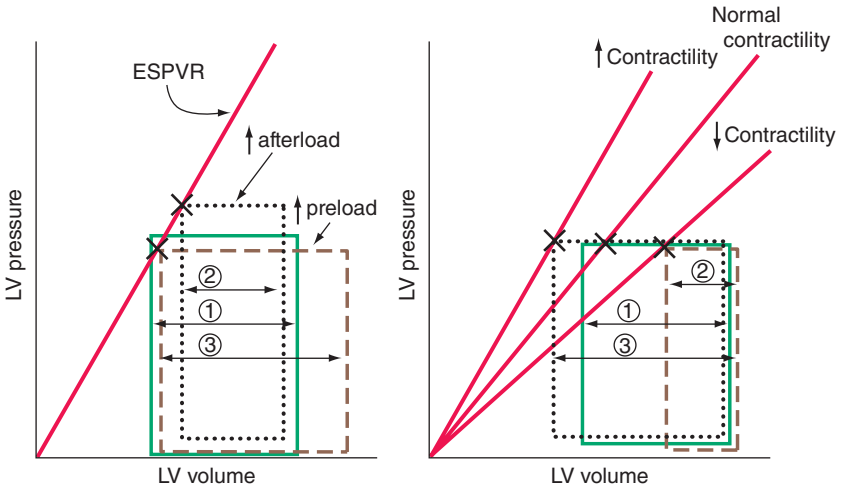

FIGURE 265e-10 The responses of the left ventricle to increased afterload, increased preload, and increased and reduced contractility are shown in the pressure-volume plane. ***Left.*** Effects of increases in preload and afterload on the pressure-volume loop. Because there has been no change in contractility, the end-systolic pressure-volume relationship (ESPVR) is unchanged. With an increase in afterload, stroke volume falls (1 → 2); with an increase in preload, stroke volume rises (1 → 3). ***Right.*** With increased myocardial contractility and constant left ventricular end-diastolic volume, the ESPVR moves to the left of the normal line (lower end-systolic volume at any end-systolic pressure) and stroke volume rises (1 → 3). With reduced myocardial contractility, the ESPVR moves to the right; end-systolic volume is increased, and stroke volume falls (1 → 2).

The end-systolic left ventricular pressure-volume relationship is a particularly useful index of ventricular performance because it does not depend on preload and afterload (Fig. 265e-10). At any level of myocardial contractility, left ventricular end-systolic volume varies inversely with end-systolic pressure; as contractility declines, end-systolic volume (at any level of end-systolic pressure) rises.

DIASTOLIC FUNCTION

Ventricular filling is influenced by the extent and speed of myocardial relaxation, which in turn depends on the rate of uptake of Ca^{2+} by the SR; the latter may be enhanced by adrenergic activation and reduced by ischemia, which reduces the ATP available for pumping Ca^{2+} into the SR (see above). The stiffness of the ventricular wall also may impede filling. Ventricular stiffness increases with hypertrophy and conditions that infiltrate the ventricle, such as amyloid, or is caused by an extrinsic constraint (e.g., pericardial compression) (Fig. 265e-11).

Ventricular filling can be assessed by continuously measuring the velocity of flow across the mitral valve using Doppler ultrasound. Normally, the velocity of inflow is more rapid in early diastole than during atrial systole; with mild to moderately impaired relaxation, the rate of early diastolic filling declines, whereas the rate of presystolic filling rises. With further impairment of filling, the pattern is "pseudo-normalized," and early ventricular filling becomes more rapid as left atrial pressure upstream to the stiff left ventricle rises.

CARDIAC METABOLISM

The heart requires a continuous supply of energy (in the form of ATP) not only to perform its mechanical pumping functions, but also to regulate intracellular and transsarcolemmal ionic movements and concentration gradients. Among its pumping functions, the development of tension, the frequency of contraction, and the level of myocardial contractility are the principal determinants of the heart's substantial energy needs, making its O_2 requirements approximately 15% of that of the entire organism.

Most ATP production depends on the oxidation of substrate (glucose and free fatty acids [FFAs]). Myocardial FFAs are derived from circulating FFAs, which result principally from lipolysis in adipose tissue, whereas the myocyte's glucose derives from plasma as well as from the cell's breakdown of its glycogen stores (glycogenolysis). These two principal sources of acetyl coenzyme A in cardiac muscle vary reciprocally. Glucose is broken down in the cytoplasm into a three-carbon product, pyruvate, which passes into the mitochondria, where it is metabolized to the two-carbon fragment, acetyl-CoA, and undergoes oxidation. FFAs are converted to acyl-CoA in the cytoplasm and acetyl-CoA in the mitochondria. Acetyl-CoA enters the citric acid (Krebs) cycle to produce ATP by oxidative phosphorylation within the mitochondria; ATP then enters the cytoplasm from the mitochondrial compartment. Intracellular ADP, resulting from the breakdown of ATP, enhances mitochondrial ATP production.

In the fasted, resting state, circulating FFA concentrations and their myocardial uptake are high, and they furnish most of the heart's acetyl-CoA (~70%). In the fed state, with elevations of blood glucose and insulin, glucose oxidation increases and FFA oxidation subsides. Increased cardiac work, the administration of inotropic agents, hypoxia, and mild ischemia all enhance myocardial glucose uptake, glucose production resulting from glycogenolysis, and glucose metabolism to pyruvate (glycolysis). By contrast, β-adrenergic stimulation, as occurs during stress, raises the circulating levels and metabolism of FFAs in favor of glucose. Severe ischemia inhibits the cytoplasmic enzyme pyruvate dehydrogenase, and despite both glycogen and glucose breakdown, glucose is metabolized only to lactic acid (anaerobic glycolysis), which does not enter the citric acid cycle. Anaerobic glycolysis produces much less ATP than does aerobic glucose metabolism, in which glucose is metabolized to pyruvate and subsequently oxidized to CO_2. High concentrations of circulating FFAs, which can occur when adrenergic stimulation is superimposed on severe ischemia, reduce oxidative phosphorylation and also cause ATP wastage; the myocardial content of ATP declines and impairs myocardial contraction. In addition, products of FFA breakdown can exert toxic effects on cardiac cell membranes and may be arrhythmogenic.

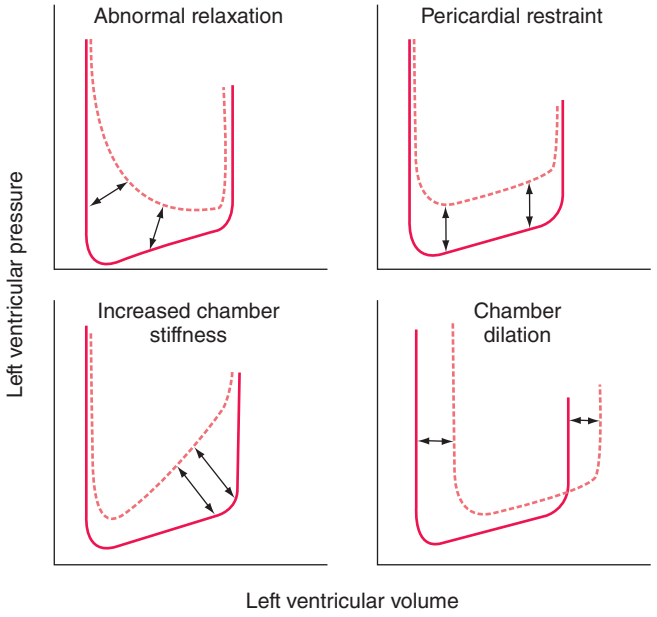

FIGURE 265e-11 Mechanisms that cause diastolic dysfunction reflected in the pressure-volume relation. The bottom half of the pressure-volume loop is depicted. *Solid lines* represent normal subjects; *broken lines* represent patients with diastolic dysfunction. *(From JD Carroll et al: The differential effects of positive inotropic and vasodilator therapy on diastolic properties in patients with congestive cardiomyopathy. Circulation 74:815, 1986; with permission.)*