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Patients who have a significant loss of cardiac pump function develop progressively severe symptoms of fatigue, dyspnea (shortness of breath), chest pain, syncope (loss of consciousness), and death. The management of these patients requires an understanding that it is an ongoing process in which the response to the initial injury causes damage beyond the insult alone. The challenge of the clinician is to keep the congestive heart failure (CHF) patient out of the hospital while reducing morbidity and mortality in this high-risk population.

Chronic CHF may be defined as the clinical condition in which an individual expels less than 40% of the blood from the left ventricle per heartbeat (ejection fraction [EF] < 40%). A normal individual expels about 55 to 65% of the blood from the left ventricle per heartbeat (EF = 55–65%). The rationale for choosing the 40% EF is based on clinical findings demonstrating progressive deterioration and early mortality in individuals who have an EF below 40%.

It is remarkable that the therapeutic approach to a decreased EF is the same regardless of the etiology. The principles that guide the pharmacological management of CHF is the same for patients who had damage from a myocardial infarction (MI), viral infection, valvular disease, alcohol, and so on. This chapter reviews the recommended approach to the pharmacological management of systolic dysfunction. An historic perspective will be followed to provide an appreciation of the evolution in our understanding of the pathophysiology of this condition.

The management of heart failure in the presence of normal systolic function is not reviewed. This form of heart failure commonly occurs in the elderly with chronic hypertension and left ventricular hypertrophy. The failure of the left ventricle to relax during diastole (diastolic dysfunction) results in elevated end diastolic pressure.
pressures and volumes. The shortness of breath (dyspnea), chest pain, and fatigue that result from elevated pulmonary venous pressures are similar in both systolic and diastolic dysfunction. Also excluded from discussion are nondrug therapies for CHF, such as coronary artery bypass, percutaneous coronary interventions, electronic pacemakers, and cardiac transplantation.

A considerable body of literature supports abnormalities in myocardial excitation–contraction coupling in CHF. An appreciation of the principles involved in this cell signaling process is crucial to understand current and future pharmacotherapies for CHF. A brief overview of myocardial excitation–contraction coupling will be provided.

MYOCARDIAL EXCITATION–CONTRACTION COUPLING

The physiological processes that begin with cardiac sarcolemmal membrane depolarization and culminate in contraction are collectively defined as myocardial excitation–contraction coupling. Depolarization of the cardiac myocyte sarcolemmal membrane during the action potential results in the intracellular entry of extracellular calcium. The major regulators of the transsarcolemmal entry of calcium include L-type calcium channels and autonomic receptors (Fig. 15.1). These membrane-bound proteins all contribute to the influx of a minute quantity of calcium from outside the cell into the myocyte. The entry of this small quantity of calcium causes the release of the large reservoir of calcium stored in the sarcoplasmic reticulum (SR) through the SR calcium release channel (ryanodine receptor). This large reservoir of calcium interacts with tropomyosin to allow the actin and myosin filaments to overlap, resulting in systolic myocardial contraction. Diastolic relaxation results from the resequestration of this large reservoir of calcium back into the sarcoplasmic reticulum through the SR calcium adenosine triphosphatase (ATPase). Calcium exits the cell through the Na\(^+\)-Ca\(^{2+}\) exchanger and sarcolemmal Ca\(^{2+}\) ATPase.

Autonomic receptors further regulate calcium influx through the sarcolemma (Fig. 15.1). \(\beta\)-Adrenergic stimulation results in the association of a catalytic subunit of a G protein coupled to the \(\beta\)-receptor. This stimulates the enzyme adenylyl cyclase to convert ATP to cyclic adenosine monophosphate (cAMP). Increasing cAMP production results in a cAMP-dependent phosphorylation of the L-type calcium channel and a subsequent increase in the probability of the open state of the channel. This translates to an increase in transsarcolemmal calcium influx during phase 2 (the plateau phase) of the cardiac muscle action potential. The effects of transient increases in intracellular levels of cAMP are tightly controlled by phosphodiesterases and phosphatases that prevent indefinite phosphorylation and activation of regulatory proteins. \(\alpha\)-Adrenergic receptor stimulation results in the phospholipase C–mediated breakdown of phosphatidylcholine to inositol triphosphate and diacyl glycerol; these second messengers further enhance mobilization of both transsarcolemmal calcium influx and SR calcium efflux.

Binding of angiotensin II to its cardiac myocyte receptor acutely increases Ca\(^{2+}\) influx through sarcolemmal L-type calcium channels. The long-term effects of chronic angiotensin II receptor stimulation include cardiac myocyte hypertrophy through enhanced expression of growth factor genes.

The maintenance of a resting membrane potential in cardiac myocytes, as well as all cells, depends on metabolic energy (ATP) that is used by the Na\(^+\)-K\(^+\) ATPase to drive the gradients for Na\(^+\) and K\(^+\) between the intracellular and extracellular spaces. Cardiac glycosides are known to bind to this protein.

CARDIAC GLYCOSIDES

Historical Background

In “An Account of the Foxglove” William Withering related his experiences while in private practice more than 200 years ago. He traveled between two towns where he took care of the wealthy patients on a fee-for-service basis in one town and the poor people for free in the other. He encountered during one of his commutes a practitioner of the healing arts who was referred to as a witch. She provided care for people with obvious signs and symptoms of fluid overload who were diagnosed with dropsy (later called CHF). She gave these patients a group of herbs that contained digitalis, and it was Withering who identified Digitalis purpurea as the active plant in this mixture. Unfortunately, he lacked any insight into potential mechanisms of action. Although Withering thought that digitalis worked by inducing emesis, he was actually describing digitalis toxicity and not the mechanism of action at all.

Digitalization

Digitalis remains notorious today for its very narrow dosage window for therapeutic efficacy without toxicity. A unique process, digitalization, for dosing digitalis (digoxin [Lanoxin]; digitoxin [Crystodigin]) has been widely accepted over the years as a means of minimizing toxicity. This process is to start patients on several repeated doses of digitalis over 24 to 36 hours before establishing a lower daily maintenance dose. Digitalis has become the mainstay of therapy for CHF despite its
**FIGURE 15.1**
Principles of excitation-contraction coupling in the cardiac myocyte. Calcium enters the myocyte through L-type calcium channels that are modulated by α- and β-adrenergic receptors. This small quantity of calcium triggers release of the large reservoir of intracellular calcium stored in the SR by activation of the SR calcium release channel (ryanodine receptor). Calcium is resequestered in the SR by the SR calcium–ATPase. Calcium is extruded from the cell largely through the Na\(^+\)/Ca\(^2+\) exchanger and the sarcolemmal calcium ATPase. β-Adrenergic agonists (e.g., dobutamine) bind to the β-adrenoceptor and activate a stimulatory G protein to couple with adenyl cyclase to convert ATP to cAMP. Phosphodiesterase inhibitors (e.g., milrinone) increase intracellular cAMP levels by blocking the degradation of cAMP by phosphodiesterases. β-Adrenergic antagonists (e.g., metoprolol, carvedilol) bind to the same site and prevent endogenous catecholamines (e.g., norepinephrine) from binding to that site and activating a stimulatory G protein. α-Adrenergic antagonists (e.g., prazosin) and angiotensin II receptor blockers (e.g., valsartan, losartan) similarly prevent the endogenous mediators (i.e., norepinephrine, angiotensin II, respectively) from increasing intracellular ionized free calcium levels in the cardiac myocyte. ACE inhibitors (e.g., captopril, fosinopril, lisinopril) block conversion of inert angiotensin I to active angiotensin II by ACE. Digitalis glycosides initially increase intracellular Na\(^+\) levels by binding to the Na\(^+\)/K\(^+\) ATPase. The increase in intracellular Na\(^+\) causes the Na\(^+\)/Ca\(^2+\) exchanger to extrude Na\(^+\) from the myocyte in exchange for extracellular Ca\(^{2+}\). This increases intracellular ionized free calcium levels sufficiently to enhance contractility.
toxicity, the lack of understanding of its mode of action, and the lack of any definitive evidence describing its safety and efficacy.

**Toxicity**

Digitalis toxicity includes nausea, vomiting, anorexia, fatigue, and a characteristic visual disturbance (green-yellow halos around bright objects). Cardiac toxicities have included tachyarrhythmias and bradyarrhythmias, including supraventricular and ventricular tachycardia and atrioventricular (A-V) block. The most classic (but not most frequent) manifestations of digitalis toxicity include atrial tachycardia with A-V block. Treatment for digitalis toxicity ranges from mild cases that respond to simply stopping the drug to the use of antidigitalis antibodies in life-threatening situations. The availability of a radioimmunoassay for digitalis levels and antidigitalis antibodies, useful in reversing digitalis’s actions, have minimized the frequency of fatal toxicity.

**Clinical Use**

Randomized clinical trials have been conducted to explore the safety and efficacy of digitalis in the management of CHF. The first major trial showed an improvement in quality of life but no mortality benefit. A second major clinical trial revealed that treatment with digitalis diminished the combined end points of death and hospitalizations but did not specifically improve overall survival. Thus, no studies have demonstrated that digitalis therapy improves survival in CHF patients. However, digitalis does decrease morbidity by diminishing the number of admissions to the hospital for symptoms such as dyspnea (shortness of breath) and fatigue. Current guidelines for the treatment of CHF indicate that physicians must at least consider including digitalis in the regimen. The consensus now is to prescribe a dose that achieves a digitalis blood level of 0.8 to 1.2 ng/dL. This lower dose reduces the incidence of side effects while optimizing the benefit.

**Mechanism of Action**

Digitalis has the unique characteristic of increasing contractility (positive inotropy) while decreasing heart rate (negative chronotropy). This pharmacological profile results from indirect as well as direct effects of digitalis glycosides on the heart. Digitalis is a fat-soluble steroid that crosses the blood-brain barrier and enhances vagal tone. The slowing and/or conversion of a patient with supraventricular arrhythmia (e.g., atrial fibrillation, supraventricular tachycardia) with digitalis results from enhancement of vagal tone. This increased vagal activity increases acetylcholine release, which in turn is coupled to the opening of a K⁺ channel. Opening of this K⁺ channel results in closing of the L-type sarcolemmal Ca⁺⁺ channel. Ca⁺⁺ channel inhibition slows the heart rate and/or converts the rhythm to a sinus mechanism.

Digitalis works directly on the heart through an action on the sodium–potassium (Na⁺—K⁺) ATPase. Since all living cells have a resting membrane potential, there is an electrochemical gradient across the cell membrane that is not at a steady state electrically. There is an imbalance in that all cells are intracellularly negative compared to the outside of the cell. The maintenance of this gradient requires metabolic energy to maintain this difference in ions. This electrochemical gradient is lost after death. The activity of the Na⁺—K⁺ ATPase results in serum sodium levels of roughly 140 to 145 mmol and serum potassium around 5 mmol. Inside cells the Na⁺ concentration is low and the K⁺ concentration is high. The reason for this difference between the intracellular and extracellular sodium and potassium is the action of the Na⁺—K⁺ ATPase enzyme. Digitalis binds to this enzyme and inhibits its activity. This results in an elevation in intracellular Na⁺ that leads to an increase in extrusion of Na⁺ through the Na⁺—Ca⁺⁺ exchanger, which functions to maintain a relatively constant level of both Na⁺ and Ca⁺⁺ in the cell. The Na⁺—Ca⁺⁺ exchanger normally extrudes Ca⁺⁺ in exchange for Na⁺. However, in the presence of increased intracellular Na⁺, it will extrude Na⁺ by exchanging it for extracellular Ca⁺⁺. This reversal in the activity of the Na⁺—Ca⁺⁺ exchanger results in an increase in intracellular ionized free Ca⁺⁺ that enhances myocardial contractility.

The current hypothesis regarding the cellular basis for the positive inotropic effect of digitalis helps to explain some of the wide individual variability in the dosage required to develop digitalis toxicity. Differences in pH, ischemia, Na⁺, K⁺, and Ca⁺⁺ can each alter the likelihood of developing toxicity within the same patient and between individuals.
appropriate neurohumoral activation by the kidney in response to perceived volume depletion from hemorrhage. Mechanisms that result in vasoconstriction are normally compensatory in the short term for acute bleeding. These same adaptive mechanisms become damaging in chronic heart failure.

The usefulness of diuretics in the management of CHF cannot be overstated. Before diuretics were available, rotating tourniquets were used to diminish venous return by ligating the lower extremities. Less venous blood returned to the right side of the heart and pooled in the legs. This procedure diminished the effective intravascular volume that would otherwise have accumulated in the lungs. The availability of loop diuretics (particularly furosemide) has resulted in the virtual elimination of this practice.

**Loop Diuretics**

Diuretics and their mechanisms of action will be discussed in detail in Chapter 21. Loop diuretics, such as furosemide (*Lasix*), block the Na–K–2Cl– symporter in the ascending limb of the loop of Henle. The resultant effect is delivery of more Na⁺ to the distal tubule and enhanced urinary loss of Na⁺ and water. Unfortunately, the resultant increase in urinary excretion of H⁺ and K⁺ can lead to arrhythmias. The potential for arrhythmias is exacerbated by the loss of Mg²⁺ and Ca²⁺ and an underlying vulnerability of the myocardium in CHF. However, loop diuretics are still part of the mainstay of therapy for CHF despite these potential problems and the absence of well-controlled multicenter clinical trials. The rationale for their use is so compelling that placebo-controlled studies appear unethical. Moreover, furosemide was accepted as the standard of care in all of the clinical trials that form the basis for recommended therapy for CHF. The use of the potassium-sparing diuretic spironolactone has been shown to improve survival and is discussed below.

**Spironolactone**

Spironolactone (*Aldactone*) is the only diuretic that has been shown in a double-blind multicenter prospective clinical trial to improve survival in CHF. The addition of spironolactone to digitalis and an angiotensin-converting enzyme (ACE) inhibitor significantly improved survival among patients with chronic severe heart failure. This study was conducted with patients who were not taking a β-adrenoceptor blocking agent. It is unclear at present whether the addition of spironolactone to a combination of digitalis, ACE inhibitor, and a β-blocker will also confer additional benefit.

Spironolactone competitively inhibits the binding of aldosterone to cytosolic mineralocorticoid receptors in the epithelial cells in the late distal tubule and collecting duct of the kidney. Aldosterone enhances salt and water retention at the expense of enhanced renal K⁺ and H⁺ excretion. Spironolactone enhances diuresis by blocking sodium and water retention while retaining potassium. An obvious potential side effect is hyperkalemia, which is aggravated by the potassium-retaining properties of the ACE inhibitors. The likely concomitant use of the loop diuretic furosemide, which depletes K⁺, dictates careful monitoring of serum potassium to avoid life-threatening rhythm disturbances.

There is also evidence for the existence of mineralocorticoid receptors on cardiac myocytes. This raises the intriguing possibility that spironolactone could mediate important direct effects on the myocardium in CHF.

**HYDRALAZINE AND NITRATES**

A major advance in the pharmacological management of CHF has been the demonstration that afterload reduction improved survival. The concept of afterload reduction was developed for the treatment of mitral regurgitation. It was noted that a decrease in systemic vascular resistance, as reflected in lower arterial blood pressure, resulted in an increase in the percentage of blood that flowed from the left ventricle to the aorta as opposed to the left atrium (decreased regurgitant fraction). The decrease in backup of blood into the lungs provided considerable symptomatic relief from dyspnea, fatigue, and chest pain. It was reasoned that patients with CHF often also have mitral regurgitation and might similarly benefit from more forward (left ventricle to aorta), as opposed to backward (left ventricle to left atrium), blood flow. A VA Cooperative Study in which vasodilators were added to digitalis and furosemide was the first to demonstrate a significant improvement in survival in CHF. Patients were given either prazosin as an α-adrenoceptor blocking agent or the combination of the direct vasodilator hydralazine and a nitric oxide–mediated vasodilator, that is, one of the nitrates. There were fewer deaths among the patients on the combination of hydralazine and nitrates. Patients taking prazosin did not benefit, probably because chronic therapy with prazosin results in tachyphylaxis. The mechanisms of action of prazosin, hydralazine, and organic nitrates are discussed in more detail elsewhere.

**ANGIOTENSIN-CONVERTING ENZYME INHIBITORS**

The relative ease of administration and superior efficacy of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers (ARB) have largely relegated hydralazine and nitrate therapy to second-line therapies for CHF. The demonstration of the survival benefit conferred by vasodilator therapy resulted
in a paradigm shift in the approach to CHF. It was recognized that the way to improve survival in heart failure was not by directly addressing the weakened heart pump but rather by reversing the inappropriate peripheral vasoconstriction that results from neurohumoral activation.

Captopril (Capoten) was the original prototype product, and it was administered three times a day. A once-a-day preparation was subsequently patented and marketed. Prospective multicenter double-blind placebo-controlled clinical trials have repeatedly demonstrated an early and persistent survival benefit with ACE inhibitors in CHF patients. ACE inhibitors were found superior to hydralazine and nitrates in a direct comparison. **ACE inhibitors are now clearly the agents of first choice in the pharmacological management of CHF.** There are also a number of additional reasons to use ACE inhibitors. The HOPE trial and other studies demonstrated additional survival and renal protective benefits of ACE inhibition in diabetic and/or hypertensive patients long before they develop CHF.

Our understanding of the mechanism of action of ACE inhibitors has evolved along with our growing appreciation of the physiological and pathophysiological role of angiotensin II. Initially, angiotensin II was shown to be elaborated in response to low blood flow to the kidney in animal models of hypertension. Low flow to the kidney occurs when damage to the heart results in a low cardiac output. The low EF criterion for CHF noted previously is a noninvasively determined surrogate marker for a low cardiac output. The low flow to the kidney is perceived as bleeding. The appropriate response by the kidney to low flow is to elaborate renin. Renin circulates to the liver. Renin in the liver converts angiotensinogen to angiotensin I. Angiotensin I travels to the lung, where it is converted to angiotensin II by ACE.

Angiotensin II binds to its receptor and increases intracellular ionized free calcium. This increase in intracellular ionized free calcium causes vasoconstriction by vascular smooth muscle cells, aldosterone secretion by adrenal glomerulosa cells, increased central sympathetic outflow, and enhanced thirst. This system is activated as part of the normal host response to stressful injury, such as bleeding or trauma. The systemic angiotensin II levels rise acutely to retain fluid and improve short-term survival following injury. Unfortunately, these short-term adaptive mechanisms are not designed to protect against the long-term consequences of chronic low blood flow from CHF. The extraordinary success of ACE inhibitors in CHF clearly demonstrates the harmful effects of chronic angiotensin II activation.

Further refinement of this basic understanding followed. First of all, ACE inhibitors not only block the conversion of angiotensin I to angiotensin II; they also block the breakdown of bradykinin. Kinins are vasodilators and serve as part of the yin–yang of the vascular system (i.e., vasoconstrictors vs. vasodilators). The use of an ACE inhibitor results in the elaboration of more kinins and less angiotensin II. Thus, the benefits of ACE inhibitors may derive from their elaboration of more kinins in addition to their inhibition of angiotensin II formation.

Efforts to elucidate the mechanisms responsible for the pharmacological efficacy of ACE inhibitors have been further complicated by the discovery of alternative pathways for forming angiotensin II independent of the conversion of angiotensin I to angiotensin II. Other cellular enzymes, such as chymases and trypsin, can also elaborate angiotensin II. And finally, at least two distinct angiotensin II receptors have been cloned and sequenced; they are confusingly named the type 1 and type 2 angiotensin II (AT-1; AT-2) receptors.

Elaboration of angiotensin II can result in either of two effects on an individual cell, depending on the relative numbers of AT-1 and AT-2 receptors. Relatively selective AT-1 receptor blockers have been developed in an effort to achieve superior efficacy with enhanced selectivity. Thus far, clinical studies indicate that ARBs may be as effective as ACE inhibitors and have fewer side effects. The consensus in their use is to try an ACE inhibitor as the first-line therapy before using an ARB, such as valsartan or losartan. However, ACE inhibitors can induce a very troubling cough in susceptible individuals as a result of the increase in kinins. ARBs serve as a very good substitute for such patients.

### β-ADRENOCEPTOR BLOCKING DRUGS

For many years the prevailing view was that β-blockers are contraindicated in CHF. The physiological rationale for not using β-blockers in heart failure was certainly well founded. Heart failure patients have a decrease in cardiac output. Since cardiac output is a function of stroke volume times heart rate (CO = SV × HR), an increased heart rate would be necessary to maintain an adequate cardiac output in the presence of the relatively fixed decrease in stroke volume observed in CHF. A rapid increase in heart rate does play an important role in the physiological response to acute hemorrhage. Thus, a decrease in heart rate, along with a depression in contractility produced by β-blockers, would be expected to precipitate catastrophic decompensation; and this certainly can happen in the acute setting.

Several subsequent studies have led to the incorporation of β-blocker therapy, using either carvedilol or metoprolol, into the standard of care for CHF. Patients already taking digitalis, furosemide, and an ACE inhibitor were prescribed a β-blocker in these studies. Surprisingly, the long-term use of β-blockers in CHF improved ventricular function and prolonged survival. The assumption that an increased heart rate is neces-
sary to maintain an adequate cardiac output in the face of a reduced stroke volume is clearly not true in CHF.

The benefits of the use of β-blockade appear to exceed by far the risks of bronchospasm in patients diagnosed with chronic obstructive pulmonary disease (COPD) and/or suppression of hypoglycemic responses in diabetics. COPD is very different from bronchospastic asthma. Young people with asthma have highly reactive airways and can die within hours of a bronchospasm in response to an exposure to an external agent. This highly reversible dynamic condition contrasts sharply with the destruction of connective tissue in lung parenchyma and dead airway sacs that are not very reactive. This is a very different phenomenon.

β-Blockers are adrenoceptor antagonists that bind to the β-receptor at the same site as do endogenous β-adrenergic agonists, such as norepinephrine. Norepinephrine binds to the adrenergic receptor, which activates a G protein, which participates in the conversion of ATP to cAMP via adenylyl cyclase. cAMP activates protein kinase A (protein kinase A, or PKA) to phosphorylate proteins, such as the sarcoplasmic L-type Ca²⁺ channel, that subsequently increase calcium, increase heart rate, conduction, and contraction. β-Blockers bind to the same receptor as does norepinephrine but do not facilitate G protein coupling. Occupation of the binding site by the β-blocker prevents norepinephrine from binding to it and stimulating cAMP formation.

Circulating plasma norepinephrine levels correlate inversely with survival in CHF; that is, higher levels of norepinephrine are associated with a decrease in survival. It appears that norepinephrine levels are more than just markers of disease severity: norepinephrine is actually directly toxic to cardiac myocytes, at least in culture. The addition of either an α- or β-blocker confers partial protection from norepinephrine damage. Combined α- and β-blockade confers additive protection. These data from animal studies may be relevant to human heart failure, since they suggest that both α- and β-adrenoceptor blockade may be beneficial in the management of CHF. This rationale favors the use of the combined nonselective β- and α-blocker carvedilol over the relatively selective β₁-antagonist metoprolol. In addition, in CHF the number of β₁-receptors decreases while the number of β₂-receptors increases, and the ratio of β₁- to β₂-receptors changes. Thus, the β₁-selectivity of metoprolol may not confer any advantage over the less specific β-blocker carvedilol. It is clear from clinical trial data that β-adrenoceptor blockers are not all the same. Use of some has produced improvements in survival, and others have produced no improvements at all. The mechanisms responsible for these benefits are not yet established. Speculation includes up-regulation of β-adrenoceptors, improved G-protein coupling, altered regulation of nitric oxide, and so on.

### Study Questions

1. A 40-year-old man goes to the emergency department because of an intractable cough for the past few days. No one else in his household has any cough, fever, upper respiratory infection, and so on. He was released from the hospital a week ago with the diagnosis of idiopathic dilated cardiomyopathy following an extensive evaluation that revealed normal coronary anatomy and a left ventricular EF of 38%. He was discharged with prescriptions for digoxin, furosemide, captopril, and carvedilol. He has been more active and has noted improvement in his dyspnea and fatigue that prompted his initial presentation 10 days ago. He appreciates all of the care that he received and apologizes for making a fuss over the cough. He states that his wife made him come in because she was concerned that it might be his heart. He states that the cough is different from the congested feeling he had 10 days ago. On examination, he was afebrile; his heart rate was 60 beats per minute; blood pressure, 100/60. Neck veins were

### cAMP-ELEVATING AGENTS

The immediate effect of increasing intracellular cAMP levels is an increase in contractility. This has been observed repeatedly in acutely ill patients in the intensive care unit with the intravenous infusion of either β-adrenergic agonists (e.g., dobutamine) or the phosphodiesterase inhibitors milrinone (Corotrope) and amrinone (Inocor). Binding of dobutamine to cardiac myocyte β-adrenoceptors results in G-protein coupling, activation of adenylyl cyclase, and the conversion of ATP to cAMP.

Administration of either milrinone or amrinone increases cAMP levels by preventing its degradation by cardiac myocyte phosphodiesterases. Both classes of cAMP-elevating agents have been shown to be helpful for the acute short-term management of the decompensated patient. Unfortunately, the long-term continuous use of either of these classes of agents in the outpatient setting has been associated with an increase in mortality in CHF. However, the use of these drugs in appropriately selected patients is highly effective for symptomatic relief.
flat; carotid upstrokes were normal. Chest and lungs were clear. Heart revealed a regular rate and rhythm without murmurs, gallops, or rubs. Abdomen was soft and not tender. Bowel sounds were present without organomegaly. Extremities revealed no cyanosis, clubbing, or edema. Chest radiograph and electrocardiogram revealed no acute changes and no active disease. The physician was satisfied that he was hemodynamically stable and the cough was not resulting from worsening heart failure. What is a reasonable next step?  
(A) Admit to the hospital to exclude (rule out) a myocardial infarction  
(B) Apply a PPD skin test to exclude tuberculosis  
(C) Substitute an angiotensin II receptor blocker for the ACE inhibitor  
(D) Provide reassurance and continue with current medications  
(E) Immediately stop the \( \beta \)-adrenergic blocker, carvedilol

2. A 67 year old woman has had fatigue and shortness of breath over the past few months. She has diabetes and hypertension for which she has been treated for 25 years with appropriate medications. She is status post three myocardial infarctions (MI \( \times 3 \)) and has known inoperable coronary artery disease and CHF. She has been very compliant with her complicated medical regimen, which includes digitalis, an ACE inhibitor (fosinopril), loop diuretic (furosemide), \( \beta \)-adrenergic receptor blocker (carvedilol) and aldosterone antagonist (spironolactone). On examination she was noted to be in acute respiratory distress with a respiratory rate of 24, a heart rate of 60, and blood pressure of 110/60. She was anxious and uncomfortable but polite and cooperative. Neck veins were elevated to 8 cm with the patient partially supine. Lungs revealed rales to the angles of the scapulae and no active disease. The physician was satisfied that he was hemodynamically stable and the cough was not resulting from worsening heart failure. What is a reasonable next step?  
(A) Admit to the hospital to exclude (rule out) a myocardial infarction  
(B) Apply a PPD skin test to exclude tuberculosis  
(C) Substitute an angiotensin II receptor blocker for the ACE inhibitor  
(D) Provide reassurance and continue with current medications  
(E) Immediately stop the \( \beta \)-adrenergic blocker, carvedilol

3. Digitalis functions to improve congestive heart failure by  
(A) Induction of emesis  
(B) Activation of \( \alpha \)-adrenergic receptors  
(C) Improving survival in patients of heart failure  
(D) Binding to and inhibiting the Na–K ATPase enzyme in cardiac myocytes  
(E) Deactivation of the angiotensin receptor

4. The combination of hydralazine and nitrates has been shown to improve survival in patients of heart failure. All of the following statements about this combination are true except:  
(A) The combination serves to decrease both afterload and preload.  
(B) Prazosin is as effective as the combination in treatment of congestive heart failure.  
(C) The concept of afterload reduction is principally derived from patients of significant mitral regurgitation.  
(D) The VA cooperative study was a landmark trial demonstrating the beneficial effect of hydralazine and nitrates combination in patients of heart failure.  
(E) \( \beta \)-Blockers have been effective in the treatment of heart failure. They primarily exert their effect by  
(A) Binding to the receptor that binds norepinephrine  
(B) Inducing a prominent diuretic effect  
(C) Increasing contractility  
(D) Improving asthma control  
(E) Increasing heart rate to meet the additional demands placed upon the heart in CHF

**ANSWERS**

1. C. The most likely diagnosis is ACE inhibitor–induced cough. A reasonable approach is to substitute an ARB (angiotensin II receptor blocker) such as valsartan or losartan for the ACE inhibitor, captopril. Reassure and encourage the patient and spouse that you think the cough will resolve a few days after stopping the ACE inhibitor. There is generally no benefit to trying any other ACE inhibitor, as the side effect is a class effect resulting from enhanced kinin activity from ACE inhibition. Myocardial infarction is extremely unlikely in this patient based on the catheterization data showing normal coronary anatomy. Abrupt withdrawal of a \( \beta \)-blocker may precipitate tachycardia and hypertension and should be avoided.

2. A. This woman with CHF has obviously decompensated despite compliance with standard care. She is symptomatic and may benefit from a short course of high-intensity intravenous therapy with a cAMP-elevating agent (e.g., dobutamine, milrinone, amrinone). This may be a reversible event or part of the inevitable decline of the disease process. Approximately 45\% of CHF patients die suddenly of a presumed electrical event (e.g., ventricular tachycardia, asystole). The others die slowly of progressive deterioration. Many patients at the end stages of CHF prefer to try repeated outpatient inotropic (cAMP elevating) therapy for symptomatic...
relief even though it may be associated with a higher incidence of sudden death.

3. D. Inhibition of Na–K ATPase leads to an elevation of intracellular Na⁺. This results in an increase in intracellular Ca²⁺ and an enhanced myocardial contractibility. There is no definitive evidence that digitalis improves survival of patients in heart failure, but it clearly improves the symptoms of this condition.

4. B. Prazosin has been shown not to be as effective as the combination of hydralazine and nitrates.

5. A. The salutary effect of β-blockers appears to be due solely to its binding to the β-receptor, which prevents norepinephrine binding and stimulates cAMP formation. The other choices do not occur.

SUPPLEMENTAL READING

CASE STUDY Therapy for Inoperable Coronary Artery Disease

A 75-year-old man has inoperable coronary artery disease with an EF of 31%. He is receiving digoxin, furosemide, and an ACE inhibitor. He is unable to walk more than 50 feet on flat ground before getting short of breath (dyspnea on exertion at 50 feet). His heart rate at rest is 85 beats per minute and his blood pressure while seated is 130/85. His neck veins are flat; carotid upstrokes are normal; lungs are clear; and heart examination reveals no murmurs, gallops, or rubs. His extremities reveal no cyanosis, clubbing, or edema. The remainder of the physical examination is unremarkable. What is your next therapeutic option?

ANSWER: Start a low-dose β-adrenergic blocker. Presently the choices are either the β1-selective adrenergic blocker, metoprolol, or the combined nonselective β- and α-adrenergic blocker carvedilol. The target heart rate at rest should be in the range of 50 to 60 beats per minute. The target blood pressure should be in the range of 90 to 110 systolic, or orthostatic symptoms of light-headedness develop.