

Cardiovascular Physiology

OBJECTIVES

1. To define autorhythmicity, sinoatrial node, pacemaker cells, and vagus nerves
2. To understand the effects of the sympathetic and parasympathetic nervous systems on heart rate
3. To understand the five phases of a cardiac action potential
4. To list at least two key differences between cardiac muscle and skeletal muscle
5. To define effective refractory period and relative refractory period
6. To understand and explain the effects of each of the following on the heart: epinephrine, pilocarpine, atropine, digitalis, temperature, Na^+ , Ca^{2+} , K^+

Cardiac muscle is different from other types of muscle in that cardiac muscle contracts spontaneously, without any external stimuli, whereas other muscles require signals from the nervous system in order to contract. The heart's ability to trigger its own contractions is called **autorhythmicity**. If cardiac muscle cells are isolated, placed into cell culture, and observed under the microscope, the cells can be seen to undergo contractions. No other muscle cells will contract like this unless stimulated in some manner.

Each cardiac cell has its own intrinsic rate of contraction. However, if two cells of different contraction rates are joined together, the two will contract at the rate of the faster cell. In the heart, the cells with the fastest contraction rates join together to form the **sinoatrial node (SA node)**—the “pacemaker” of the heart. Cells in the SA node, called **pacemaker cells**, direct the contraction rate of the entire heart by generating action potentials on a regular basis. These cells (and consequently, heart rate) are under the influence of the *sympathetic nervous system*, which releases the neurotransmitter norepinephrine, and the *parasympathetic nervous system*, which releases the neurotransmitter acetylcholine. Sympathetic neurons cause pacemaker cells to generate action potentials more frequently, and thus increase heart rate. In contrast, parasympathetic neurons have the opposite effect—they cause a decrease in the frequency of action potentials generated by pacemaker cells, and thus decrease heart rate. The heart simultaneously receives both sympathetic and parasympathetic signals in a “push-pull” manner: Increases in one are accompanied by decreases in the other. In healthy adults, resting heart rate is about 70 beats per minute, although this varies depending on factors such as a person's age, physical fitness, and emotional state.

The heart receives sympathetic input via several nerves extending from the spinal cord, and receives parasympathetic input via a single pair of cranial nerves called **vagus nerves**. Once stimulated by a nerve, cardiac muscle cells depolarize. There are five main phases of depolarization (see Figure 6.1). *Phase 0* is characterized by a rapid upswing in membrane potential. Depolarization causes voltage-gated sodium channels in the cell membrane to open, increasing the flow of sodium ions into the cell and increasing the membrane potential. In *phase 1*, the open sodium channels begin to inactivate, decreasing the flow of sodium ions into the cell and causing the membrane potential to fall slightly. At the same time, however, voltage-gated potassium channels close while voltage-gated calcium channels open. The

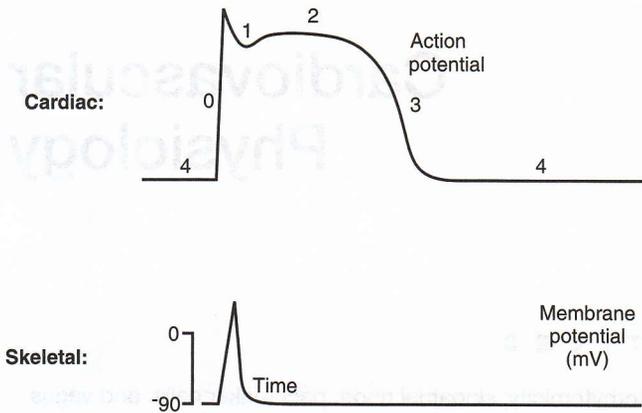


FIGURE 6.1 The stages of the cardiac action potential are shown on the top graph. Notice the difference between the cardiac action potential graph and the skeletal muscle action potential graph below it.

subsequent decrease in the flow of potassium out of the cell and increase in the flow of calcium into the cell act to depolarize the membrane and curb the fall in membrane potential caused by the inactivation of sodium channels. In *phase 2*, known as the *plateau phase*, the membrane remains in a depolarized state. Potassium channels stay closed and calcium channels stay open. This plateau lasts about 0.2 second. The internal potential then gradually falls to more negative values during *phase 3*, when a second set of potassium channels that began opening in phases 1 and 2 allow significant amounts of potassium to flow out of the cell. The fall in potential causes calcium channels to begin closing, reducing the flow of calcium into the cell and repolarizing the membrane until the resting potential is reached. The period of resting potential until the next depolarization is known as *phase 4*.

Electrical Stimulation

In the following experiments we will be examining the effects of direct stimulation and vagus nerve stimulation of a frog heart. The frog heart is a three-chambered structure, with two atria and a single ventricle. When a frog heart is removed from the frog's body, it will continue to beat for some time—convenient for experimental purposes. Although there are obvious differences between a frog heart and a human heart (e.g., human heart rate is faster), their underlying physiological mechanisms are very similar.

Choose **Frog Cardiovascular Physiology** from the main menu. The opening screen for the “Electrical Stimulation” experiment will appear (see Figure 6.2).

At the left you will see a heart suspended by a thread with a hook through the heart apex. The heartbeat is visible on the oscilloscope monitor in the upper right quarter of the screen. (Note that the heartbeat trace is *not* the same graph as the graph in Figure 6.1. The heartbeat trace shows muscle contraction, whereas Figure 6.1 shows cardiac action potential.) Observe the trace of the normal heartbeat. There is a small rise just prior to the larger rise. The smaller rise is *atrial contraction*, while the larger rise is *ventricular contraction*

(Figure 6.3a). In response to stimuli being administered to the heart, the trace may exhibit *extrasystoles*, or extra beats, followed by a *compensatory pause* (Figure 6.3b).

In the lower left corner of the monitor is a **Heart Rate** window, which displays the heart rate in beats per minute (bpm). To the right of this is a status window displaying the status of the heartbeat. The status window will display one of the following: *Heart Rate Normal* (heart rate at resting condition), *Heart Rate Changing* (which will correspond to changes in the **Heart Rate** window), or *Heart Rate Stable* (heart rate is steady but is either higher or lower than at resting condition).

The white tube visible at the bottom right of the heart represents the vagus nerve. Recall that this is the nerve that delivers signals from the parasympathetic nervous system to the heart. Below the heart is a tray, and below the tray are two electrodes: one is labeled **Direct Heart Stimulation**, the other **Vagus Nerve Stimulation**. You will be clicking and dragging each of these electrodes to the electrode holder (the vertical post with four green squares). The electrode holder is emerging from a box called the *stimulator*. By clicking the **Single Stimulus** or **Multiple Stimulus** buttons after placing an electrode in the electrode holder, you will administer electrical stimuli to the frog heart.

Examine the heartbeat tracing again. This is the “baseline” heartbeat against which all others will be compared. Note that the resting heartbeat is between 59 and 61 bpm.

ACTIVITY 1

Direct Heart Stimulation

In Exercise 2, Skeletal Muscle Physiology, we witnessed the phenomenon of *summation* in skeletal muscles. Recall that summation was the result of the skeletal muscle being stimulated with such frequency that twitches overlapped and resulted in a stronger contraction than a stand-alone twitch. This was possible because skeletal muscle has a relatively short **refractory period** (a period during which no action potentials can be generated). Unlike skeletal muscle, cardiac muscle has a relatively *long* refractory period, and is thus incapable of summation. In fact, cardiac muscle is incapable of reacting to any stimulus before about the middle of phase 3, and will not respond to a normal cardiac stimulus before phase 4. The period of time between the beginning of the cardiac action potential and the approximate middle of phase 3 is the **effective refractory period**. The period of time between the effective refractory period and phase 4 is the **relative refractory period**. The refractory period of cardiac muscle is about 250 milliseconds—almost as long as the contraction of the heart.

In this activity we will use direct heart stimulation to better understand the refractory period of cardiac muscle.

1. Click on the **Direct Heart Stimulation** electrode and drag it to the electrode holder (the post with the four green squares). Release the electrode; it will click into place, touching the ventricle of the heart.
2. Look at the heartbeat trace. Recall that the smaller rise is atrial contraction and the larger rise is ventricular contraction. Click **Single Stimulus** right at the beginning of ventricular contraction.

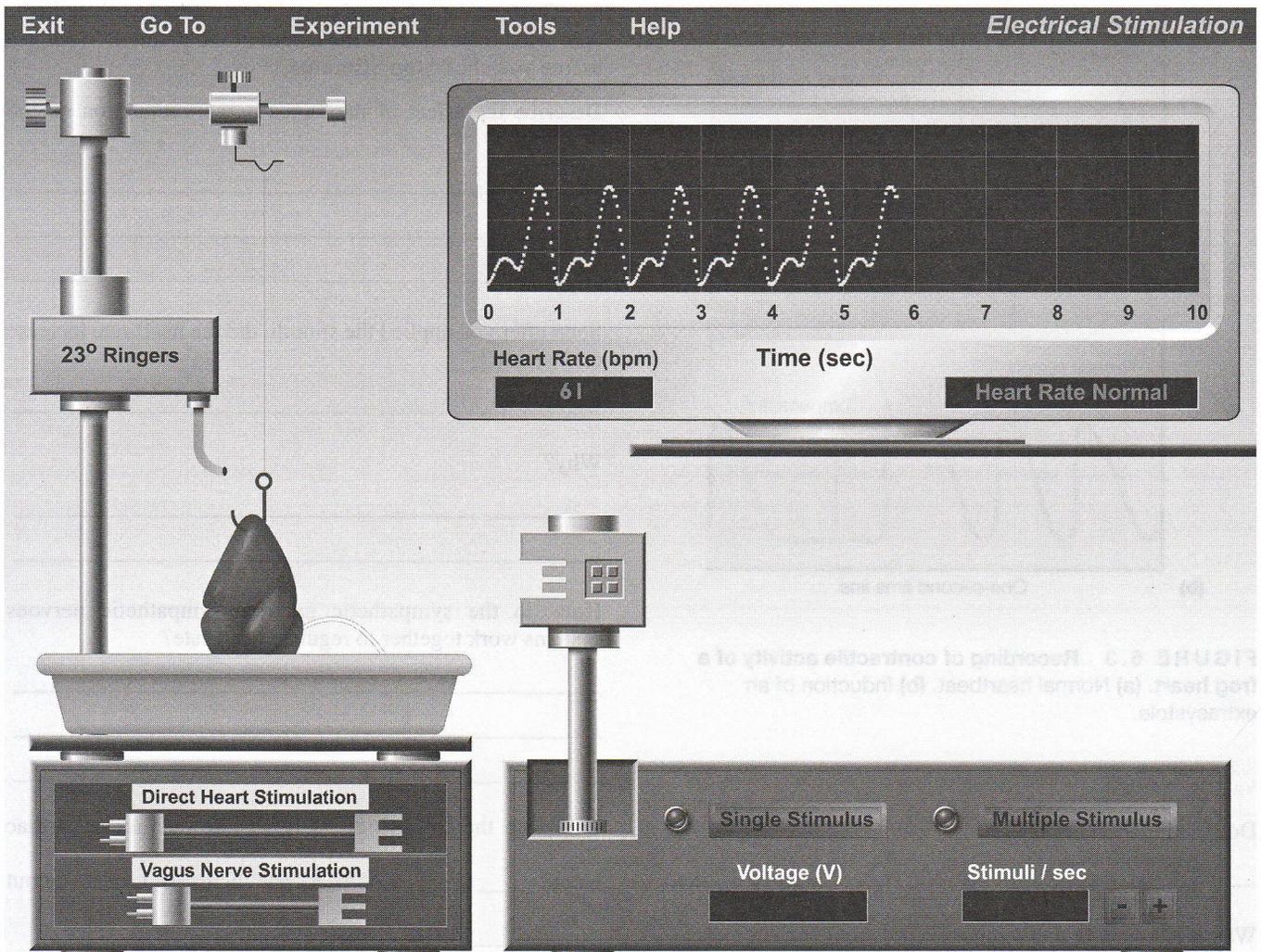


FIGURE 6.2 Opening screen of the Electrical Stimulation experiment.

Did you see any change in the trace?

Why/why not?

3. Click **Single Stimulus** again, this time near the peak of ventricular contraction.

Did you see any change in the trace?

Why/why not?

4. Click **Single Stimulus** again, this time during the “fall” of ventricular contraction. If you do not see any change in the trace, try clicking **Single Stimulus** twice in quick succession until you do see a change.

Describe the change you see in the trace. How does it differ from the baseline trace?

5. Next, click on **Multiple Stimulus** (note that the button changes to **Stop Stimulus**). This will administer repeated stimuli (20 per second) to the heart. After a few seconds, click **Stop Stimulus** to stop the stimulations.

What effect do the repeated stimuli have on the heartbeat trace? Describe the trace.

What part of the trace shows the refractory period?

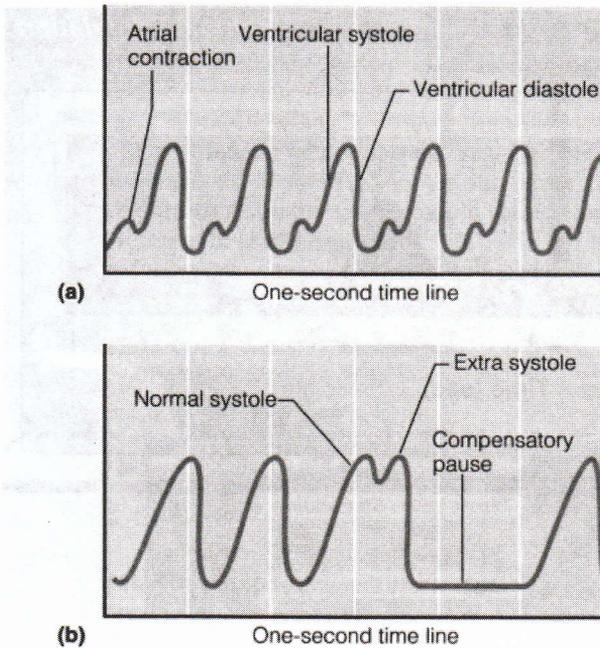


FIGURE 6.3 Recording of contractile activity of a frog heart. (a) Normal heartbeat. (b) Induction of an extrasystole.

Does summation occur?

Why is it important that summation not occur in heart muscle?

6. Return the **Direct Heart Stimulation** electrode to its original location. ■

ACTIVITY 2

Vagus Nerve Stimulation

In this activity we will be indirectly stimulating the heart by stimulating the vagus nerve. Recall that the vagus nerve carries parasympathetic signals to the heart.

1. Click the **Vagus Nerve Stimulation** electrode and drag it to the electrode holder. Notice that when the electrode clicks into place, the vagus nerve will be draped over it. Any stimuli applied will go directly to the vagus nerve and indirectly to the heart.
2. Click **Multiple Stimulus**. Note that the number of stimuli is preset to 50 stimuli/second.

3. Observe the effects of stimulation on the heartbeat trace. Allow the trace to cross the length of the monitor five times before you click **Stop Stimulus**.

Describe the effect of the vagus nerve stimulation on the heartbeat.

Soon after you applied the stimuli, did the heart rate increase or decrease?

Why?

How do the sympathetic and parasympathetic nervous systems work together to regulate heart rate?

Complete the following: As heart rate decreases, cardiac output _____.

As heart rate increases, cardiac output _____.

Research has shown that in the absence of neural or hormonal influences, the SA node generates action potentials at a frequency of approximately 100 beats per minute. Yet, the average resting heart rate is 70 beats per minute. What does this tell you about the parasympathetic nervous system in relation to the sympathetic nervous system and hormones?

Modifiers of Heart Rate

Next we will observe the effects of various drugs, hormones, and ions on heart rate. Click **Experiment** at the top of the screen and then select **Modifiers of Heart Rate**. You will see the opening screen shown in Figure 6.4. Notice the seven dropper bottles resting on a shelf above the monitor. You will be administering drops of each bottle's contents onto the frog heart and observing the effects. You will also be keeping a record of your data by clicking the **Record Data** button on the data collection box at the bottom of the screen. You may print your recorded data at any time by clicking **Tools** at the top of the screen and then selecting **Print Data**.

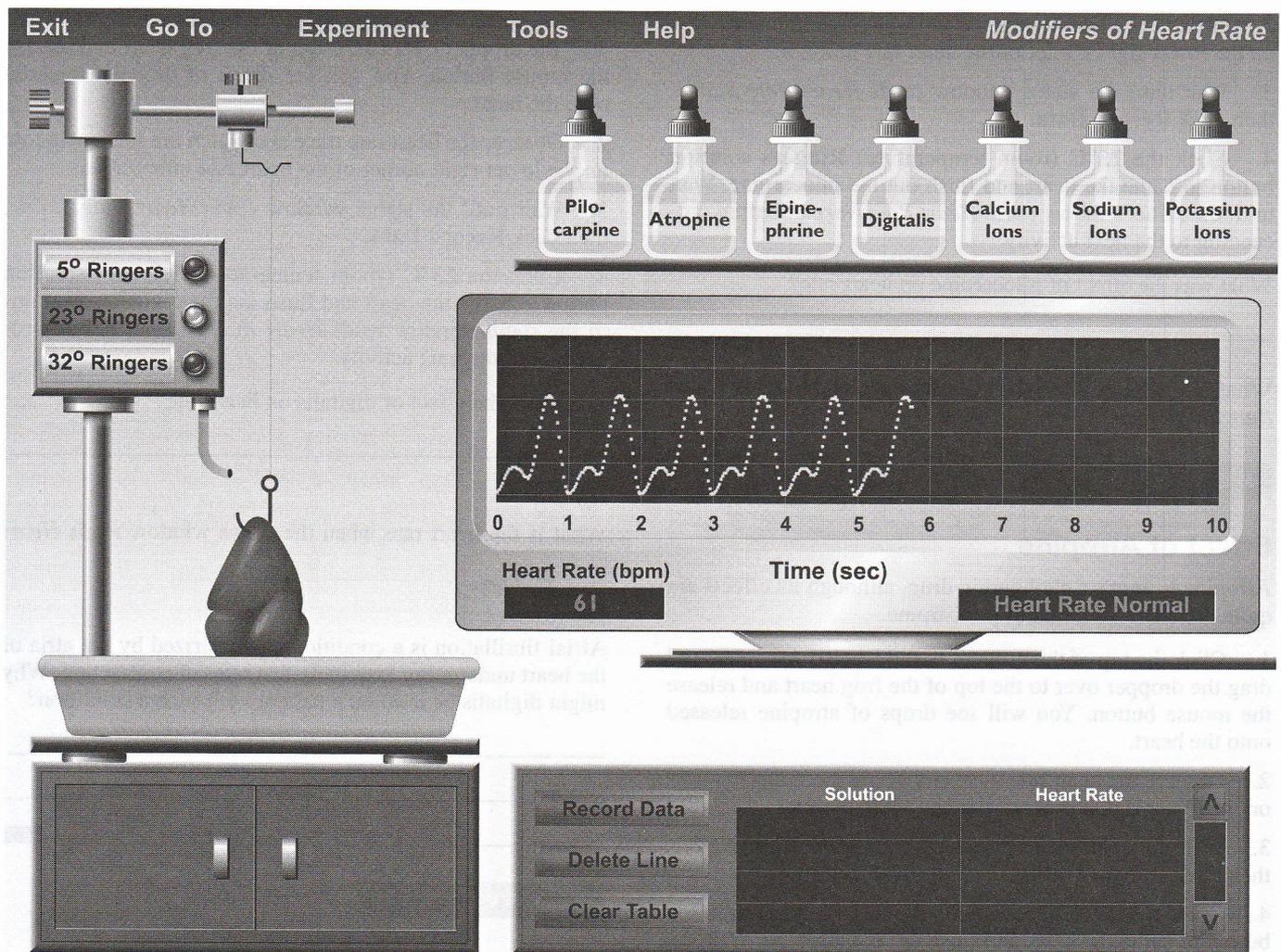


FIGURE 6.4 Opening screen of the Modifiers of Heart Rate experiment.

ACTIVITY 3

Effect of Epinephrine

Epinephrine is a hormone secreted by the adrenal glands. It travels through the bloodstream to the heart, on which it has a significant effect. Epinephrine is an important mediator of rapid fuel mobilization, or increasing metabolic rate.

1. Click the top of the dropper bottle labeled **Epinephrine** and drag the dropper over to the top of the frog heart and release the mouse button. You will see drops of epinephrine released onto the heart.
2. Observe the heart rate trace and watch the status window on the lower right corner of the heart rate monitor.
3. Wait until the status window reads *Heart Rate Stable*, then click **Record Data**.
4. Click the **23°C** (room temperature) **Ringers** solution button to bathe the heart and flush out the epinephrine. Wait until the status window reads *Heart Rate Normal* before proceeding to the next activity.

What was the effect of epinephrine on heart rate?

Does this effect mimic the effect of the sympathetic nervous system or that of the parasympathetic nervous system?

What is the heart rate when the status window reads *Heart Rate Stable*?

ACTIVITY 4

Effect of Pilocarpine

Pilocarpine is a *cholinergic* drug—that is, a drug that inhibits, mimics, or enhances the action of acetylcholine in the body.

1. Click the top of the dropper bottle labeled **Pilocarpine** and drag the dropper over to the top of the frog heart and release the mouse button. You will see drops of pilocarpine released onto the heart.

2. Observe the heart rate trace and watch the status window on the lower right corner of the heart rate monitor.
3. Wait until the status window reads *Heart Rate Stable*, then click **Record Data**.
4. Click the **23°C** (room temperature) **Ringers** solution button to bathe the heart and flush out the pilocarpine. Wait until the status window reads *Heart Rate Normal* before proceeding to the next activity.

What was the effect of pilocarpine on heart rate?

What is the heart rate when the status window reads *Heart Rate Stable*?

ACTIVITY 5

Effect of Atropine

Atropine is another cholinergic drug, although its effects are quite different from that of pilocarpine.

1. Click the top of the dropper bottle labeled **Atropine** and drag the dropper over to the top of the frog heart and release the mouse button. You will see drops of atropine released onto the heart.
2. Observe the heart rate trace and watch the status window on the lower right corner of the heart rate monitor.
3. Wait until the status window reads *Heart Rate Stable*, then click **Record Data**.
4. Click the **23°C** (room temperature) **Ringers** solution button to bathe the heart and flush out the atropine. Wait until the status window reads *Heart Rate Normal* before proceeding to the next activity.

What was the effect of atropine on heart rate?

What is the heart rate when the status window reads *Heart Rate Stable*?

Circle the correct boldfaced term: Atropine *inhibits* / *mimics* / *enhances* the action of acetylcholine on heart rate.

If you were to administer drops of pilocarpine to the heart and then administer atropine immediately afterward, what effect would you expect to see on the heart rate?

ACTIVITY 6

Effect of Digitalis

Digitalis (also known as digoxin and digitoxin) is a drug that interferes with the normal conduction pathway in the heart by blocking the conduction of the atrial impulses to the ventricles.

1. Click the top of the dropper bottle labeled **Digitalis** and drag the dropper over to the top of the frog heart and release the mouse button. You will see drops of digitalis released onto the heart.

2. Observe the heart rate trace and watch the status window on the lower right corner of the heart rate monitor.

3. Wait until the status window reads *Heart Rate Stable*, then click **Record Data**.

4. Click the **23°C** (room temperature) **Ringers** solution button to bathe the heart and flush out the digitalis. Wait until the status window reads *Heart Rate Normal* before proceeding to the next activity.

What was the effect of digitalis on heart rate?

What is the heart rate when the status window reads *Heart Rate Stable*?

Atrial fibrillation is a condition characterized by the atria of the heart undergoing extremely fast rates of contraction. Why might digitalis be used on a patient with such a condition?

ACTIVITY 7

Effect of Temperature

The frog is a *poikilothermic* animal; its internal body temperature changes depending on the temperature of its external environment. In contrast, humans are *homeothermic*. Our bodies remain at the same temperature (around 37°C) unless we are sick.

1. The frog heart is currently being bathed in room temperature Ringers solution. Click the **5° Ringers** solution button to observe the effects of lowering the temperature.

2. Observe the heart rate trace and watch the status window on the lower right corner of the heart rate monitor.

3. Wait until the status window reads *Heart Rate Stable*, then click **Record Data**.

4. Click the **23° Ringers** solution button to bathe the heart and return it to room temperature. Wait until the status window reads *Heart Rate Normal* before proceeding.

5. Now click on the **32° Ringers** solution button to observe the effects of raising the temperature.

6. Observe the heart rate trace and watch the status window on the lower right corner of the heart rate monitor.

7. Wait until the status window reads *Heart Rate Stable*, then click **Record Data**.