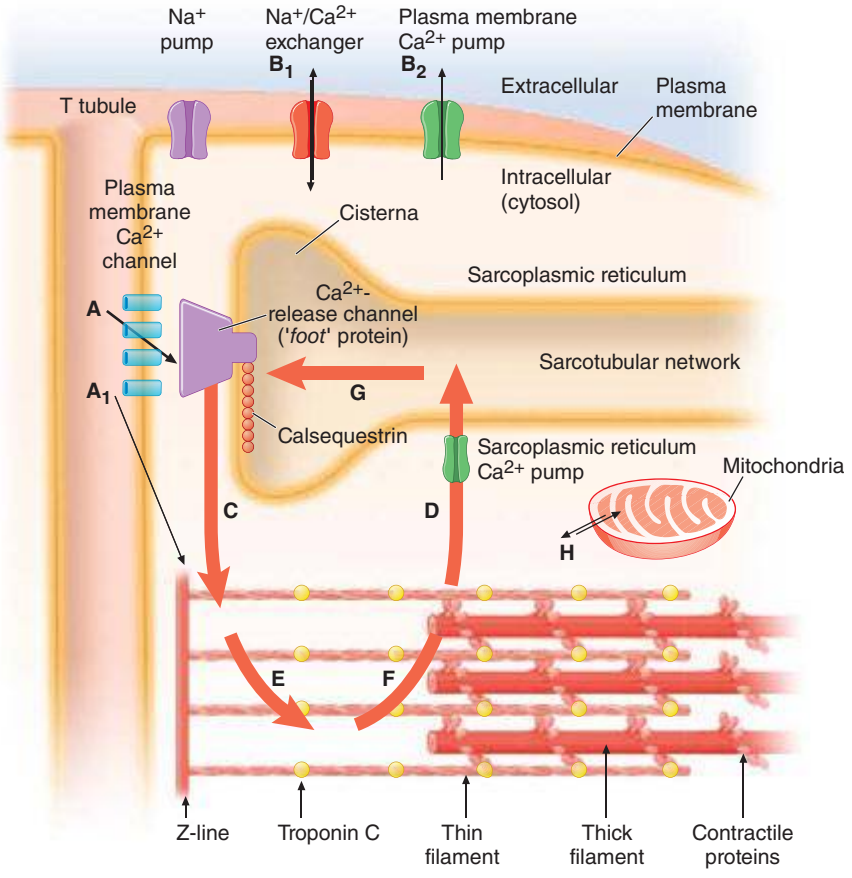


**FIGURE 265e-7 The $Ca^{2+}$ fluxes and key structures involved in cardiac excitation-contraction coupling.** The *arrows* denote the direction of $Ca^{2+}$ fluxes. The *thickness* of each arrow indicates the magnitude of the calcium flux. Two $Ca^{2+}$ cycles regulate excitation-contraction coupling and relaxation. The larger cycle is entirely intracellular and involves $Ca^{2+}$ fluxes into and out of the sarcoplasmic reticulum, as well as $Ca^{2+}$ binding to and release from troponin C. The smaller extracellular $Ca^{2+}$ cycle occurs when this cation moves into and out of the cell. The action potential opens plasma membrane $Ca^{2+}$ channels to allow passive entry of $Ca^{2+}$ into the cell from the extracellular fluid (*arrow A*). Only a small portion of the $Ca^{2+}$ that enters the cell directly activates the contractile proteins (*arrow* $A_1$). The extracellular cycle is completed when $Ca^{2+}$ is actively transported back out to the extracellular fluid by way of two plasma membrane fluxes mediated by the sodium-calcium exchanger (*arrow* $B_1$) and the plasma membrane calcium pump (*arrow* $B_2$). In the intracellular $Ca^{2+}$ cycle, passive $Ca^{2+}$ release occurs through channels in the cisternae (*arrow C*) and initiates contraction; active $Ca^{2+}$ uptake by the $Ca^{2+}$ pump of the sarcotubular network (*arrow D*) relaxes the heart. Diffusion of $Ca^{2+}$ within the sarcoplasmic reticulum (*arrow G*) returns this activator cation to the cisternae, where it is stored in a complex with calsequestrin and other calcium-binding proteins. $Ca^{2+}$ released from the sarcoplasmic reticulum initiates systole when it binds to troponin C *(arrow E)*. Lowering of cytosolic [$Ca^{2+}$] by the sarcoplasmic reticulum (SR) causes this ion to dissociate from troponin (*arrow F*) and relaxes the heart. $Ca^{2+}$ also may move between mitochondria and cytoplasm (H). *(Adapted from AM Katz: Physiology of the Heart, 4th ed. Philadelphia, Lippincott, Williams & Wilkins, 2005, with permission.)*

## VENTRICULAR AFTERLOAD

In the intact heart, as in isolated cardiac muscle, the extent and velocity of shortening of ventricular muscle fibers at any level of preload and of myocardial contractility relate inversely to the afterload, i.e., the load that opposes shortening. In the intact heart, the afterload may be defined as the tension developed in the ventricular wall during ejection. Afterload is determined by the aortic pressure as well as by the volume and thickness of the ventricular cavity. Laplace's law states that the tension of the myocardial fiber is the product of the intracavitary ventricular pressure and ventricular radius divided by wall thickness. Therefore, at any particular level of aortic pressure, the afterload on a dilated left ventricle exceeds that on a normal-sized ventricle. Conversely, at the same aortic pressure and ventricular diastolic volume, the afterload on a hypertrophied ventricle is lower than of a normal chamber. The aortic pressure in turn depends on the peripheral vascular resistance, the physical characteristics of the arterial tree, and the volume of blood it contains at the onset of ejection.

Ventricular afterload critically regulates cardiovascular performance **(Fig. 265e-9)**. As already noted, elevations in both preload and contractility increase myocardial fiber shortening, whereas increases in afterload reduce it. The extent of myocardial fiber shortening and left ventricular size determine stroke volume. An increase in arterial pressure induced by vasoconstriction, for example, augments afterload, which opposes myocardial fiber shortening, reducing stroke volume.

When myocardial contractility becomes impaired and the ventricle dilates, afterload rises (Laplace's law) and limits cardiac output. Increased afterload also may result from neural and humoral stimuli that occur in response to a fall in cardiac output. This increased afterload may reduce cardiac output further, thereby increasing ventricular volume and initiating a vicious circle, especially in patients with ischemic heart disease and limited myocardial $O_2$ supply. Treatment with vasodilators has the opposite effect; when afterload is reduced, cardiac output rises **(Chap. 279)**.

Under normal circumstances, the various influences acting on cardiac performance enumerated above interact in a complex fashion to maintain cardiac output at a level appropriate to the requirements of the metabolizing tissues (Fig. 265e-9); interference with a single mechanism may not influence the cardiac output. For example, a moderate reduction of blood volume or the loss of the atrial contribution to ventricular contraction ordinarily can be sustained without a reduction in the cardiac output at rest. Under these circumstances, other factors, such as increases in the frequency of adrenergic nerve impulses to the heart, heart rate, and venous tone, will serve as compensatory mechanisms and sustain cardiac output in a normal individual.

## EXERCISE

The integrated response to exercise illustrates the interactions among the three determinants of stroke volume: preload, afterload, and contractility (Fig. 265e-8). Hyperventilation, the pumping action of the exercising muscles, and venoconstriction during exercise all augment venous return and hence ventricular filling and preload (Table 265e-2). Simultaneously, the increase in the adrenergic nerve impulse traffic to the myocardium, the increased concentration of circulating catecholamines, and the tachycardia that occur during exercise combine to augment the contractility of the myocardium (Fig. 265e-8, curves 1 and 2) and together elevate stroke volume and stroke work, without a change in or even a reduction of end-diastolic pressure and volume (Fig. 265e-8, points A and B). Vasodilation occurs in the exercising muscles, thus tending to limit the increase in arterial pressure that otherwise would occur as cardiac output rises to levels as high as five times greater than basal levels during maximal exercise. This vasodilation ultimately allows the achievement of a greatly elevated cardiac output during exercise at an arterial pressure only moderately higher than in the resting state.