco or illicit drugs. On examination, the patient has a faint systolic murmur at the left sternal border in the supine position that increases to 3/6 in intensity with Valsalva maneuver. Echocardiogram shows interventricular septal hypertrophy and increased left ventricular mass. The patient is started on high-dose beta blocker therapy. On follow-up 4 weeks later, he reports significant improvement in his shortness of breath. Physical examination reveals no murmurs supine or with Valsalva. Which of the following best accounts for improvement of this patient's symptoms?

☐ A. Dilation of epicardial coronary arteries

☐ B. Increase in left ventricular outflow tract flow velocity

☐ C. Reduction in left ventricular contractility

☐ D. Reduction in left ventricular mass

☐ E. Reduction in left ventricular preload

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A 25-year-old man comes to the office due to shortness of breath. He states that even moderate exertion forces him to stop to catch his breath. The patient has no family history of sudden cardiac death. He does not use tobacco or illicit drugs. On examination, the patient has a faint systolic murmur at the left sternal border in the supine position that increases to 3/6 in intensity with Valsalva maneuver. Echocardiogram shows interventricular septal hypertrophy and increased left ventricular mass. The patient is started on high-dose beta blocker therapy. On follow-up 4 weeks later, he reports significant improvement in his shortness of breath. Physical examination reveals no murmurs supine or with Valsalva. Which of the following best accounts for improvement of this patient's symptoms?

- ☐ A. Dilation of epicardial coronary arteries [2%]
- ☐ B. Increase in left ventricular outflow tract flow velocity [16%]
- ☒ C. Reduction in left ventricular contractility [63%]
- ☐ D. Reduction in left ventricular mass [4%]
- ☐ E. Reduction in left ventricular preload [13%]

Omitted

Correct answer
C63%
Answered correctly2 Seconds
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Explanation

This patient's echocardiogram shows increased left ventricular (LV) mass with predominant **interventricular septal hypertrophy**, which are classic findings for **hypertrophic cardiomyopathy (HCM)**. Many patients with HCM have LV outflow tract obstruction that can lead to symptoms of poor cardiac output (eg, dyspnea, syncope). The outflow tract obstruction worsens with **decreased LV blood volume** (as can occur during

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Explanation

This patient's echocardiogram shows increased left ventricular (LV) mass with predominant **interventricular septal hypertrophy**, which are classic findings for **hypertrophic cardiomyopathy** (HCM). Many patients with HCM have LV outflow tract obstruction that can lead to symptoms of poor cardiac output (eg, dyspnea, syncope). The outflow tract obstruction worsens with **decreased LV blood volume** (as can occur during exercise due to decreased LV filling time and increased LV contractility); on physical examination, this effect is evidenced by a systolic murmur that **increases in intensity** with **maneuvers** that decrease LV blood volume (eg, Valsalva strain phase, abrupt standing).

In patients with HCM and symptomatic LV outflow tract obstruction, **beta blockers** (eg, metoprolol, nadolol) improve symptoms mostly via an **increase in LV volume** that reduces LV outflow tract obstruction and improves cardiac output. This occurs via the following 2 mechanisms:

- Negative chronotropy **reduces heart rate** to lengthen diastolic filling time
- Negative inotropy **reduces LV contractility** to reduce the amount of blood ejected during systole

As decreased afterload can also reduce LV blood volume and worsen LV outflow tract obstruction in HCM, beta blockers have the added benefit of having minimal peripheral vasodilatory effect (ie, minimal afterload reduction).

(Choice A) Some patients with HCM may experience anginal symptoms due to inadequate blood supply to the increased myocardial mass. Beta blockers may help alleviate these symptoms by decreasing LV wall stress to reduce myocardial oxygen demand and improve the coronary artery perfusion gradient; however, they have minimal dilatory effect on the coronary arteries.

(Choice B) By increasing the cross-sectional area of the LV outflow tract, beta blockers tend to decrease flow velocity (flow velocity = volumetric flow rate / cross-sectional area). Consequently, the intensity of the HCM murmur is also decreased.

(Choice D) Over time, beta blockers may reduce the compensatory LV hypertrophy that can occur in HCM due to prolonged contraction against the outflow tract obstruction (similar to aortic stenosis); however, this effect would not be evident within 4 weeks.

(Choice E) Beta blockers increase LV preload to reduce LV outflow tract obstruction and improve symptoms.

Educational objective:

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or poor cardiac output (eg, dyspnea, syncope). The outflow tract obstruction worsens with **decreased LV blood volume** (as can occur during exercise due to decreased LV filling time and increased LV contractility); on physical examination, this effect is evidenced by a systolic murmur that **increases in intensity** with **maneuvers** that decrease LV blood volume (eg, Valsalva strain phase, abrupt standing).

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(Choice B) By increasing the cross-sectional area of the LV outflow tract, beta blockers tend to decrease flow velocity (flow velocity = volumetric flow rate / cross-sectional area). Consequently, the intensity of the HCM murmur is also decreased.

(Choice D) Over time, beta blockers may reduce the compensatory LV hypertrophy that can occur in HCM due to prolonged contraction against the outflow tract obstruction (similar to aortic stenosis); however, this effect would not be evident within 4 weeks.

(Choice E) Beta blockers increase LV preload to reduce LV outflow tract obstruction and improve symptoms.

Educational objective:

Many patients with hypertrophic cardiomyopathy have poor cardiac reserve (eg, exercise intolerance) due to left ventricular (LV) outflow tract obstruction. This outflow obstruction is worsened by decreased LV blood volume. Beta blockers decrease heart rate and LV contractility to increase LV blood volume, reduce LV outflow tract obstruction, and improve symptoms.



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A 45-year-old man comes to the hospital with acute onset of severe chest pain and diaphoresis. The patient describes the pain as "squeezing," different from any discomfort he has ever had. He has a past medical history of hypertension, and his father underwent coronary artery bypass grafting at age 50. The patient is diagnosed with acute ST-elevation myocardial infarction and undergoes an urgent coronary intervention with stent placement into the right coronary artery. He is also started on high-intensity atorvastatin therapy, along with antiplatelet therapy and appropriate medications to control blood pressure. Four weeks later, the patient's total cholesterol level is 140 mg/dL, down from 200 mg/dL before discharge. Which of the following has most likely increased as the result of the therapy?

☐ A. ApoB-100 concentration

☐ B. Biliary excretion of cholesterol

☐ C. LDL receptor density

☐ D. Plasma free fatty acids

☐ E. VLDL concentration

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A 45-year-old man comes to the hospital with acute onset of severe chest pain and diaphoresis. The patient describes the pain as "squeezing," different from any discomfort he has ever had. He has a past medical history of hypertension, and his father underwent coronary artery bypass grafting at age 50. The patient is diagnosed with acute ST-elevation myocardial infarction and undergoes an urgent coronary intervention with stent placement into the right coronary artery. He is also started on high-intensity atorvastatin therapy, along with antiplatelet therapy and appropriate medications to control blood pressure. Four weeks later, the patient's total cholesterol level is 140 mg/dL, down from 200 mg/dL before discharge. Which of the following has most likely increased as the result of the therapy?

☐

A. ApoB-100 concentration [8%]

☐

B. Biliary excretion of cholesterol [8%]

☒

C. LDL receptor density [74%]

☐

D. Plasma free fatty acids [5%]

☐

E. VLDL concentration [3%]

Omitted

Correct answer
C

74%

Answered correctly

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Explanation

Statins' mechanism of action

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HMG-CoA

⊖ Statins

↓

Mevalonate

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Cholesterol

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HMG-CoA reductase inhibitors (**statins**) inhibit the rate-limiting enzyme in hepatic cholesterol synthesis. In response to these changes, hepatocytes increase their surface expression of the **LDL receptor** to increase uptake of circulating LDL. Treatment generally produces a 20%-50% reduction in serum cholesterol and LDL concentration.

High-intensity statin therapy reduces the risk of **acute coronary events**. This risk reduction is greater than that seen with other classes of lipid-lowering medications and is likely due to additional properties of statins. Besides effects on lipids, statins have anti-inflammatory properties, improve endothelial dysfunction, and appear to stabilize atherosclerotic plaques.

(Choice A) ApoB-100 is an apoprotein present in VLDL and LDL. Decreases in circulating LDL and VLDL will cause the ApoB-100 concentration to decrease as well.

(Choice B) The biliary excretion of cholesterol decreases in patients on statins due to decreased de novo hepatic synthesis of cholesterol

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HMG-CoA reductase inhibitors (**statins**) inhibit the rate-limiting enzyme in hepatic cholesterol synthesis. In response to these changes, hepatocytes increase their surface expression of the **LDL receptor** to increase uptake of circulating LDL. Treatment generally produces a 20%-50% reduction in serum cholesterol and LDL concentration.

High-intensity statin therapy reduces the risk of **acute coronary events**. This risk reduction is greater than that seen with other classes of lipid-lowering medications and is likely due to additional properties of statins. Besides effects on lipids, statins have anti-inflammatory properties, improve endothelial dysfunction, and appear to stabilize atherosclerotic plaques.

(Choice A) ApoB-100 is an apoprotein present in VLDL and LDL. Decreases in circulating LDL and VLDL will cause the ApoB-100 concentration to decrease as well.

(Choice B) The biliary excretion of cholesterol decreases in patients on statins due to decreased de novo hepatic synthesis of cholesterol.

(Choice D) Statins lower serum triglycerides modestly and have only a minimal effect on plasma free fatty acid concentrations.

(Choice E) Statins produce small decreases in VLDL. Fibrates and nicotinic acid therapy decrease hepatic production of VLDL and are the mainstay of treatment for primary hypertriglyceridemia (increased VLDL).

Educational objective:

Treatment with statins causes hepatocytes to increase their LDL receptor density, leading to increased uptake of circulating LDL.

References

- Statins: a new insight into their mechanisms of action and consequent pleiotropic effects.

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A 44-year-old man reports exertional shortness of breath and palpitations. On examination, he has a systolic murmur at the left sternal border and cardiac apex, which gets louder when he stands up. He is diagnosed with obstructive hypertrophic cardiomyopathy and paroxysmal atrial fibrillation, and is started on a medication. Changes in the action potential of ventricular muscle cells before and after administration of medication are shown in the image below

Black curve = Before administration of medication
Red curve = After administration of medication

The patient is most likely being treated with which of the following medications?

☐ A. Adenosine

☐ B. Digoxin

☐ C. Diltiazem

☐ D. Disopyramide

☐ E. Flecainide

☐ F. Lidocaine

☐ G. Propranolol

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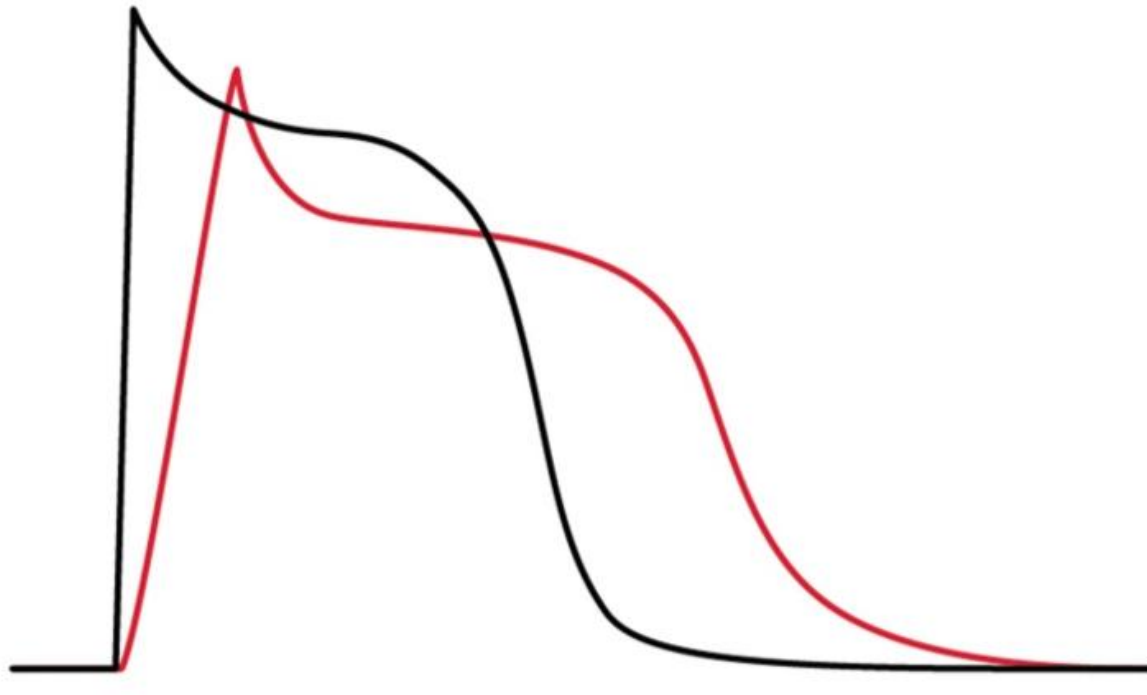
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☐ B. Digoxin

☐ C. Diltiazem

☐ D. Disopyramide

☐ E. Flecainide

☐ F. Lidocaine

☐ G. Propranolol

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A 44-year-old man reports exertional shortness of breath and palpitations. On examination, he has a systolic murmur at the left sternal border and cardiac apex, which gets louder when he stands up. He is diagnosed with obstructive hypertrophic cardiomyopathy and paroxysmal atrial fibrillation, and is started on a medication. Changes in the action potential of ventricular muscle cells before and after administration of medication are shown in the image below

Black curve = Before administration of medication

Red curve = After administration of medication

The patient is most likely being treated with which of the following medications?

- ☐ A. Adenosine [3%]
- ☐ B. Digoxin [5%]
- ☐ C. Diltiazem [6%]
- ☒ D. Disopyramide [55%]
- ☐ E. Flecainide [15%]
- ☐ F. Lidocaine [10%]
- ☐ G. Propranolol [3%]

Omitted

Correct answer
D



55%
Answered correctly



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Explanation

The illustration shows predominant slowing of phase 0 depolarization and prolongation of phase 3 repolarization (red curve) of **ventricular action potential** after administration of the drug. This action is usually seen with the use of class IA antiarrhythmics drugs (quinidine, procainamide, and disopyramide).

Class I antiarrhythmic drugs block **sodium channels** and inhibit initial phase 0 depolarization of action potential, thereby slowing conduction. Class IA agents also have moderate potassium channel-blocking activity, leading to a slow rate of repolarization and prolongation of action potential duration in the cardiac myocytes.

(Choice A) Adenosine activates potassium channels and increases potassium conductance by interacting with A1 receptors on the surface of cardiac cells. This causes membrane hyperpolarization, resulting in transient slowing of the sinus rate and an increase in atrioventricular (AV) nodal conduction delay. Adenosine does not modulate the ventricular myocyte action potential.

(Choice B) Digoxin exerts its antiarrhythmic effects by increasing vagal output to the AV node and conduction system, thereby slowing conduction in these tissues. It does not alter the ventricular myocyte action potential, but it does increase intracellular calcium in ventricular myocytes, leading to increased cardiac contractility.

(Choice C) Calcium channel blockers are class IV antiarrhythmic drugs (eg, verapamil, diltiazem) that inhibit L-type calcium channels, slowing depolarization in the sinoatrial and AV nodes and decreasing calcium entry into cardiomyocytes. Calcium channel blockers slow the sinus rate, prolong AV node conduction, and depress myocardial contractility.

(Choice E) Flecainide is a class IC antiarrhythmic that strongly blocks sodium channels. It exhibits a slow rate of receptor dissociation that makes it more effective at higher rates of depolarization (use dependence). **Class IC drugs** slow phase 0 depolarization but do not affect action potential duration.

(Choice F) Lidocaine is a class IB antiarrhythmic drug that has weak sodium channel-blocking activity at rest; however, it is quite effective in

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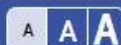
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Settings

(Choice A) Adenosine activates potassium channels and increases potassium conductance by interacting with A₁ receptors on the surface of cardiac cells. This causes membrane hyperpolarization, resulting in transient slowing of the sinus rate and an increase in atrioventricular (AV) nodal conduction delay. Adenosine does not modulate the ventricular myocyte action potential.

(Choice B) Digoxin exerts its antiarrhythmic effects by increasing vagal output to the AV node and conduction system, thereby slowing conduction in these tissues. It does not alter the ventricular myocyte action potential, but it does increase intracellular calcium in ventricular myocytes, leading to increased cardiac contractility.

(Choice C) Calcium channel blockers are class IV antiarrhythmic drugs (eg, verapamil, diltiazem) that inhibit L-type calcium channels, slowing depolarization in the sinoatrial and AV nodes and decreasing calcium entry into cardiomyocytes. Calcium channel blockers slow the sinus rate, prolong AV node conduction, and depress myocardial contractility.

(Choice E) Flecainide is a class IC antiarrhythmic that strongly blocks sodium channels. It exhibits a slow rate of receptor dissociation that makes it more effective at higher rates of depolarization (use dependence). **Class IC drugs** slow phase 0 depolarization but do not affect action potential duration.

(Choice F) Lidocaine is a class IB antiarrhythmic drug that has weak sodium channel-blocking activity at rest; however, it is quite effective in blocking sodium channels in depolarized cardiac myocytes. **Class IB drugs** also shorten phase 3 repolarization (blockade of "plateau" Na⁺ current), thereby decreasing action potential duration.

(Choice G) Propranolol is a beta-adrenergic blocking agent that slows conduction through the AV node and prolongs phase 4 depolarization in cardiac pacemaker cells. Beta blockers do not affect ventricular myocyte action potential; their primary site of action is on the AV node and cells with automaticity.

Educational objective:

The class IA antiarrhythmics (quinidine, procainamide, and disopyramide) are sodium channel-blocking agents that depress phase 0 depolarization. They also prolong repolarization due to moderate potassium channel- blocking activity, increasing action potential duration in cardiac myocytes.

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Exhibit Display

SA node action potential

The graph displays the SA node action potential. The y-axis represents membrane potential in millivolts (mV), ranging from -80 to 0. The x-axis represents time. The curve shows a slow depolarization (phase 4) from -80 mV towards 0 mV, followed by a rapid upstroke (phase 0) reaching a peak of approximately +10 mV, and then a rapid repolarization (phase 3) back to -80 mV. A dashed line at 0 mV indicates the resting potential level.

Phase	Membrane Potential (mV)	Ion Movement
0	Peak (+10)	Ca ²⁺ influx
3	Repolarization (-80)	K ⁺ efflux
4	Depolarization (-80)	Na ⁺ and Ca ²⁺ influx

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Ventricular muscle action potential

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-20

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A 64-year-old woman comes to the hospital due to sudden-onset right arm weakness and difficulty speaking, which completely resolved within 20 minutes. The patient has had no shaking movements, headache, nausea, photophobia, or anxiety. She has a history of hypertension and hypercholesterolemia and takes amlodipine and rosuvastatin, respectively. Her blood pressure is 125/70 mm Hg and pulse is 78/min and regular. Neurologic examination is unremarkable. Fingerstick glucose is within normal limits. ECG shows normal sinus rhythm. Carotid Doppler reveals mild left common carotid artery stenosis. MRI of the brain and echocardiogram are unremarkable. If the patient is started on an additional medication that is indicated for her condition, which of the following adverse effects is most likely to occur?

☐

A. Central nervous system depression

☐

B. Gastrointestinal bleeding

☐

C. Hyperpnea and vertigo

☐

D. Orthostatic hypotension

☐

E. Sexual dysfunction

☐

F. Urinary bladder cancer

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A 64-year-old woman comes to the hospital due to sudden-onset right arm weakness and difficulty speaking, which completely resolved within 20 minutes. The patient has had no shaking movements, headache, nausea, photophobia, or anxiety. She has a history of hypertension and hypercholesterolemia and takes amlodipine and rosuvastatin, respectively. Her blood pressure is 125/70 mm Hg and pulse is 78/min and regular. Neurologic examination is unremarkable. Fingerstick glucose is within normal limits. ECG shows normal sinus rhythm. Carotid Doppler reveals mild left common carotid artery stenosis. MRI of the brain and echocardiogram are unremarkable. If the patient is started on an additional medication that is indicated for her condition, which of the following adverse effects is most likely to occur?

☐ A. Central nervous system depression [2%]

☒ B. Gastrointestinal bleeding [63%]

☐ C. Hyperpnea and vertigo [2%]

☐ D. Orthostatic hypotension [28%]

☐ E. Sexual dysfunction [2%]

☐ F. Urinary bladder cancer [0%]

Omitted

Correct answer
B

63%

Answered correctly

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Explanation

This patient, with hypertension, hypercholesterolemia, and sudden-onset neurologic deficits (eg, right arm weakness, difficulty speaking) that fully

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This patient, with hypertension, hypercholesterolemia, and sudden-onset neurologic deficits (eg, right arm weakness, difficulty speaking) that fully resolved within minutes, most likely had a **transient ischemic attack (TIA)**. In addition to optimal blood pressure control and statin therapy, **low-dose aspirin** is commonly used to **prevent ischemic stroke** in patients with TIA. It works by irreversibly acetylating/inhibiting the cyclooxygenase (COX) enzymes. At low doses, aspirin predominantly **inhibits COX-1**, preventing platelet synthesis of thromboxane A2, which **impairs platelet aggregation** and reduces vasoconstriction.

At least 2 distinct COX-1-dependent mechanisms contribute to the increased risk of upper **gastrointestinal (GI) bleeding** associated with aspirin therapy: Inhibition of platelet aggregation and impairment of prostaglandin-dependent GI mucosal protection. The risk of upper GI bleeding increases with higher doses but is increased 2- to 3-fold even with low-dose aspirin. Proton pump inhibitors can help reduce the risk of upper GI bleeding in patients taking aspirin.

(Choice A) Central nervous system depression is commonly seen with benzodiazepine use as these agents potentiate the effect of GABA (a major inhibitory neurotransmitter) on GABA-A receptors.

(Choice C) Very high doses of aspirin can cause salicylism (eg, vertigo, tinnitus, hearing loss) and hyperpnea (stimulates respiratory drive). Hyperpnea may result in respiratory alkalosis, whereas systemic salicylate accumulation often leads to a concurrent metabolic acidosis.

(Choice D) Orthostatic hypotension may occur with use of antihypertensive medications due to vasodilation (eg, nitrates, calcium channel blockers) and volume depletion (eg, loop and thiazide diuretics).

(Choice E) Sexual dysfunction is a common side effect of antidepressants (eg, selective serotonin inhibitors, tricyclics) and some antihypertensives (eg, thiazide diuretics, spironolactone, clonidine).

(Choice F) Pioglitazone (a thiazolidinedione) increases insulin sensitivity in patients with type II diabetes mellitus by binding to peroxisome proliferator-activated receptors. Long-term use may be associated with urinary bladder cancer.

Educational objective:

Gastrointestinal (GI) mucosal injury and bleeding are the most common side effects of aspirin. These are due primarily to cyclooxygenase-1 inhibition, which results in impaired prostaglandin-dependent GI mucosal defense and decreased platelet aggregation.

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impairs platelet aggregation and reduces vasoconstriction.

At least 2 distinct COX-1-dependent mechanisms contribute to the increased risk of upper **gastrointestinal (GI) bleeding** associated with aspirin therapy: Inhibition of platelet aggregation and impairment of prostaglandin-dependent GI mucosal protection. The risk of upper GI bleeding increases with higher doses but is increased 2- to 3-fold even with low-dose aspirin. Proton pump inhibitors can help reduce the risk of upper GI bleeding in patients taking aspirin.

(Choice A)

 Central nervous system depression is commonly seen with benzodiazepine use as these agents potentiate the effect of GABA (a major inhibitory neurotransmitter) on GABA-A receptors.

(Choice C)

 Very high doses of aspirin can cause salicylism (eg, vertigo, tinnitus, hearing loss) and hyperpnea (stimulates respiratory drive). Hyperpnea may result in respiratory alkalosis, whereas systemic salicylate accumulation often leads to a concurrent metabolic acidosis.

(Choice D)

 Orthostatic hypotension may occur with use of antihypertensive medications due to vasodilation (eg, nitrates, calcium channel blockers) and volume depletion (eg, loop and thiazide diuretics).

(Choice E)

 Sexual dysfunction is a common side effect of antidepressants (eg, selective serotonin inhibitors, tricyclics) and some antihypertensives (eg, thiazide diuretics, spironolactone, clonidine).

(Choice F)

 Pioglitazone (a thiazolidinedione) increases insulin sensitivity in patients with type II diabetes mellitus by binding to peroxisome proliferator-activated receptors. Long-term use may be associated with urinary bladder cancer.

Educational objective:

Gastrointestinal (GI) mucosal injury and bleeding are the most common side effects of aspirin. These are due primarily to cyclooxygenase-1 inhibition, which results in impaired prostaglandin-dependent GI mucosal defense and decreased platelet aggregation.

References

Long-term use of aspirin and the risk of gastrointestinal bleeding.

Systematic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials.

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A 76-year-old man is brought to the emergency department with severe midsternal chest pain and diaphoresis. Past medical history is significant for hypertension, type 2 diabetes mellitus, and asymptomatic right carotid artery stenosis. His blood pressure is 120/70 mm Hg and pulse is 75/min. Lungs are clear on auscultation. ECG shows ST segment elevations greater than 1 mm in leads II, III, and aVF. The patient receives aspirin immediately upon arrival followed by alteplase and a low-dose beta blocker. A single dose of intravenous morphine is given for pain control. Several hours later, the patient is found to be comatose with asymmetric pupils and an irregular breathing pattern. What is the most likely cause of this patient's current condition?

- ☐ A. Carotid artery thrombosis
- ☐ B. Dissection of the ascending aorta
- ☐ C. Interventricular septum perforation
- ☐ D. Intracerebral hemorrhage
- ☐ E. Myocardial reperfusion injury
- ☐ F. Opioid overdose
- ☐ G. Pulmonary embolism

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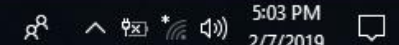
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A 76-year-old man is brought to the emergency department with severe midsternal chest pain and diaphoresis. Past medical history is significant for hypertension, type 2 diabetes mellitus, and asymptomatic right carotid artery stenosis. His blood pressure is 120/70 mm Hg and pulse is 75/min. Lungs are clear on auscultation. ECG shows ST segment elevations greater than 1 mm in leads II, III, and aVF. The patient receives aspirin immediately upon arrival followed by alteplase and a low-dose beta blocker. A single dose of intravenous morphine is given for pain control. Several hours later, the patient is found to be comatose with asymmetric pupils and an irregular breathing pattern. What is the most likely cause of this patient's current condition?

A. Carotid artery thrombosis [12%]

B. Dissection of the ascending aorta [1%]

C. Interventricular septum perforation [1%]

D. Intracerebral hemorrhage [57%]

E. Myocardial reperfusion injury [7%]

F. Opioid overdose [17%]

G. Pulmonary embolism [2%]

Omitted

Correct answer D

57%

Answered correctly

2 Seconds

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Explanation

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Correct answer D

57% Answered correctly

2 Seconds Time Spent

08/23/2018 Last Updated

Explanation

This patient's presentation of chest pain and diaphoresis along with a history of systemic atherosclerosis and type 2 diabetes mellitus is suggestive of acute coronary syndrome. ECG findings are consistent with an inferior ST elevation **myocardial infarction** (STEMI). Percutaneous coronary intervention (PCI) or **fibrinolysis** to achieve myocardial reperfusion is recommended for acute MI patients who present within 12 hours of symptom onset. **PCI is preferred** over fibrinolytic therapy due to lower rates of intracerebral hemorrhage (ICH) and recurrent MI; however, it may not be available at all institutions. In such cases, treatment with fibrinolytics (tenecteplase, alteplase) improves clinical outcomes in the absence of contraindications (eg, gastrointestinal bleeding, recent surgery).

Alteplase binds fibrin in the thrombus (clot) and **converts** entrapped **plasminogen to plasmin**. Plasmin hydrolyzes key bonds in the fibrin matrix **causing clot lysis** and restoration of coronary arterial blood flow. The most common adverse effect of fibrinolytic therapy is **hemorrhage**. This patient has signs of ICH, such as decreased level of consciousness, asymmetric pupils, and irregular breathing.

(Choice A) Carotid artery thrombosis can cause an ischemic stroke with fluctuating symptoms that may progress with periods of improvement. Abrupt onset of symptoms along with loss of consciousness after treatment with thrombolytics favors ICH over thrombotic stroke.

(Choice B) Aortic dissection typically presents with severe, tearing chest pain that radiates to the interscapular area. It occurs most commonly in patients with hypertension and Marfan/Ehlers-Danlos syndrome. Chest x-ray typically reveals a widened mediastinum.

(Choice C) Interventricular septum perforation results in a left-to-right shunt and symptoms of acute heart failure. It presents with chest pain, dyspnea, symptoms of cardiogenic shock, and a harsh holosystolic murmur on the left sternal border.

(Choice E) Reperfusion of ischemic myocardium may result in paradoxical cardiomyocyte dysfunction, a phenomenon known as reperfusion injury. This can occur in patients treated with PCI, thrombolytics, or coronary artery bypass grafting. Clinical manifestations include arrhythmias, myocardial stunning (prolonged but reversible contractile dysfunction), and myocyte death.

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contraindications (eg, gastrointestinal bleeding, recent surgery).

Alteplase binds fibrin in the thrombus (clot) and **converts** entrapped **plasminogen to plasmin**. Plasmin hydrolyzes key bonds in the fibrin matrix **causing clot lysis** and restoration of coronary arterial blood flow. The most common adverse effect of fibrinolytic therapy is **hemorrhage**. This patient has signs of ICH, such as decreased level of consciousness, asymmetric pupils, and irregular breathing.

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(Choice F) Opioid overdose typically presents with small, constricted pupils (miosis) and respiratory depression (respirations usually <12/min).

(Choice G) Pulmonary embolism (PE) presents with acute onset of dyspnea, pleuritic chest pain, and possibly hemoptysis. Tachycardia, hypotension, cyanosis, and loss of consciousness can occur when PE is severe.

Educational objective:

Fibrinolytic therapy for acute ST segment elevation myocardial infarction is a reasonable reperfusion technique for patients with no contraindications to thrombolysis. Fibrinolytic agents such as alteplase bind to fibrin in the thrombus (clot) and activate plasmin, which leads to thrombolysis. The most common adverse effect of thrombolysis is hemorrhage (eg, gastrointestinal, intracerebral).

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A physician is conducting a clinical trial for a new hemodynamic drug developed for a variety of indications. The drug's pharmacodynamic profile indicates that it is a pure adrenergic agonist with no significant antagonistic properties. It is infused into a volunteer, and hemodynamic parameters are recorded in the graphs below.

Administration of the drug to healthy individuals would most likely result in which of the following physiologic changes?

A. Decreased atrioventricular node conduction velocity

B. Decreased cardiac afterload

C. Decreased pulmonary capillary wedge pressure

D. Decreased venous tone

E. Increased renal perfusion

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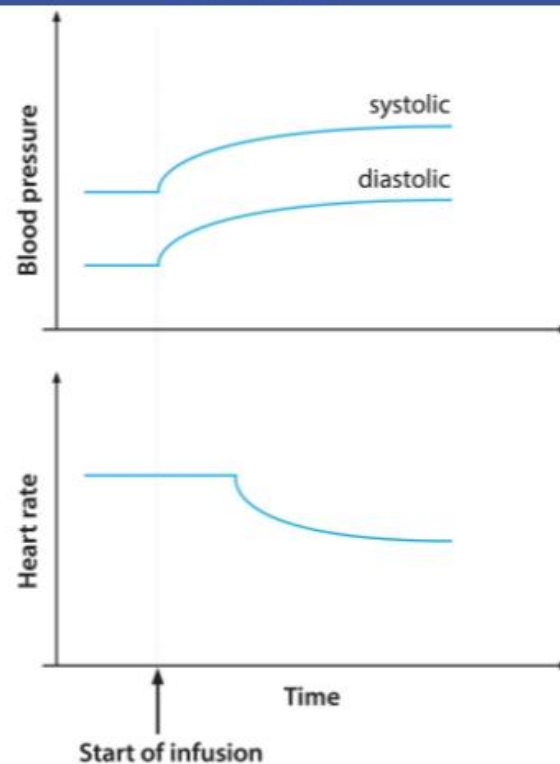


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A physician is conducting a clinical trial for a new hemodynamic drug developed for a variety of indications. The drug's pharmacodynamic profile indicates that it is a pure adrenergic agonist with no significant antagonistic properties. It is infused into a volunteer, and hemodynamic parameters are recorded in the graphs below.

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☐ C. Decreased pulmonary capillary wedge pressure

☐ D. Decreased venous tone

☐ E. Increased renal perfusion

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A physician is conducting a clinical trial for a new hemodynamic drug developed for a variety of indications. The drug's pharmacodynamic profile indicates that it is a pure adrenergic agonist with no significant antagonistic properties. It is infused into a volunteer, and hemodynamic parameters are recorded in the graphs below.

Administration of the drug to healthy individuals would most likely result in which of the following physiologic changes?

- ☒ A. Decreased atrioventricular node conduction velocity [56%]
- ☐ B. Decreased cardiac afterload [7%]
- ☐ C. Decreased pulmonary capillary wedge pressure [7%]
- ☐ D. Decreased venous tone [7%]
- ☐ E. Increased renal perfusion [20%]

Omitted

Correct answer
A



56%
Answered correctly



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Explanation

Administration of the drug caused an increase in systolic and diastolic blood pressures and a reflexive (delayed) decrease in heart rate; these are the typical effects of a **selective α_1 -adrenergic agonist** (eg, phenylephrine, methoxamine). Activation of α_1 -adrenoreceptors (in blood vessels of skin and viscera) leads to **vasoconstriction** and increased systemic blood pressure. Stimulation of baroreceptors in the carotid sinus and aortic arch causes a **reflexive increase in vagal influence** on the heart. The increased vagal tone results in inhibition of pacemaker activity of the

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Explanation

Administration of the drug caused an increase in systolic and diastolic blood pressures and a reflexive (delayed) decrease in heart rate; these are the typical effects of a **selective α_1 -adrenergic agonist** (eg, phenylephrine, methoxamine). Activation of α_1 -adrenoreceptors (in blood vessels of skin and viscera) leads to **vasoconstriction** and increased systemic blood pressure. Stimulation of baroreceptors in the carotid sinus and aortic arch causes a **reflexive increase in vagal influence** on the heart. The increased vagal tone results in inhibition of pacemaker activity of the sinoatrial node, slowed conduction through the atrioventricular node, and decreased myocardial contractility.

(Choice B) The vasoconstriction caused by α_1 -adrenergic agonists increases blood pressure and cardiac afterload, requiring increased myocardial effort to expel the blood.

(Choices C and D) Pulmonary capillary wedge pressure reflects left atrial pressure. It is increased after administration of α_1 -adrenergic agonists due to increases in cardiac afterload (elevates left ventricular end-diastolic pressure) and venous tone (results in augmented venous return).

(Choice E) α_1 -adrenergic agonists cause vasoconstriction of the renal and splanchnic arteries, decreasing perfusion to the kidneys and other viscera.

Educational objective:

α -adrenergic agonists increase systolic and diastolic blood pressure by stimulating α_1 -adrenoreceptors in the vascular walls, causing vasoconstriction. The elevated systemic blood pressure then causes a reflexive increase in vagal tone, resulting in decreased heart rate and slowed atrioventricular node conduction.

References

- Sympathetic neural mechanisms in human cardiovascular health and disease.
- Neural control of the circulation.
- WB4101- and CEC-sensitive positive inotropic actions of phenylephrine in rat cardiac muscle.

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A 66-year-old man is evaluated for recurrent syncope. He has had 3 episodes of dizziness and palpitations followed by brief loss of consciousness over the last 6 months. He has no chest pain or dyspnea. The patient has a history of hypertension and hyperlipidemia. There is no family history of sudden death. Initial evaluation shows normal ECG and echocardiogram. A cardiac electrophysiologic study is performed. During the study, intravenous infusion of a medication is administered and produces the responses shown below.

Which of the following medications was most likely administered to this patient?

A. Acetylcholine

B. Adenosine

C. Clonidine

D. Esmolol

E. Isoproterenol

F. Norepinephrine

G. Phenylephrine

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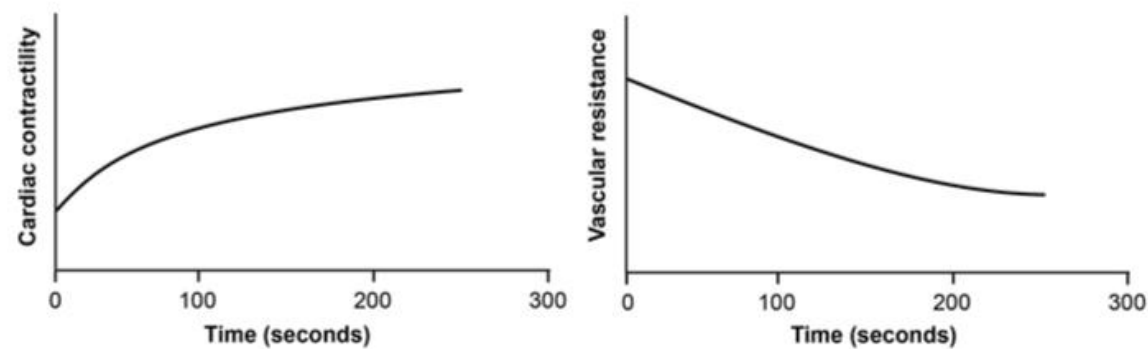


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C. Clonidine

D. Esmolol

E. Isoproterenol

F. Norepinephrine

G. Phenylephrine

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A 66-year-old man is evaluated for recurrent syncope. He has had 3 episodes of dizziness and palpitations followed by brief loss of consciousness over the last 6 months. He has no chest pain or dyspnea. The patient has a history of hypertension and hyperlipidemia. There is no family history of sudden death. Initial evaluation shows normal ECG and echocardiogram. A cardiac electrophysiologic study is performed. During the study, intravenous infusion of a medication is administered and produces the responses shown below.

Which of the following medications was most likely administered to this patient?

A. Acetylcholine [1%]

B. Adenosine [11%]

C. Clonidine [5%]

D. Esmolol [7%]

E. Isoproterenol [55%]

F. Norepinephrine [12%]

G. Phenylephrine [5%]

Omitted

Correct answer

E

55%

Answered correctly

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Explanation

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Explanation

The effects seen in the graphs above are most similar to those elicited by **isoproterenol**, a nonselective β adrenergic agonist. Isoproterenol **increases cardiac contractility** (positive inotropic effect) by acting on myocardial β -1 adrenergic receptors. It also binds to β -2 adrenergic receptors and causes vasodilation by relaxation of vascular smooth muscle, leading to **decreased vascular resistance** and mean arterial blood pressure. Isoproterenol has negligible effects on α -1 adrenergic receptors.

(Choice A) Acetylcholine binds to M_2 muscarinic receptors in the heart and M_3 receptors in the vasculature and causes decreased heart rate and conduction velocity and vasodilation (indirectly mediated by endothelial nitric oxide release). Acetylcholine has no significant effect on ventricular contractility.

(Choice B) Adenosine acts on A_1 receptors on cardiac cells and activates potassium channels, increasing potassium conductance. This leads to transient conduction delay through the atrioventricular node. Adenosine can also cause peripheral vasodilation, but it attenuates the adrenergic-mediated increase in myocardial contractility.

(Choice C) Clonidine stimulates α_2 adrenoceptors in the brainstem, resulting in reduced sympathetic outflow from the central nervous system, leading to a decrease in peripheral vascular resistance, heart rate, and blood pressure. It has no effect on cardiac contractility.

(Choice D) Esmolol is a selective β -1 adrenergic blocking agent with negative inotropic and chronotropic effects. It would cause a decrease in cardiac contractility.

(Choice F) Norepinephrine acts on α -1 receptors, causing vasoconstriction and an increase in systemic vascular resistance. Norepinephrine also acts as a weak agonist at β -1 receptors, with a modest increase in myocardial contractility.

(Choice G) Phenylephrine is a sympathomimetic drug with pure α adrenergic agonist activity. Infusion of this drug causes vasoconstriction with an increase in systemic vascular resistance.

Educational objective:

Isoproterenol is a β -1 and β -2 adrenergic receptor agonist that causes increased myocardial contractility and decreased systemic vascular

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The effects seen in the graphs above are most similar to those elicited by **isoproterenol**, a nonselective β adrenergic agonist. Isoproterenol **increases cardiac contractility** (positive inotropic effect) by acting on myocardial β -1 adrenergic receptors. It also binds to β -2 adrenergic receptors and causes vasodilation by relaxation of vascular smooth muscle, leading to **decreased vascular resistance** and mean arterial blood pressure. Isoproterenol has negligible effects on α -1 adrenergic receptors.

(Choice A) Acetylcholine binds to M_2 muscarinic receptors in the heart and M_3 receptors in the vasculature and causes decreased heart rate and conduction velocity and vasodilation (indirectly mediated by endothelial nitric oxide release). Acetylcholine has no significant effect on ventricular contractility.

(Choice B) Adenosine acts on A_1 receptors on cardiac cells and activates potassium channels, increasing potassium conductance. This leads to transient conduction delay through the atrioventricular node. Adenosine can also cause peripheral vasodilation, but it attenuates the adrenergic-mediated increase in myocardial contractility.

(Choice C) Clonidine stimulates α_2 adrenoceptors in the brainstem, resulting in reduced sympathetic outflow from the central nervous system, leading to a decrease in peripheral vascular resistance, heart rate, and blood pressure. It has no effect on cardiac contractility.

(Choice D) Esmolol is a selective β -1 adrenergic blocking agent with negative inotropic and chronotropic effects. It would cause a decrease in cardiac contractility.

(Choice F) Norepinephrine acts on α -1 receptors, causing vasoconstriction and an increase in systemic vascular resistance. Norepinephrine also acts as a weak agonist at β -1 receptors, with a modest increase in myocardial contractility.

(Choice G) Phenylephrine is a sympathomimetic drug with pure α adrenergic agonist activity. Infusion of this drug causes vasoconstriction with an increase in systemic vascular resistance.

Educational objective:

Isoproterenol is a β -1 and β -2 adrenergic receptor agonist that causes increased myocardial contractility and decreased systemic vascular resistance.

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A 47-year-old man with known coronary artery disease comes to the emergency department with chest tightness, sweating, and palpitations. His symptoms began abruptly 2 hours ago while he was at work. Six months ago, the patient underwent percutaneous angioplasty of the right coronary artery. Past medical history also includes anxiety and panic attacks. Blood pressure is 180/90 mm Hg and pulse is 110/min with a regular rhythm. An esmolol infusion produces rapid symptom relief and heart rate slowing. Which of the following portions of the ECG will be affected most significantly by the medication?

A. A

B. B

C. C

D. D

E. E

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Exhibit Display

Normal ECG

The image shows a normal ECG waveform. The P wave is followed by a QRS complex and a T wave. The intervals are labeled as follows: A is the QT interval (from the start of the QRS complex to the end of the T wave), B is the PR interval (from the end of the P wave to the start of the QRS complex), C is the ST interval (from the end of the QRS complex to the start of the T wave), D is the QTc interval (from the start of the QRS complex to the end of the T wave), and E is the QTd interval (from the end of the P wave to the end of the T wave).

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Text Zoom

A 47-year-old man with known coronary artery disease comes to the emergency department with chest tightness, sweating, and palpitations. His symptoms began abruptly 2 hours ago while he was at work. Six months ago, the patient underwent percutaneous angioplasty of the right coronary artery. Past medical history also includes anxiety and panic attacks. Blood pressure is 180/90 mm Hg and pulse is 110/min with a regular rhythm. An esmolol infusion produces rapid symptom relief and heart rate slowing. Which of the following portions of the ECG will be affected most significantly by the medication?

A. A

B. B

C. C

D. D

E. E

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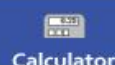
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A 47-year-old man with known coronary artery disease comes to the emergency department with chest tightness, sweating, and palpitations. His symptoms began abruptly 2 hours ago while he was at work. Six months ago, the patient underwent percutaneous angioplasty of the right coronary artery. Past medical history also includes anxiety and panic attacks. Blood pressure is 180/90 mm Hg and pulse is 110/min with a regular rhythm. An esmolol infusion produces rapid symptom relief and heart rate slowing. Which of the following portions of the ECG will be affected most significantly by the medication?

- ☐ A. A [4%]
- ☒ B. B [63%]
- ☐ C. C [15%]
- ☐ D. D [4%]
- ☐ E. E [12%]

Omitted

Correct answer
B



63%
Answered correctly



2 Seconds
Time Spent



12/27/2018
Last Updated

Explanation

On an ECG, the P wave represents atrial depolarization and the QRS complex represents ventricular depolarization. The **PR interval** is the period from the beginning of atrial depolarization (**start of P wave**) to the beginning of ventricular depolarization (**start of QRS complex**). The longer the PR interval, the longer it takes for an electrical stimulus to travel from the SA node to the ventricles via the AV node, bundle of His, and

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Explanation

On an ECG, the P wave represents atrial depolarization and the QRS complex represents ventricular depolarization. The **PR interval** is the period from the beginning of atrial depolarization (**start of P wave**) to the beginning of ventricular depolarization (**start of QRS complex**). The longer the PR interval, the longer it takes for an electrical stimulus to travel from the SA node to the ventricles via the AV node, bundle of His, and fascicular branches. Drugs that slow AV nodal conduction, such as **beta blockers**, will **prolong** the PR interval. Beta blockers (except sotalol, which also has class III properties) do not have any specific effects on QRS or QT interval durations.

(Choice A) The T wave represents ventricular repolarization. It is not affected by beta-adrenergic blockers. Myocardial ischemia can cause T wave inversion.

(Choice C) The QRS complex represents ventricular depolarization. It is not affected by beta-adrenergic blockers. A widened QRS complex can occur in the setting of ventricular automaticity, left or right bundle branch blocks, or ventricular pacemakers.

(Choice D) The ST-segment is a period of electrocardiographic inactivity that extends between ventricular depolarization and repolarization. It is not affected by beta-adrenergic blockers. ST-segment elevation or depression is usually a sign of myocardial ischemia.

(Choice E) The QT interval represents the time needed for ventricular depolarization and repolarization (ventricular electrical systole). Long QT syndrome can be congenital or acquired. Antiarrhythmics such as quinidine and sotalol are most frequently associated with acquired long QT. However, most beta blockers have a minimal effect on the resting QT interval.

Educational objective:

Beta blockers decrease AV nodal conduction, leading to an increased AV nodal refractory period. This correlates to PR interval prolongation on an ECG.

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A 50-year-old man has recurrent episodes of paroxysmal atrial fibrillation accompanied by uncomfortable palpitations and chest pressure. Echocardiogram reveals normal biventricular function and no significant valvular disease. Coronary angiography reveals no obstructive coronary artery disease. The patient is started on medication to reduce his symptoms. Two weeks later, he is seen in the emergency department for lightheadedness, weakness, and presyncope. ECG reveals sinus bradycardia at a rate of 53/min with QTc prolongation (508 msec). Telemetry monitoring reveals a short episode of self-resolved torsades de pointes. Which of the following medications was most likely used to treat this patient's palpitations?

☐

A. Diltiazem

☐

B. Metoprolol

☐

C. Mexiletine

☐

D. Ranolazine

☐

E. Sotalol

Submit

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Text Zoom

A 50-year-old man has recurrent episodes of paroxysmal atrial fibrillation accompanied by uncomfortable palpitations and chest pressure. Echocardiogram reveals normal biventricular function and no significant valvular disease. Coronary angiography reveals no obstructive coronary artery disease. The patient is started on medication to reduce his symptoms. Two weeks later, he is seen in the emergency department for lightheadedness, weakness, and presyncope. ECG reveals sinus bradycardia at a rate of 53/min with QTc prolongation (508 msec). Telemetry monitoring reveals a short episode of self-resolved torsades de pointes. Which of the following medications was most likely used to treat this patient's palpitations?

☐ A. Diltiazem [12%]

☐ B. Metoprolol [4%]

☐ C. Mexiletine [7%]

☐ D. Ranolazine [3%]

☒ E. Sotalol [71%]

Omitted

Correct answer
E

71%

Answered correctly

2 Seconds

Time Spent

09/12/2018

Last Updated

Explanation

Paroxysmal atrial fibrillation is usually treated with rate or rhythm control strategies. Rate control uses AV nodal-blocking drugs (beta blockers, calcium channel blockers) to prevent rapid ventricular response, whereas **rhythm control** attempts to maintain sinus rhythm with antiarrhythmic

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Explanation

Paroxysmal atrial fibrillation is usually treated with rate or rhythm control strategies. Rate control uses AV nodal-blocking drugs (beta blockers, calcium channel blockers) to prevent rapid ventricular response, whereas **rhythm control** attempts to maintain sinus rhythm with antiarrhythmic drugs (eg, sotalol, flecainide, amiodarone).

The QT interval represents both ventricular depolarization and repolarization (total duration of ventricular action potential). However, ventricular depolarization normally contributes only a small amount of time to the interval, and in practice, the QT interval is primarily used as a measure of ventricular repolarization. **Class III antiarrhythmics** (eg, sotalol, amiodarone, dofetilide) predominantly **block potassium channels** and inhibit outward repolarizing currents during phase 3 of the cardiomyocyte action potential. This leads to increased action potential duration and **QT interval prolongation**, which predisposes to the development of polymorphic ventricular tachycardia (**torsades de pointes** [TdP]). Amiodarone has a lesser proarrhythmic effect than other class III drugs; therefore, TdP is less frequently observed with amiodarone than with sotalol.

(Choice A) Diltiazem is a class IV antiarrhythmic drug (calcium channel blocker) that inhibits L-type calcium channels during phase 2 (**cardiomyocyte action potential**) and phase 0 (nodal action potential) depolarization. It slows the sinus rate, prolongs conduction through the AV node, and depresses myocardial contractility (negative inotropic effect) but does not prolong the QT interval.

(Choice B) Metoprolol is a class II antiarrhythmic drug that is a selective beta-1 receptor antagonist. It acts as a negative inotropic and chronotropic agent by decreasing myocardial contractility and heart rate. Unlike sotalol, beta blockers do not have any potassium channel-blocking properties and do not prolong the QT interval.

(Choice C) Mexiletine is a class IB antiarrhythmic drug that blocks sodium channels, inhibiting the initial depolarization phase (phase 0) of the cardiomyocyte action potential. It is occasionally used to maintain sinus rhythm in patients with paroxysmal symptomatic atrial fibrillation, but it does not prolong the QT interval.

(Choice D) Ranolazine is an antianginal agent and exerts its effect by inhibiting the late phase of inward sodium channels in ischemic cardiac myocytes. It also blocks potassium channels and causes a dose-dependent increase in QT interval; however, TdP has not been reported in ranolazine use.

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Settings

Interval prolongation, which predisposes to the development of polymorphic ventricular tachycardia (**torsades de pointes** [TdP]). Amiodarone has a lesser proarrhythmic effect than other class III drugs; therefore, TdP is less frequently observed with amiodarone than with sotalol.

(Choice A) Diltiazem is a class IV antiarrhythmic drug (calcium channel blocker) that inhibits L-type calcium channels during phase 2 (**cardiomyocyte action potential**) and phase 0 (nodal action potential) depolarization. It slows the sinus rate, prolongs conduction through the AV node, and depresses myocardial contractility (negative inotropic effect) but does not prolong the QT interval.

(Choice B) Metoprolol is a class II antiarrhythmic drug that is a selective beta-1 receptor antagonist. It acts as a negative inotropic and chronotropic agent by decreasing myocardial contractility and heart rate. Unlike sotalol, beta blockers do not have any potassium channel-blocking properties and do not prolong the QT interval.

(Choice C) Mexiletine is a class IB antiarrhythmic drug that blocks sodium channels, inhibiting the initial depolarization phase (phase 0) of the cardiomyocyte action potential. It is occasionally used to maintain sinus rhythm in patients with paroxysmal symptomatic atrial fibrillation, but it does not prolong the QT interval.

(Choice D) Ranolazine is an antianginal agent and exerts its effect by inhibiting the late phase of inward sodium channels in ischemic cardiac myocytes. It also blocks potassium channels and causes a dose-dependent increase in QT interval; however, TdP has not been reported in ranolazine use.

Educational objective:

Sotalol has both beta adrenergic-blocking and class III antiarrhythmic (K⁺ channel-blocking) properties and is occasionally used in treatment of atrial fibrillation. Major side effects of sotalol include bradycardia, proarrhythmia, and most commonly torsades de pointes due to QT interval prolongation.

References

- [Drug-induced arrhythmia: pharmacogenomic prescribing?](#)

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A 71-year-old man with chronic stable angina comes to the office for routine follow-up. He has occasional episodes of chest pain that improve after taking sublingual nitroglycerin. The patient also has a history of hypertension and hypercholesterolemia and takes multiple medications for his conditions. Blood pressure is 140/80 mm Hg and pulse is 68/min and regular. Examination reveals normal heart sounds. While discussing a plan to start isosorbide dinitrate therapy, the patient becomes concerned about the high dose of oral isosorbide dinitrate compared to sublingual nitroglycerin. Which of the following is the most likely reason for using a high dose of oral nitrate?

A. Drug tolerance prevention

B. High first-pass metabolism

C. High serum protein binding

D. High volume of distribution

E. Low intestinal absorption

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Text Zoom

A 71-year-old man with chronic stable angina comes to the office for routine follow-up. He has occasional episodes of chest pain that improve after taking sublingual nitroglycerin. The patient also has a history of hypertension and hypercholesterolemia and takes multiple medications for his conditions. Blood pressure is 140/80 mm Hg and pulse is 68/min and regular. Examination reveals normal heart sounds. While discussing a plan to start isosorbide dinitrate therapy, the patient becomes concerned about the high dose of oral isosorbide dinitrate compared to sublingual nitroglycerin. Which of the following is the most likely reason for using a high dose of oral nitrate?

A. Drug tolerance prevention [6%]

B. High first-pass metabolism [77%]

C. High serum protein binding [2%]

D. High volume of distribution [4%]

E. Low intestinal absorption [8%]

Omitted

Correct answer
B

77%

Answered correctly

3 Seconds

Time Spent

09/12/2018

Last Updated

Explanation

Nitrates, beta blockers, and calcium channel blockers are the mainstay of therapy for patients with chronic stable angina. Sublingual nitroglycerin is the therapy of choice in acute episodes for immediate relief of angina and for prevention of angina prior to engaging in strenuous physical activity. Chronic nitrate therapy with long-acting oral formulations (isosorbide dinitrate or mononitrate) is used to prevent recurrent anginal episodes in patients with chronic stable angina.

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Explanation

Nitrates, beta blockers, and calcium channel blockers are the mainstay of therapy for patients with chronic stable angina. Sublingual nitroglycerin is the therapy of choice in acute episodes for immediate relief of angina and for prevention of angina prior to engaging in strenuous physical activity. Chronic nitrate therapy with long-acting oral formulations (isosorbide dinitrate or mononitrate) is used to prevent recurrent anginal episodes in patients with chronic stable angina.

Sublingual nitroglycerin is absorbed rapidly from oral mucosa directly into the venous circulation and has a rapid onset of action within 2-5 minutes. Long-acting **isosorbide dinitrate** is absorbed via the gastrointestinal tract and undergoes **extensive first-pass metabolism** in the liver prior to release in the systemic circulation. This leads to **low bioavailability** and the need for much higher doses of oral formulations as compared to sublingual nitroglycerin.

(Choice A) Chronic nitrate therapy on a regular basis leads to nitrate tolerance, with attenuation of blood pressure response and anti-anginal effects. Higher doses do not prevent nitrate tolerance. On the contrary, use of sublingual nitroglycerin on an intermittent, as-needed basis (nitrate-free intervals) prevents the development of nitrate tolerance.

(Choices C and D) The oral nitrate preparations do not have high serum protein binding or volume of distribution.

(Choice E) Isosorbide dinitrate has rapid and nearly complete intestinal absorption. Its low bioavailability is due to considerable first-pass hepatic metabolism.

Educational objective:

Isosorbide dinitrate has a low bioavailability due to extensive first-pass hepatic metabolism prior to release in systemic circulation. Sublingual nitroglycerin is absorbed directly from oral mucosa into the venous circulation and has a higher bioavailability.

References

- Clinical pharmacokinetics of nitrates.

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A 60-year-old man who was recently diagnosed with hypertension comes to the office for follow-up. He was treated with lisinopril but stopped a week ago due to a dry, nagging cough. Past medical history is notable for type 2 diabetes mellitus with moderately increased albuminuria but normal creatinine clearance. His other medications include metformin and rosuvastatin. The patient does not smoke or drink alcohol. His blood pressure is 150/92 mm Hg. BMI is 31 kg/m². Physical examination, including the heart and lungs, is unremarkable. Which of the following is the best treatment for this patient's hypertension?

☐ A. Diltiazem

☐ B. Hydralazine

☐ C. Metoprolol

☐ D. Ramipril

☐ E. Valsartan

Submit

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A 60-year-old man who was recently diagnosed with hypertension comes to the office for follow-up. He was treated with lisinopril but stopped a week ago due to a dry, nagging cough. Past medical history is notable for type 2 diabetes mellitus with moderately increased albuminuria but normal creatinine clearance. His other medications include metformin and rosuvastatin. The patient does not smoke or drink alcohol. His blood pressure is 150/92 mm Hg. BMI is 31 kg/m². Physical examination, including the heart and lungs, is unremarkable. Which of the following is the best treatment for this patient's hypertension?

☐ A. Diltiazem [2%]

☐ B. Hydralazine [3%]

☐ C. Metoprolol [5%]

☐ D. Ramipril [3%]

☒ E. Valsartan [85%]

Omitted

Correct answer

E

85%

Answered correctly

3 Seconds

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Explanation

Diabetes causes impaired autoregulation of glomerular blood flow, leading to significant elevations of intraglomerular pressures and chronic glomerular injury. Patients with diabetes and hypertension are at especially high long-term risk for chronic kidney disease. Angiotensin-converting enzyme (ACE) inhibitors (eg, lisinopril) cause preferential dilation of the **glomerular efferent arteriole**, lowering intraglomerular pressures and reducing the risk of chronic glomerular injury.

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Explanation

Diabetes causes impaired autoregulation of glomerular blood flow, leading to significant elevations of intraglomerular pressures and chronic glomerular injury. Patients with diabetes and hypertension are at especially high long-term risk for chronic kidney disease. Angiotensin-converting enzyme (ACE) inhibitors (eg, lisinopril) cause preferential dilation of the **glomerular efferent arteriole**, lowering intraglomerular pressures and reducing the risk of chronic glomerular injury.

In addition to converting angiotensin I to angiotensin II, ACE normally degrades **bradykinin** and substance P. Inhibition of ACE leads to elevated bradykinin and substance P levels and a nonproductive cough. **Angiotensin receptor blockers** (ARBs) have hemodynamic effects similar to those of ACE inhibitors but do not affect bradykinin levels and do not cause a cough. Replacing this patient's ACE inhibitor with an ARB (eg, losartan, valsartan) will eliminate the cough while still providing the same long-term renovascular benefits.

(Choices A, B, and C) Careful blood pressure control can help reduce the long-term risk of kidney injury, regardless of the agent used. However, none of these drugs are as effective as ACE inhibitors or ARBs for preventing the progression of chronic kidney disease.

(Choice D) Replacement of one ACE inhibitor with another carries a high likelihood of inducing the same nonproductive cough.

Educational objective:

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) reduce the risk of chronic kidney disease in patients with hypertension and diabetes. ACE inhibitors raise levels of bradykinin and can cause a nonproductive cough, an effect not seen with ARBs.

References

- The RAAS in the pathogenesis and treatment of diabetic nephropathy.
- Angiotensin-converting enzyme inhibitor-induced cough: ACCP evidence-based clinical practice guidelines.

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Exhibit Display

Renin-angiotensin-aldosterone system & antihypertensives

• ↓ Renal blood flow
• Sympathetic stimulation

↓
β-blockers

Angiotensinogen

↓
Renin

Direct renin inhibitor

↓
Angiotensin I

↓
ACE

ACE inhibitors

↓
Angiotensin II

ARBs

↓
Aldosterone

Aldosterone antagonist

↓
↑ Renal Na⁺ reabsorption

Systemic vasoconstriction

Efferent arteriolar vasoconstriction

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β-blockers

Angiotensin I

ACE — **ACE inhibitors**

Angiotensin II — **ARBs**

Aldosterone — **Aldosterone antagonist**

↑ Renal Na⁺ reabsorption

Systemic vasoconstriction

Efferent arteriolar vasoconstriction

↑ Blood pressure

Maintains GFR

GFR = glomerular filtration rate.
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A 68-year-old man comes to the emergency department due to lightheadedness, generalized weakness, and palpitations. The patient has a prolonged history of hypertension and takes amlodipine. He does not use tobacco or alcohol. His blood pressure is 110/60 mm Hg and pulse is 144/min and irregular. ECG shows an irregularly irregular rhythm and absent P waves. The patient is started on beta blocker therapy for rate control, with improvement in his heart rate. Long-term anticoagulation is initiated to prevent atrial thrombus formation, and he is eventually discharged home on warfarin. Which of the following is the best test to monitor the anticoagulation effect of warfarin in this patient?

☐ A. Activated partial thromboplastin time

☐ B. Bleeding time

☐ C. Fibrin split products

☐ D. Fibrinogen levels

☐ E. Prothrombin time

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Block Time Remaining: 00:02:12

TUTOR

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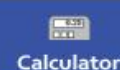
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A 68-year-old man comes to the emergency department due to lightheadedness, generalized weakness, and palpitations. The patient has a prolonged history of hypertension and takes amlodipine. He does not use tobacco or alcohol. His blood pressure is 110/60 mm Hg and pulse is 144/min and irregular. ECG shows an irregularly irregular rhythm and absent P waves. The patient is started on beta blocker therapy for rate control, with improvement in his heart rate. Long-term anticoagulation is initiated to prevent atrial thrombus formation, and he is eventually discharged home on warfarin. Which of the following is the best test to monitor the anticoagulation effect of warfarin in this patient?

- ☐ A. Activated partial thromboplastin time [12%]
- ☐ B. Bleeding time [2%]
- ☐ C. Fibrin split products [1%]
- ☐ D. Fibrinogen levels [0%]
- ☒ E. Prothrombin time [83%]

Omitted

Correct answer
E 83%
Answered correctly 2 Seconds
Time Spent 12/12/2018
Last Updated

Explanation

This patient's ECG (irregularly irregular rhythm with absent P waves) suggests **atrial fibrillation (AF)**, which alters cardiac flow dynamics, making thrombus formation more common. If this thrombus detaches from the atrial wall, there is a risk of stroke. The oral anticoagulant **warfarin** (Coumadin) reduces thrombus formation risk by inhibiting the activation of vitamin K-dependent clotting factors II, VII, IX, and X (**vitamin K**

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This patient's ECG (irregularly irregular rhythm with absent P waves) suggests **atrial fibrillation (AF)**, which alters cardiac flow dynamics, making thrombus formation more common. If this thrombus detaches from the atrial wall, there is a risk of stroke. The oral anticoagulant **warfarin** (Coumadin) reduces thrombus formation risk by inhibiting the activation of vitamin K-dependent clotting factors II, VII, IX, and X (**vitamin K antagonist**). This leads to decreased levels of these factors, particularly **factor VII**, and therefore prolongs the **prothrombin time (PT)**. Another useful laboratory value is the **International Normalized Ratio (INR)**, a ratio of the patient's PT to a control (usual INR target for AF: 2.0-3.0). Examples of indications include AF, deep venous thrombosis, and pulmonary thromboembolism. Outpatients who take warfarin typically have their INR checked every few weeks (more frequently initially).

The most common side effect is excessive anticoagulation leading to bleeding (which can require vitamin K and fresh frozen plasma if rapid reversal is needed). Skin necrosis can occur during the first few days of treatment due to a transient hypercoagulable state (reduction in protein C anticoagulant activity before affecting other factors' procoagulant activity); for this reason, heparin is typically administered temporarily at the start of warfarin therapy ("heparin bridge"). Warfarin should not be used during pregnancy because it is teratogenic and can cause fetal bleeding.

(Choice A) Activated partial thromboplastin time (aPTT) is used to monitor unfractionated heparin, which primarily affects the intrinsic coagulation pathway.

(Choice B) Bleeding time is used for the assessment of platelet function. Increased bleeding time can be seen with thrombocytopenia, von Willebrand disease, defects of platelet aggregation, disseminated intravascular coagulation (DIC), and aspirin therapy.

(Choices C and D) The combination of a decreased fibrinogen level and the presence of fibrin split products (such as D-dimer) is characteristic of DIC.

Educational objective:

Warfarin is an oral anticoagulant that inhibits the carboxylation of vitamin K-dependent coagulation factors II, VII, IX, and X. It is used in atrial fibrillation, deep venous thrombosis, and pulmonary thromboembolism. Prothrombin time (PT)/International Normalized Ratio (INR) should be monitored regularly during treatment with warfarin. Activated partial thromboplastin time (aPTT) is used for monitoring unfractionated heparin.

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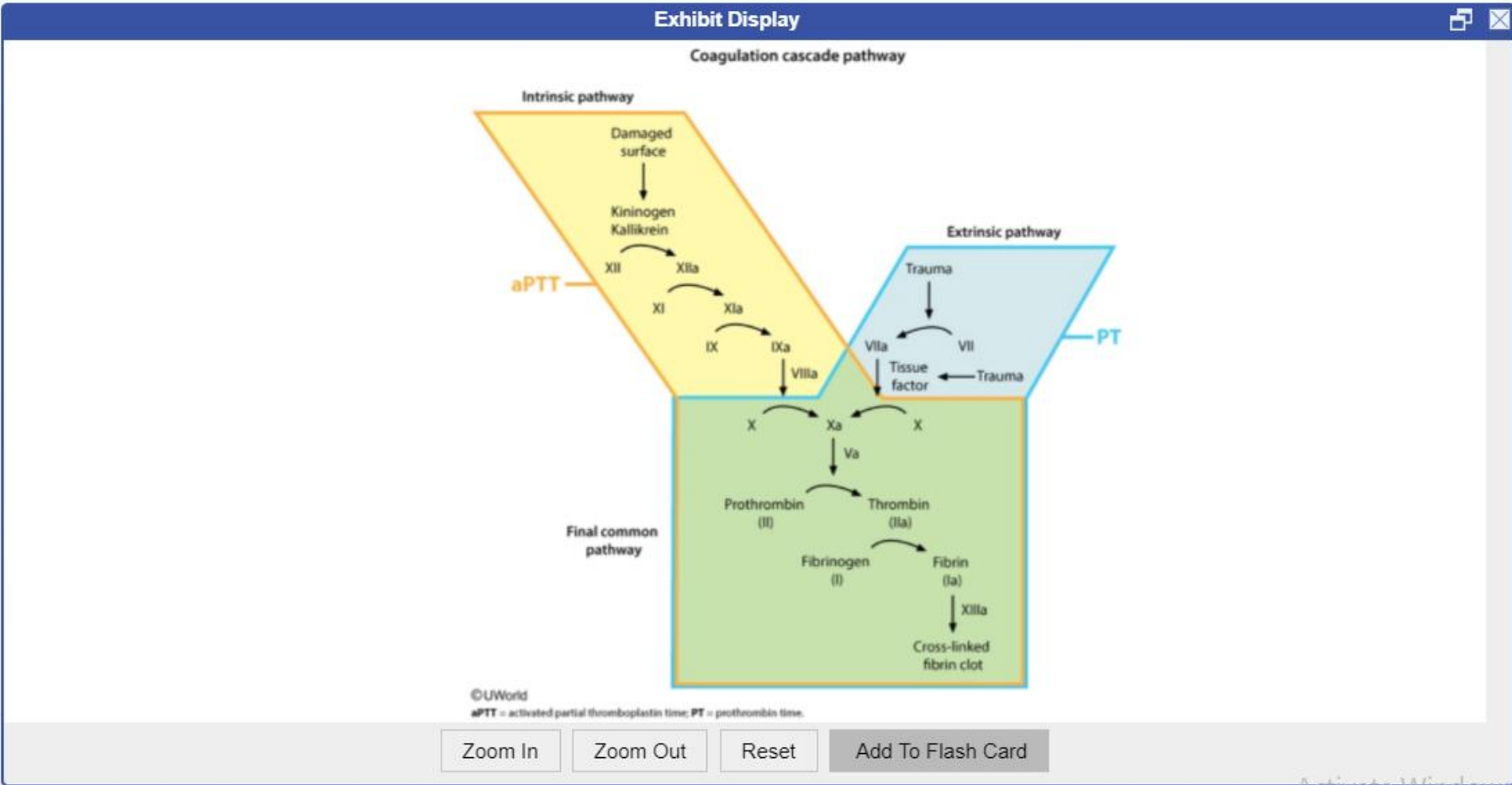
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A 54-year-old man is transferred to the hospital from his cardiologist's office due to atrial fibrillation with rapid ventricular response. His symptoms began 24 hours earlier with palpitations, lightheadedness, and chest tightness. The patient has had similar episodes several times during the last year. Past history is notable for mitral valve repair 3 years ago for severe symptomatic mitral regurgitation. The patient undergoes direct current cardioversion due to worsening hemodynamic instability, with resolution of the arrhythmia and all associated symptoms. He is considered for long-term amiodarone therapy to prevent future arrhythmic episodes. Which of the following should be tested before initiating this medication?

A. 24-hour urinary cortisol

B. 24-hour urinary metanephrines

C. Oral glucose tolerance test

D. Serum prolactin

E. Serum testosterone

F. Serum TSH

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A 54-year-old man is transferred to the hospital from his cardiologist's office due to atrial fibrillation with rapid ventricular response. His symptoms began 24 hours earlier with palpitations, lightheadedness, and chest tightness. The patient has had similar episodes several times during the last year. Past history is notable for mitral valve repair 3 years ago for severe symptomatic mitral regurgitation. The patient undergoes direct current cardioversion due to worsening hemodynamic instability, with resolution of the arrhythmia and all associated symptoms. He is considered for long-term amiodarone therapy to prevent future arrhythmic episodes. Which of the following should be tested before initiating this medication?

- ☐ A. 24-hour urinary cortisol [4%]
- ☐ B. 24-hour urinary metanephrines [9%]
- ☐ C. Oral glucose tolerance test [7%]
- ☐ D. Serum prolactin [1%]
- ☐ E. Serum testosterone [1%]
- ☒ F. Serum TSH [77%]

Omitted

Correct answer
F



77%
Answered correctly



3 Seconds
Time Spent



09/02/2018
Last Updated

Explanation

Amiodarone is a class III anti-arrhythmic agent used to suppress life-threatening rhythm disturbances. Because it is 40% iodine by weight, amiodarone can cause a number of alterations in thyroid function. It can cause **hypothyroidism** due to decreased production of thyroid

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Question Id: 625

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Explanation

Amiodarone is a class III anti-arrhythmic agent used to suppress life-threatening rhythm disturbances. Because it is 40% iodine by weight, amiodarone can cause a number of alterations in thyroid function. It can cause **hypothyroidism** due to decreased production of thyroid hormone. Individuals with pre-existing autoimmune thyroid disease are at greatest risk and so should be screened for subclinical hypothyroidism with a **serum TSH** assay prior to initiating amiodarone therapy. Amiodarone can also cause **hyperthyroidism** due to increased **thyroid hormone synthesis** or **destructive thyroiditis** with release of preformed thyroid hormone.

(Choices A and B) Amiodarone is not associated with altered function of the adrenal cortex or medulla.

(Choice C) The oral glucose tolerance test is used to screen for diabetes mellitus, primarily in pregnant women. Amiodarone is not associated with significant alterations in insulin sensitivity or blood glucose levels.

(Choice D) Release of prolactin is primarily regulated by inhibitory effects of dopamine from the hypothalamus. Release is stimulated to a small degree by thyrotropin-releasing hormone and therefore may be mildly affected by amiodarone. However, these effects would not be clinically significant.

(Choice E) Amiodarone can cause erectile dysfunction, which may be related to its alpha and beta adrenoreceptor blocking effect. Amiodarone does not significantly alter serum testosterone levels.

Educational objective:
Amiodarone is 40% iodine by weight. It can cause hypothyroidism due to decreased production of thyroid hormone. Amiodarone can also cause hyperthyroidism due to increased thyroid hormone synthesis or destructive thyroiditis with release of preformed thyroid hormone.

References

- Effects of amiodarone therapy on thyroid function.

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Question Id: 14844



A 52-year-old woman with a history of locally advanced breast cancer comes to the office for follow-up. The patient is undergoing trastuzumab-based chemotherapy but has not received radiation therapy. She has no symptoms except mild fatigue. Blood pressure is 120/72 mm Hg and pulse is 85/min and regular. The patient is afebrile. Transthoracic echocardiography reveals a left ventricular ejection fraction of 40% with no evidence of valvular disease. Cardiac assessment prior to chemotherapy initiation was normal. Which of the following pathologic findings is most likely to be present in this patient's heart?

- ☐ A. Abnormal protein accumulation in the extracellular space
- ☐ B. Focal ischemic cardiomyocyte necrosis
- ☐ C. Myocardial tumor cell infiltration
- ☐ D. Patchy cardiomyocyte necrosis with diffuse myocardial fibrosis
- ☐ E. Reduced cardiomyocyte contractility with no fibrosis

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Block Time Remaining: 00:02:17

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A 52-year-old woman with a history of locally advanced breast cancer comes to the office for follow-up. The patient is undergoing trastuzumab-based chemotherapy but has not received radiation therapy. She has no symptoms except mild fatigue. Blood pressure is 120/72 mm Hg and pulse is 85/min and regular. The patient is afebrile. Transthoracic echocardiography reveals a left ventricular ejection fraction of 40% with no evidence of valvular disease. Cardiac assessment prior to chemotherapy initiation was normal. Which of the following pathologic findings is most likely to be present in this patient's heart?

- ☐ A. Abnormal protein accumulation in the extracellular space [11%]
- ☐ B. Focal ischemic cardiomyocyte necrosis [3%]
- ☐ C. Myocardial tumor cell infiltration [3%]
- ☐ D. Patchy cardiomyocyte necrosis with diffuse myocardial fibrosis [26%]
- ☒ E. Reduced cardiomyocyte contractility with no fibrosis [54%]

Omitted

Correct answer

E



54%

Answered correctly



2 Seconds

Time Spent



02/01/2019

Last Updated

Explanation

Trastuzumab is a monoclonal antibody used in the treatment of **breast cancer** caused by tumor cells that overexpress human epidermal growth factor receptor-2 (**HER2**). By binding to HER2, trastuzumab blocks downstream signaling that promotes cellular proliferation and thereby encourages malignant cell apoptosis.

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Trastuzumab is a monoclonal antibody used in the treatment of **breast cancer** caused by tumor cells that overexpress human epidermal growth factor receptor-2 (**HER2**). By binding to HER2, trastuzumab blocks downstream signaling that promotes cellular proliferation and thereby encourages malignant cell apoptosis.

The major adverse effect of trastuzumab is a risk of **cardiotoxicity**, likely because HER2 signaling plays a role in minimizing oxidative stress on cardiomyocytes and preserving cardiomyocyte function. Cardiotoxicity typically manifests as a **decrease in myocardial contractility** (myocardial stunning) **without cardiomyocyte destruction** or myocardial fibrosis. Patients usually experience an asymptomatic decline in left ventricular ejection fraction; however, overt heart failure can also occur. Unlike the cardiotoxicity that occurs with anthracyclines (eg, doxorubicin), trastuzumab-induced cardiotoxicity is not related to the cumulative chemotherapy dose and is **often reversible** with discontinuation of therapy.

(Choice A) Abnormal protein accumulation in the cardiac extracellular space is seen in patients with amyloidosis, namely with the light-chain (AL) and transthyretin (ATTR) subtypes. The disease typically manifests initially as restrictive cardiomyopathy with impaired diastolic function and preserved ejection fraction.

(Choice B) Focal ischemic cardiomyocyte necrosis leading to left ventricular systolic dysfunction is seen in patients with a prior myocardial infarction due to coronary heart disease.

(Choice C) Breast cancer is one of the most common malignancies to metastasize to the heart, typically causing pericardial effusion that may gradually progress to cardiac tamponade. However, tamponade predominantly affects diastolic filling of the right-sided heart chambers and does not decrease left ventricular ejection fraction.

(Choice D) Anthracycline-induced cardiotoxicity occurs due to oxidative damage of cellular membranes, leading to cardiomyocyte necrosis and death with eventual myocardial fibrosis.

Educational objective:

Trastuzumab is a monoclonal antibody that blocks human epidermal growth factor receptor-2 (HER2) to disrupt malignant cell signaling and encourage apoptosis. Because HER2 helps preserve cardiomyocyte function, trastuzumab can cause cardiotoxicity that manifests as a decrease in myocardial contractility without cardiomyocyte destruction or myocardial fibrosis.

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A 67-year-old man with nonischemic cardiomyopathy comes to the office for follow-up. He recently was hospitalized for acute decompensated heart failure. The patient's symptoms have improved with multidrug treatment, but he has persistent shortness of breath on mild exertion. He has a history of hypertension and hypercholesterolemia. Blood pressure is 115/70 mm Hg and pulse is 66/min. There is a third heart sound on heart auscultation and mild lower extremity pitting edema. A recent echocardiogram showed a left ventricular ejection fraction of 30%. Which of the following diuretics would most likely improve survival if added to this patient's current regimen?

☐ A. Acetazolamide

☐ B. Furosemide

☐ C. Hydrochlorothiazide

☐ D. Mannitol

☐ E. Spironolactone

☐ F. Triamterene

Submit

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A 67-year-old man with nonischemic cardiomyopathy comes to the office for follow-up. He recently was hospitalized for acute decompensated heart failure. The patient's symptoms have improved with multidrug treatment, but he has persistent shortness of breath on mild exertion. He has a history of hypertension and hypercholesterolemia. Blood pressure is 115/70 mm Hg and pulse is 66/min. There is a third heart sound on heart auscultation and mild lower extremity pitting edema. A recent echocardiogram showed a left ventricular ejection fraction of 30%. Which of the following diuretics would most likely improve survival if added to this patient's current regimen?

- ☐ A. Acetazolamide [1%]
- ☐ B. Furosemide [27%]
- ☐ C. Hydrochlorothiazide [16%]
- ☐ D. Mannitol [1%]
- ☒ E. Spironolactone [50%]
- ☐ F. Triamterene [2%]

Omitted

Correct answer
E50%
Answered correctly2 Seconds
Time Spent08/22/2018
Last Updated

Explanation

Mineralocorticoid receptor antagonists (eg, spironolactone, eplerenone) prevent aldosterone from binding to its receptor in the distal renal tubules. This leads to increased sodium and water excretion while conserving potassium ions (**potassium-sparing diuresis**). These antagonists

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Explanation

Mineralocorticoid receptor antagonists (eg, spironolactone, eplerenone) prevent aldosterone from binding to its receptor in the distal renal tubules. This leads to increased sodium and water excretion while conserving potassium ions (**potassium-sparing diuresis**). These antagonists also block the deleterious effect of aldosterone on the heart, causing regression of myocardial fibrosis and **improvement in ventricular remodeling**.

Mineralocorticoid receptor antagonists reduce morbidity and **improve survival** in patients with congestive heart failure and decreased ejection fraction. Therefore, they are recommended in addition to standard heart failure therapy (ACE inhibitors and beta blockers). They should not be used in patients with hyperkalemia or renal failure. The most common side effects are hyperkalemia and gynecomastia (spironolactone >> eplerenone).

(Choices A, C, and F) Acetazolamide (carbonic anhydrase inhibitor), hydrochlorothiazide (thiazide diuretic), and triamterene (epithelial sodium channel blocker) have a variably lower diuretic effect compared to loop diuretics and are not as efficacious for treating heart failure symptoms.

(Choice B) Furosemide is a loop diuretic frequently used for treatment of pulmonary congestion and fluid retention in heart failure patients. Although loop diuretics improve symptoms significantly, they do not provide survival benefit (ie, improved morbidity but not mortality) in these patients.

(Choice D) Mannitol is an intravenous osmotic diuretic used primarily to lower intracranial pressure and treat acute glaucoma. It is not used to treat heart failure as it can cause an initial rise in extracellular fluid volume, exacerbating pulmonary congestion and peripheral fluid retention.

Educational objective:

Mineralocorticoid receptor antagonists (eg, spironolactone, eplerenone) improve survival in patients with congestive heart failure and reduced left ventricular ejection fraction. They should not be used in patients with hyperkalemia or renal failure.

References

The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldosterone Evaluation Study.

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A 62-year-old man is hospitalized for chest pain and palpitations. His past medical history is significant for coronary artery disease, ischemic cardiomyopathy, paroxysmal atrial fibrillation, and hypertension. Blood pressure on admission is 135/78 mm Hg and pulse is 78/min. During hospitalization, the patient has 2 episodes of brief loss of consciousness. ECG recording during the episodes shows polymorphic QRS complexes that change in amplitude and cycle length. Between the episodes, his ECG shows QT interval prolongation but is otherwise unremarkable. Which of the following medications is most likely responsible for this patient's condition?

A. Digoxin

B. Diltiazem

C. Lidocaine

D. Metoprolol

E. Sotalol

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A 62-year-old man is hospitalized for chest pain and palpitations. His past medical history is significant for coronary artery disease, ischemic cardiomyopathy, paroxysmal atrial fibrillation, and hypertension. Blood pressure on admission is 135/78 mm Hg and pulse is 78/min. During hospitalization, the patient has 2 episodes of brief loss of consciousness. ECG recording during the episodes shows polymorphic QRS complexes that change in amplitude and cycle length. Between the episodes, his ECG shows QT interval prolongation but is otherwise unremarkable. Which of the following medications is most likely responsible for this patient's condition?

- ☐ A. Digoxin [16%]
- ☐ B. Diltiazem [8%]
- ☐ C. Lidocaine [10%]
- ☐ D. Metoprolol [2%]
- ☒ E. Sotalol [62%]

Omitted

Correct answer
E 62%
Answered correctly 8 Seconds
Time Spent 08/24/2018
Last Updated

Explanation

This patient's presentation (syncope and ECG findings) is suggestive of **long QT syndrome** with associated **torsades de pointes** (TdP, "twisting of points"). TdP is a form of polymorphic ventricular tachycardia characterized by QRS complexes of varying amplitude and cycle length giving the appearance that the tip of the QRS complex is "twisting" around the ECG baseline. TdP is differentiated from other forms of polymorphic ventricular tachycardia because it is always associated with a prolonged QT interval. It may terminate spontaneously or can degenerate into

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Explanation

This patient's presentation (syncope and ECG findings) is suggestive of **long QT syndrome** with associated **torsades de pointes** (TdP, "twisting of points"). TdP is a form of polymorphic ventricular tachycardia characterized by QRS complexes of varying amplitude and cycle length giving the appearance that the tip of the QRS complex is "twisting" around the ECG baseline. TdP is differentiated from other forms of polymorphic ventricular tachycardia because it is always associated with a prolonged QT interval. It may terminate spontaneously or can degenerate into ventricular fibrillation and sudden cardiac death.

QT prolongation may be acquired or congenital. **Acquired QT prolongation** is most frequently caused by electrolyte imbalances (hypokalemia, hypomagnesemia) and pharmacologic agents such as **class IA and III antiarrhythmics** (eg, quinidine, sotalol), antibiotics (eg, macrolides, fluoroquinolones), methadone, and antipsychotics (eg, haloperidol). Sotalol is a class III antiarrhythmic agent (K⁺ channel blocking) used for treatment of atrial fibrillation. It prolongs action potential duration, resulting in QT interval prolongation.

(Choice A) Digoxin slows conduction through the atrioventricular node by augmenting vagal parasympathetic tone, and it increases cardiac contractility by inhibiting Na⁺/K⁺-ATPase (increasing intracellular calcium). It also decreases the action potential duration and can cause QT interval shortening.

(Choices B and D) Diltiazem (nondihydropyridine calcium channel blocker) and metoprolol (beta-1 selective antagonist) slow the sinus node discharge rate and atrioventricular nodal conduction. These agents prolong the PR interval but do not affect the QT interval.

(Choice C) Lidocaine is a class IB antiarrhythmic drug that acts by blocking sodium channels and inhibiting phase 0 depolarization. It does not prolong the QT interval.

Educational objective:

Torsades de pointes (TdP) refers to polymorphic ventricular tachycardia that occurs in the setting of a congenital or acquired prolonged QT interval. TdP is most commonly precipitated by medications that prolong the QT interval such as certain antiarrhythmics (sotalol, quinidine), antipsychotics (haloperidol), and antibiotics (macrolides, fluoroquinolones).

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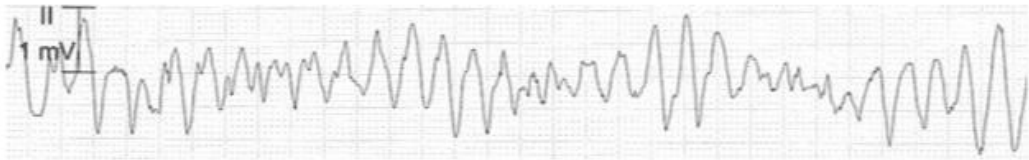
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A 37-year-old man with no significant medical history comes to the office due to intermittent palpitations. He has a healthy lifestyle, exercises daily, and does not use tobacco, alcohol, or illicit drugs. ECG shows atrial fibrillation with rapid ventricular response. Echocardiogram reveals normal heart function with no significant valvular disease. The patient is started on an antiarrhythmic medication that is known to be effective against both atrial and ventricular arrhythmias. On ECG, this medication causes QRS prolongation with only minimal increase in QT interval duration. Which of the following regions of the action potential curve is most affected by this drug?

☐ A. A

☐ B. B

☐ C. C

☐ D. D

☐ E. E

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A 37-year-old man with no significant medical history comes to the office due to intermittent palpitations. He has a healthy lifestyle, exercises daily, and does not use tobacco, alcohol, or illicit drugs. ECG shows atrial fibrillation with rapid ventricular response. Echocardiogram reveals normal heart function with no significant valvular disease. The patient is started on an antiarrhythmic medication that is known to be effective against both atrial and ventricular arrhythmias. On ECG, this medication causes QRS prolongation with only minimal increase in QT interval duration. Which of the following regions of the action potential curve is most affected by this drug?

A. A

B. B

C. C

D. D

E. E

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☐ A. A [1%]

☒ B. B [60%]

☐ C. C [3%]

☐ D. D [17%]

☐ E. E [16%]

 10/30/2018
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The **QRS complex** represents **rapid ventricular depolarization** and corresponds to **phase 0** of the ventricular myocyte action potential. The QT

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Explanation

This patient with atrial fibrillation was most likely started on a **class IC** antiarrhythmic agent, which typically cause QRS prolongation with little effect on QT interval duration.

The **QRS complex** represents rapid **ventricular depolarization** and corresponds to **phase 0** of the ventricular myocyte action potential. The QT interval represents both ventricular depolarization and repolarization (total duration of ventricular action potential). However, since ventricular depolarization (QRS duration) contributes only a small amount of time to the interval, the **QT interval** is primarily a measure of **ventricular repolarization**.

Ventricular depolarization occurs due to the opening of **voltage-dependent sodium channels**. In general, **class I antiarrhythmics** act by blocking these channels, inhibiting the initial depolarization and **prolonging QRS duration**. Specific actions are as follows:

- Class 1A (eg, procainamide) drugs have intermediate sodium channel blocking activity that increases QRS duration. Their moderate potassium channel-blocking activity also causes significant QT interval prolongation.
- Class 1B drugs (eg, lidocaine) have no significant effect on the QRS duration and do not prolong the QT interval due to their rapid dissociation from the receptor.
- Class IC drugs (eg, flecainide, propafenone) are strong sodium channel blockers that prolong QRS duration in a rate-dependent manner. The QT interval may become slightly prolonged due to QRS widening.

(Choice A) Antiarrhythmic drugs do not affect phase 4 of the myocyte action potential, but they can affect phase 4 of the pacemaker cell action potential, which is characterized by slow depolarization due to sodium influx.

(Choice C) Phase 1 of the myocyte action potential refers to a brief period of repolarization caused by a sharp decrease in sodium conductance and an increase in potassium permeability. It is not modulated to an appreciable extent by antiarrhythmic medications.

(Choice D) Calcium channel blockers (eg, verapamil, diltiazem) inhibit the L-type calcium channels during phase 2 depolarization of the myocardial action potential with additional effects on cardiac slow response tissue. They slow the sinus rate, prolong conduction through the atrioventricular node, and depress myocardial contractility (negative inotropic effect).

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Ventricular depolarization occurs due to the opening of **voltage-dependent sodium channels**. In general, **class I antiarrhythmics** act by blocking these channels, inhibiting the initial depolarization and **prolonging QRS duration**. Specific actions are as follows:

- Class 1A (eg, procainamide) drugs have intermediate sodium channel blocking activity that increases QRS duration. Their moderate potassium channel-blocking activity also causes significant QT interval prolongation.
- Class 1B drugs (eg, lidocaine) have no significant effect on the QRS duration and do not prolong the QT interval due to their rapid dissociation from the receptor.
- Class 1C drugs (eg, flecainide, propafenone) are strong sodium channel blockers that prolong QRS duration in a rate-dependent manner. The QT interval may become slightly prolonged due to QRS widening.

(Choice A) Antiarrhythmic drugs do not affect phase 4 of the myocyte action potential, but they can affect phase 4 of the pacemaker cell action potential, which is characterized by slow depolarization due to sodium influx.

(Choice C) Phase 1 of the myocyte action potential refers to a brief period of repolarization caused by a sharp decrease in sodium conductance and an increase in potassium permeability. It is not modulated to an appreciable extent by antiarrhythmic medications.

(Choice D) Calcium channel blockers (eg, verapamil, diltiazem) inhibit the L-type calcium channels during phase 2 depolarization of the myocardial action potential with additional effects on cardiac slow response tissue. They slow the sinus rate, prolong conduction through the atrioventricular node, and depress myocardial contractility (negative inotropic effect).

(Choice E) Class III antiarrhythmic drugs (eg, amiodarone, sotalol, dofetilide) predominantly block potassium channels and inhibit the outward repolarizing currents during phase 3 of the myocyte action potential. This leads to increased action potential duration and QT interval prolongation.

Educational objective:

Class 1C antiarrhythmic agents (flecainide) block the fast sodium channels responsible for ventricular depolarization (phase 0), prolonging QRS duration with little effect on the QT interval. Class 1A and class III agents cause the most QT prolongation.

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Exhibit Display

Cardiac action potentials

Pacemaker action potential

0

-20

-40

-60

-80

0

Ca²⁺

3

K⁺

4

Non-pacemaker action potential

0

-20

-40

-60

-80

0

1

2

3

K⁺

Na⁺

4

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Exhibit Display

Antiarrhythmic drugs – Vaughan Williams classification		
Class	Drugs	Predominant actions
IA	Sodium channel blockers	
	- Disopyramide - Procainamide - Quinidine	- Slows AP conduction velocity - Prolongs APD
IB	- Lidocaine - Mexiletine - Phenytoin	- No effect on AP conduction velocity - Shortens APD
IC	- Flecainide - Propafenone	- Slows AP conduction velocity - Minimal effect on APD
II	Beta receptor blockers	
	- Atenolol - Metoprolol - Esmolol - Carvedilol	- Slows sinus node discharge rate - Slows AV nodal conduction & prolongs refractoriness
III	Potassium channel blockers	
	- Amiodarone - Dronedarone - Dofetilide - Sotalol (also class II)	- No effect on AP conduction velocity - Prolongs APD
IV	Non-dihydropyridine calcium channel blockers	
	- Verapamil - Diltiazem	- Slows sinus node discharge rate - Slows AV nodal conduction & prolongs refractoriness

AP = action potential, APD = action potential duration, AV = atrioventricular.
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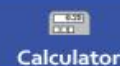


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A 57-year-old man is seen in the office after an episode of acute pancreatitis. Hospital evaluation found no evidence of gallstones. The patient does not consume alcohol, but he does have a history of severe hypertriglyceridemia. He was treated with a fibrate medication in the past but could not tolerate it due to liver toxicity. He has no history of diabetes mellitus or hypertension. On examination, the patient has no abdominal tenderness. Laboratory studies show normal hepatic and pancreatic enzyme levels, but the patient again has a severely elevated triglyceride level. The physician prescribes the appropriate medications and explains that the patient is likely to experience skin flushing and warmth after taking the pills. Which of the following is the primary agent mediating these side effects?

- ☐ A. Histamine
- ☐ B. Platelet-activating factor
- ☐ C. Prostaglandin
- ☐ D. Serotonin
- ☐ E. Substance P

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- ☐ A. Histamine [26%]
- ☐ B. Platelet-activating factor [1%]
- ☒ C. Prostaglandin [49%]
- ☐ D. Serotonin [17%]
- ☐ E. Substance P [5%]

Correct answer
C

 49%
Answered correctly

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Time Spent

12/05/2018
Last Updated

Explanation

Nicotinic acid, or **niacin**, has been used in the treatment of hyperlipidemia for almost 4 decades. It is effective in raising HDL cholesterol levels, as well as lowering triglycerides and LDL levels.

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Explanation

Nicotinic acid, or **niacin**, has been used in the treatment of hyperlipidemia for almost 4 decades. It is effective in raising HDL cholesterol levels, as well as lowering triglycerides and LDL levels.

Niacin's main side effects are cutaneous **flushing**, warmth, and itching; these are primarily mediated by release of **prostaglandins** (particularly PGD₂ and PGE₂). **Aspirin**, which inhibits prostaglandin synthesis, can significantly reduce these side effects if given 30-60 minutes before niacin administration. The side effects are also reduced with slow-release preparations or if niacin is taken with meals. They are worst when niacin is first initiated and tend to fade over time due to tachyphylaxis.

(Choice A) Vancomycin-induced "red man syndrome" is mediated by histamine release due to non-IgE- mediated mast cell degranulation.

(Choice B) Platelet-activating factor is a powerful phospholipid activator produced by a number of cells, including neutrophils, basophils, platelets, and endothelial cells. It is a mediator of platelet aggregation.

(Choice D) Serotonin syndrome is a potential side effect of selective serotonin reuptake inhibitors. It is characterized by abnormal mental status, autonomic hyperactivity, and muscular rigidity with hyperreflexia.

(Choice E) Substance P is a polypeptide neurotransmitter involved in mediating pain signals in the peripheral and central nervous systems. Topical capsaicin causes release of substance P, resulting in burning pain in the area of application. Prolonged use causes depletion of substance P, and the pain diminishes with time.

Educational objective:

Niacin is used in the treatment of hyperlipidemia. It increases HDL levels and decreases LDL levels and triglycerides. Niacin causes cutaneous flushing, which is mediated by prostaglandins and can be diminished by pretreatment with aspirin.

References

Aspirin reduces cutaneous flushing after administration of an optimized extended-release niacin formulation

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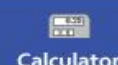
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A 54-year-old man with nonischemic cardiomyopathy comes to the office for a follow-up visit. He has been hospitalized frequently for acute decompensated heart failure, and currently has dyspnea on mild exertion. The patient also has a history of hypertension and takes multiple medications. Blood pressure is 116/70 mm Hg, and pulse is 72/min and regular. Physical examination shows elevated jugular venous pressure, bibasilar lung crackles, and lower extremity edema. Serum creatinine is 1.0 mg/dL and serum potassium is 4.2 mEq/L. Three weeks after starting digoxin therapy, the patient reports symptomatic improvement. Which of the following is the initial cellular event triggering this response to the new medication?

- ☐ A. Decreased sodium efflux from myocardial cells
- ☐ B. Increased intracellular calcium concentration
- ☐ C. Increased intracellular cyclic AMP concentration
- ☐ D. Increased potassium influx into myocardial cells
- ☐ E. Troponin sensitization to calcium

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A 54-year-old man with nonischemic cardiomyopathy comes to the office for a follow-up visit. He has been hospitalized frequently for acute decompensated heart failure, and currently has dyspnea on mild exertion. The patient also has a history of hypertension and takes multiple medications. Blood pressure is 116/70 mm Hg, and pulse is 72/min and regular. Physical examination shows elevated jugular venous pressure, bibasilar lung crackles, and lower extremity edema. Serum creatinine is 1.0 mg/dL and serum potassium is 4.2 mEq/L. Three weeks after starting digoxin therapy, the patient reports symptomatic improvement. Which of the following is the initial cellular event triggering this response to the new medication?

- ☒ A. Decreased sodium efflux from myocardial cells [59%]
☐ B. Increased intracellular calcium concentration [31%]
☐ C. Increased intracellular cyclic AMP concentration [4%]
☐ D. Increased potassium influx into myocardial cells [4%]
☐ E. Troponin sensitization to calcium [0%]

Omitted

Correct answer
A59%
Answered correctly2 Seconds
Time Spent12/14/2018
Last Updated

Explanation

Digoxin mechanism of action

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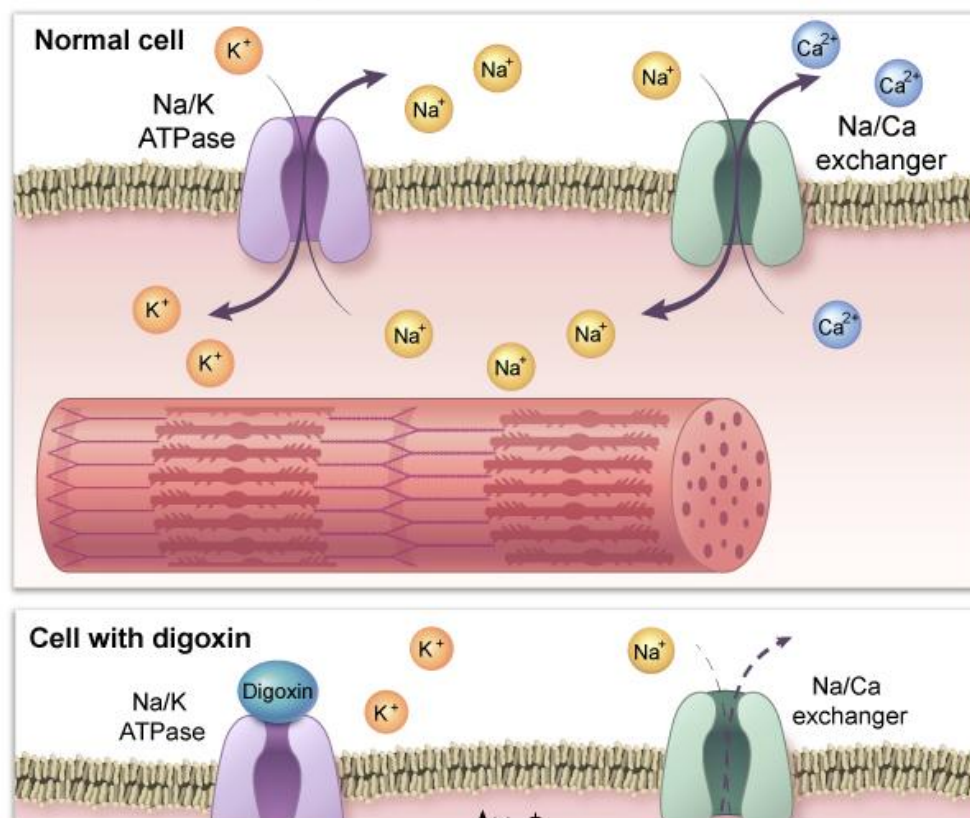


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Digoxin mechanism of action



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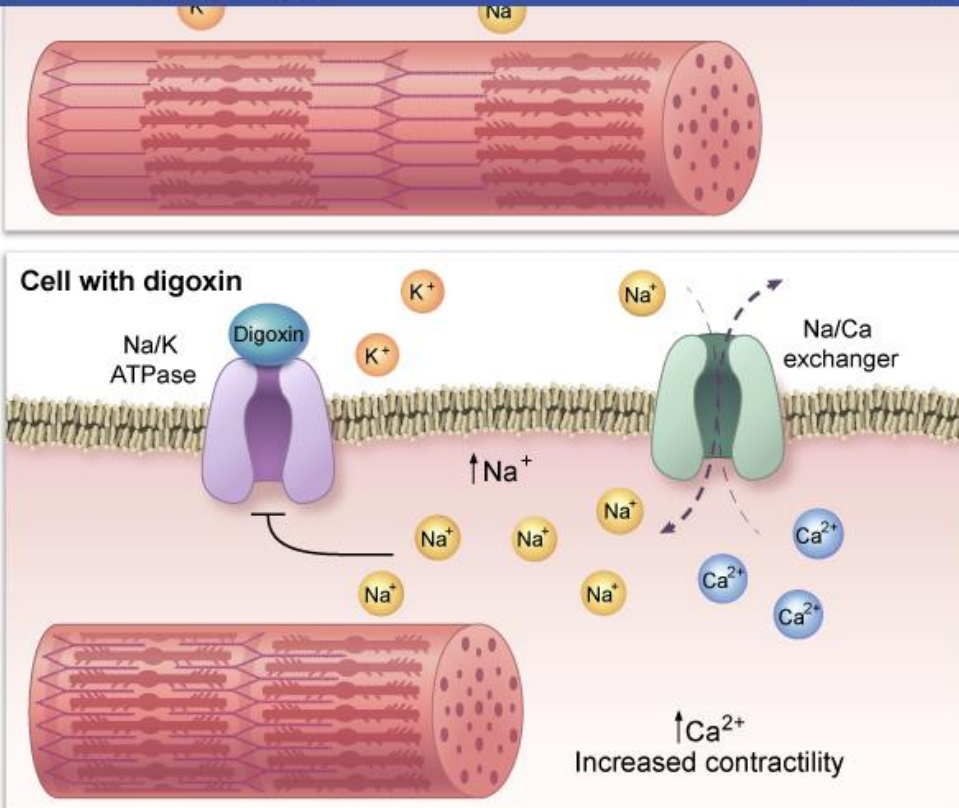


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Digoxin is a **positive inotropic agent** that provides symptomatic relief in patients with acute decompensated heart failure due to left ventricular systolic dysfunction. It also increases parasympathetic tone and slows conduction through the atrioventricular node, which can help improve cardiac function in patients with a rapid ventricular rate.

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Digoxin is a **positive inotropic agent** that provides symptomatic relief in patients with acute decompensated heart failure due to left ventricular systolic dysfunction. It also increases parasympathetic tone and slows conduction through the atrioventricular node, which can help improve cardiac function in patients with a rapid ventricular rate.

Digoxin directly **inhibits the Na-K-ATPase pump** in myocardial cells, leading to **decreased sodium efflux** and an increase in intracellular sodium levels. The decreased transmembrane sodium gradient reduces the forward activity of the sodium-calcium exchanger, leading to a secondary **decrease in calcium efflux** from the cells. Increased intracellular calcium concentration stimulates the binding of calcium to troponin C and subsequent actin-myosin cross-bridge formation, resulting in **improved myocyte contractility** and left ventricular systolic function.

(Choice B) The increase in intracellular sodium caused by digoxin reduces the forward activity of the sodium-calcium exchanger, resulting in increased intracellular calcium concentration. However, the calcium increase is a secondary effect of digoxin that occurs after the increase in intracellular sodium.

(Choice C) Cyclic AMP (cAMP), an important second messenger in excitation-contraction coupling, is formed from ATP by adenylyl cyclase. Adenylyl cyclase activity is stimulated by beta agonists and inhibited by acetylcholine. cAMP increases the conductance of the calcium channels in the sarcoplasmic reticulum. As a result, more calcium is available to bind to troponin C, strengthening the force of contraction.

(Choice D) Inhibition of the Na-K-ATPase pump by digoxin leads to a decrease in potassium influx into myocardial cells.

(Choice E) Digoxin does not cause increased troponin sensitivity to calcium; instead, it increases the amount of intracellular calcium available for troponin binding.

Educational objective:

Digoxin directly inhibits the Na-K-ATPase pump in myocardial cells, leading to a decrease in sodium efflux and an increase in intracellular sodium levels. This reduces the forward activity of the sodium-calcium exchanger, causing increased intracellular calcium concentration and improved myocyte contractility.

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