A 62-year-old woman with a history of atrial fibrillation presents to her primary care physician with worsening shortness of breath when she lies down flat in the supine position. She often has to sleep with several pillows at night and has frequent urination at night (nocturia). She has noticed that her ankles are more swollen than usual. Of note, she has run out of digoxin, which she takes to control her heart rate. On examination, she is noted to be slightly hypotensive with a blood pressure (BP) of 90/65 mm Hg. Her heart rate is 120 beats per minute (bpm) and is irregularly irregular, consistent with atrial fibrillation. She has bilateral pulmonary rales and increased jugular venous distention. Her heartbeat is irregularly irregular without a murmur. No S₃ or S₄ is noted. She has 3(+) (out of 4)-dependent peripheral edema of the legs. She is diagnosed with congestive heart failure and admitted to the hospital for further management.

◆ What is the cause of the fourth heart sound?
◆ Why does this patient not have an audible S₄?
◆ What factors affect stroke volume?
◆ How does stimulation of muscarinic receptors affect contractility?
ANSWERS TO CASE 11: MECHANICAL HEART ACTIVITY

Summary: A 62-year-old woman has atrial fibrillation with a rapid ventricular response and congestive heart failure. She has run out of digoxin.

◆ **Fourth heart sound:** Filling of the ventricle by atrial systole.

◆ **Reason this patient does not have an S₄:** She is in atrial fibrillation and has no atrial contraction.

◆ **Factors that affect stroke volume:** Contractility, preload (ventricular end-diastolic pressure and ventricular diastolic compliance), and afterload (aortic pressure).

◆ **Stimulation of muscarinic receptors:** Decreases contractility in atria (parasympathetic system).

CLINICAL CORRELATION

This 62-year-old woman has symptoms of congestive heart failure: fatigue, pedal edema, dyspnea, and orthopnea (needing to sleep on pillows). There are many causes for congestive heart failure. In this patient, atrial fibrillation with irregular ventricular rhythm leads to inadequate ventricular filling and decreased stroke volume. The likely explanation in this case is running out of medication (digoxin). Other factors that can present as congestive heart failure include myocardial infarction and cardiomyopathy (decreased contractility) as well as valvular problems (aortic valve stenosis). Clinically, these patients present with symptoms of fluid “backing up” in the cardiovascular system. They often have pulmonary edema, peripheral edema, and increased jugular distention. A chest x-ray will reveal bilateral pulmonary edema with cardiomegaly. An echocardiograph can be used to calculate the ejection fraction, a measure of contractility. The ejection fraction is the fraction of the end-diastolic volume ejected in each stroke volume (normal = 55%). Treatment of congestive heart failure depends on the etiology, but usually diuretics are given to relieve some of the excess fluid and medications are given (digitalis) to increase the contractility of the heart and improve cardiac output. A patient with atrial fibrillation would benefit from medications to decrease conduction through the atrioventricular (AV) node or cardioversion to convert heart rate back to normal sinus rhythm.
APPROACH TO PHYSIOLOGY OF CARDIAC MECHANICS

Objectives

1. Describe excitation–contraction coupling in the heart.
2. Describe factors regulating the force of myocardial contractions.
3. Describe the cardiac cycle.

Definitions

Systole: The period of time during which the heart muscle is contracting.
Diastole: The period of time during which the heart muscle is relaxed.
Heart sounds: The sounds produced by turbulent flow within the heart and by vibrations induced in structures comprising the heart.
Contractility: The ability of a muscle to shorten and/or develop force that does not depend upon a change in initial fiber length or afterload.

DISCUSSION

Cardiac and skeletal muscles have many similarities; however, there are important differences. Both are striated muscles, are excitable, and are regulated by calcium (see case 6). However, cardiac muscle fibers are smaller than skeletal muscle fibers, and, unlike skeletal muscle fibers, cardiac muscle fibers branch and are electrically coupled to one another.

Excitation of myocardial cells results from the propagation of action potentials from nodal cells, conduction fibers, or adjacent myocardial cells through low-resistance membrane junctions. There are no neuromuscular junctions as is seen in skeletal muscle. As in skeletal muscle, the mediator between membrane action potentials (excitation) and contraction is calcium. However, in contrast to skeletal muscle, a significant amount of calcium enters the cell through sarcolemma calcium channels during the action potential. This increase in calcium permeability accounts in large part for the plateau phase of the myocardial action potential, and the calcium that enters triggers the release of additional calcium from the sarcoplasmic reticulum. The entering and released calcium then binds to troponin C to initiate events that lead to contraction. Between action potentials, much of the calcium is taken back up into the sarcoplasmic reticulum by primary active transport. However, to maintain calcium balance, some calcium exits the cell by a secondary active process located on the sarcolemma. Calcium exit is coupled to and driven by the entry of sodium down its electrochemical gradient. The entering sodium then is expelled by the sodium pump.

The force of contraction of cardiac muscle can vary from beat to beat as a result of two basic mechanisms inherent to cardiac muscle. The first is the length–tension (or force) relationship, also known as the Starling law of the
heart. A basic property of all muscles is that there is an optimal length for active force development. At lengths greater and less than this optimal length ($L_o$), less active force will be developed (see Figure 11-1). In vivo, this relationship is not important for skeletal muscles because their lengths are restricted close to $L_o$ because of their attachment to tendons and bones. For the heart, however, the size of the chambers and hence the length of the cardiac muscle cells before systole will vary depending on the end-diastolic volume of blood. This volume in turn depends in large part on central venous pressure and the compliance of the ventricles. Under most conditions, myocardial cells operate at lengths at which an increase in end-diastolic muscle length leads to a more forceful contraction and a larger stroke volume. This helps balance venous return and cardiac output. The length–tension relationship may have both structural and biochemical bases. For active force to develop, myosin cross-bridges must interact with actin filaments. At $L_o$, the overlap of thick and thin filaments is such that every cross-bridge has easy access to actin (thin) filaments, allowing each one to develop force. At muscle lengths longer than $L_o$, some of the cross-bridges do not overlap thin filaments and thus cannot develop force. At muscle lengths less than $L_o$, the lateral distances over which the cross-bridges reach to attach to actin filaments is greater, and at very short lengths, thin filaments from one side can interfere with cross-bridge interactions on the other side. Biochemically, it appears that the calcium sensitivity of the actin–myosin interaction also is impaired at short muscle lengths. Thus, activation of the contractile machinery will be less.

The second mechanism responsible for regulating the force of myocardial contraction is referred to as contractility. Changes in contractility alter the force of contraction at any given muscle length, as shown in Figure 11-2. An increase in contractility will result in greater force and a greater stroke volume.

**Figure 11-1.** Relationship of muscle force and muscle length. The active and passive characteristics are added to supply a composite.
at any muscle length (chamber volume), thus increasing the ejection fraction. A decrease in contractility will have the opposite effect. The mechanisms responsible for changes in contractility mostly involve calcium metabolism and include alterations in (1) calcium entry during the action potential, (2) calcium release from the sarcoplasmic reticulum, (3) calcium binding to troponin-C, (4) calcium uptake by the sarcoplasmic reticulum, and (5) calcium extrusion from the myocyte. Physiologically, changes in contractility result mainly from changes in sympathetic nerve activity. Activation of myocardial β-adrenergic receptors by norepinephrine and epinephrine results in stimulatory G protein activation of adenylyl cyclase and resultant increases in cyclic adenosine monophosphate (cAMP). Increased cAMP activates protein kinase A to phosphorylate key proteins involved in many of the steps of calcium metabolism listed above. The result is greater activation of the myosin–actin interactions and greater force. In contrast, stimulation of muscarinic cholinergic receptors by acetylcholine results in inhibitory G protein activation, inhibition of adenylyl cyclase activity, and less phosphorylation of the same proteins. This results in lesser activation of the myosin–actin interaction and less force.

The pumping of blood by the heart can be described best by considering events during a cardiac cycle, that is, during a systole and the following diastole (see Figure 11-3). During the time marked A, atrial depolarization, as indicated by the P wave of the electrocardiograph (ECG), leads to atrial contraction (atrial systole) and complete ventricular filling. In some cases, the turbulence caused by this filling results in an audible fourth heart sound. During the time marked B, ventricular depolarization, as indicated by the QRS complex of the ECG, leads to a period of ventricular contraction during which ventricular pressure rises, closing the AV valves (producing the first heart sound), but there is no ejection of blood into the aorta. This is the period

Figure 11-2. Force versus muscle length with different contractility characteristics.
of isovolumetric ventricular contraction. During the time marked C, ventricular pressure surpasses aortic pressure and there is rapid emptying of blood, as indicated by the decrease in ventricular volume and the increase in aortic pressure. This constitutes the rapid ventricular ejection phase of the cycle. During the time indicated by D, the ventricles are repolarizing, as indicated by the T wave of the ECG; the force of ventricular contraction is decreasing; and the flow of blood into the aorta slows. This is the reduced ventricular ejection phase. During the time indicated by E, the ventricles continue to relax, and aortic pressure soon exceeds ventricular pressure. This results in closure of the aortic valve and the second heart sound. Ventricular pressure then falls with no change in volume. This is the isovolumetric ventricular relaxation phase. During the time indicated by F, ventricular pressure falls below venous pressure, the AV valve opens, and the ventricle begins to fill rapidly, as indicated by the increase in ventricular volume. This is the rapid ventricular filling phase that sometimes produces an audible third heart sound. The time indicated by G is the period of reduced ventricular filling that occurs before the next period of atrial systole.

Figure 11-3. Cardiac cycle. Pressures in the aorta, left ventricle, and atrium. Key cardiac valvular events are superimposed on the auscultation of the heart and the electrocardiograph.
COMPREHENSION QUESTIONS

[11.1] A healthy 23-year-old medical student is participating in a cardiac echocardiography study. During the isovolumetric ventricular contraction phase of the cardiac cycle, which of the following findings take place?

A. Aortic blood pressure is falling
B. Aortic valve is open
C. AV valve is open
D. Second heart sound is produced
E. Ventricular muscle is undergoing repolarization

[11.2] A 45-year-old man is seen by his cardiologist for increasing weakness and fatigue. He is diagnosed with an enlarged dilated poorly pumping heart (cardiomyopathy). The larger ventricular end-diastolic volumes (“enlarged hearts”) can compensate somewhat for the reduced contractility that occurs in this condition because stretching of the ventricular muscle cells results in which of the following?

A. Decreases efflux of calcium during ventricular repolarization
B. Enhances reuptake of calcium by the sarcoplasmic reticulum
C. Enhances influx of calcium during the action potential
D. Enhances interaction of myosin cross-bridges with actin
E. Improves conduction among muscle cells

[11.3] A 45-year-old male is prescribed an antihypertensive agent that affects calcium channel conductance. If this agent inhibits the influx of calcium into ventricular muscle cells during ventricular excitation, which of the following statements is true?

A. The amount of calcium bound to troponin C during ventricular contraction will be increased.
B. The amount of calcium released from the sarcoplasmic reticulum during ventricular contraction will be increased.
C. The force of ventricular contraction at any given ventricular volume will be decreased.
D. The overlap of thick and thin filaments during ventricular contraction will be increased.

Answers

[11.1] A. During isovolumetric ventricular contraction, ventricular myocytes are depolarized and contract forcefully. Pressure within the ventricle is rising so that it is greater than atrial pressure but less than aortic pressure. Thus, both the AV and the aortic valves are closed. The first, not the second, heart sound is heard as the AV valve closes. Because blood is still flowing out of the aorta during this time, aortic pressure is falling.
D. An increase in ventricular muscle cell length along its length-tension curve results in a more optimal interaction of cross-bridges with actin, thus producing more force than is produced at the shorter length. There is little if any effect on calcium fluxes or on conduction among muscle cells.

C. Inhibition of calcium influx during the action potential also reduces the amount of calcium released from the sarcoplasmic reticulum, resulting in less calcium bound to troponin-C and a reduction in the force of contraction. These changes occur independently of ventricular end-diastolic lengths so that force developed at all lengths will be less than it was before drug administration. Because the change in force is length-independent (a change in contractility), the overlap of thick and thin filaments plays no role.

PHYSIOLOGY PEARLS
❖ Calcium influx during excitation is a major determinant of the force of contraction in cardiac muscle but not in skeletal muscle.
❖ During the rapid ventricular ejection phase, aortic pressure is rising, but during the reduced ventricular ejection phase, aortic pressure begins to fall.
❖ The majority of filling of the ventricle with blood occurs during ventricular diastole before atrial contraction.
❖ Ventricular muscle normally begins contracting when it is at lengths less than the optimal length for force development (on the ascending slope of the length-force relationship).

REFERENCES