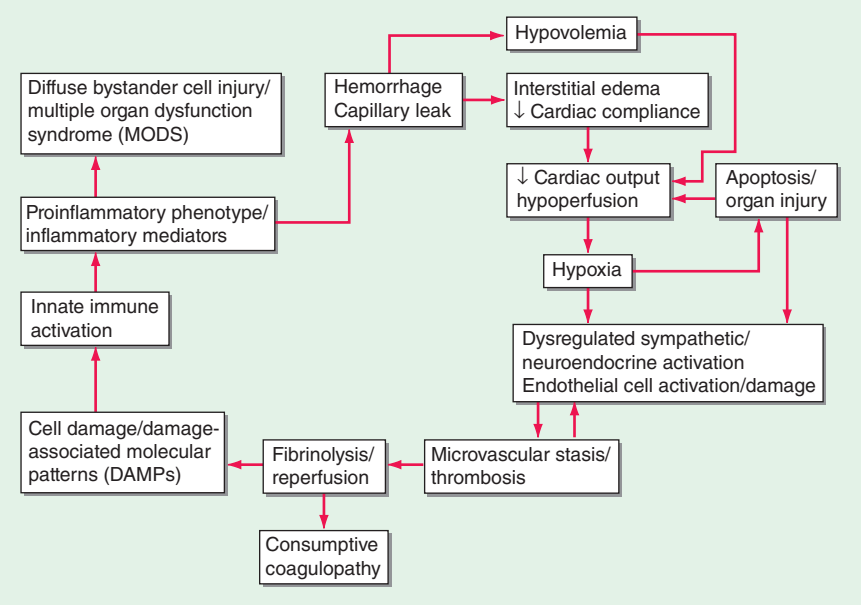

FIGURE 324-1 **Shock-induced** vicious cycle.

continuous supply of oxygen and nutrients, and neither tolerates severe ischemia for more than brief periods (minutes). Autoregulation (i.e., the maintenance of blood flow over a wide range of perfusion pressures) is critical in sustaining cerebral and coronary perfusion despite significant hypotension. However, when MAP drops to ≤60 mmHg, blood flow to these organs falls, and their function deteriorates.

Arteriolar vascular smooth muscle has both α- and β-adrenergic receptors. The α_1 receptors mediate vasoconstriction, while the β_2 receptors mediate vasodilation. Efferent sympathetic fibers release norepinephrine, which acts primarily on α_1 receptors as one of the most fundamental compensatory responses to reduced perfusion pressure. Other constrictor substances that are increased in most forms of shock include angiotensin II, vasopressin, endothelin 1, and thromboxane A_2. Both norepinephrine and epinephrine are released by the adrenal medulla, and the concentrations of these catecholamines in the bloodstream rise. Circulating vasodilators in shock include prostacyclin (prostaglandin [PG] I_2), nitric oxide (NO), and, importantly, products of local metabolism such as adenosine that match flow to the tissue's metabolic needs. The balance between these various vasoconstrictors and vasodilators influences the microcirculation and determines local perfusion.

Transport to cells depends on microcirculatory flow; capillary permeability; the diffusion of oxygen, carbon dioxide, nutrients, and products of metabolism through the interstitium; and the exchange of these products across cell membranes. Impairment of the microcirculation that is central to the pathophysiologic responses in the late stages of all forms of shock results in the derangement of cellular metabolism that is ultimately responsible for organ failure.

The endogenous response to mild or moderate hypovolemia is an attempt at restitution of intravascular volume through alterations in hydrostatic pressure and osmolarity. Constriction of arterioles leads to reductions in both the capillary hydrostatic pressure and the number of capillary beds perfused, thereby limiting the capillary surface area across which filtration occurs. When filtration is reduced while intravascular oncotic pressure remains constant or rises, there is net reabsorption of fluid into the vascular bed, in accord with Starling's law of capillary interstitial liquid exchange. Metabolic changes (including hyperglycemia and elevations in the products of glycolysis, lipolysis, and proteolysis) raise extracellular osmolarity, leading to an osmotic gradient that increases interstitial and intravascular volume at the expense of intracellular volume.

TABLE 324-1 CLASSIFICATION OF SHOCK

Hypovolemic	Septic
Traumatic	Hyperdynamic (early)
Cardiogenic	Hypodynamic (late)
Intrinsic	Neurogenic
Compressive	Hypoadrenal

CELLULAR RESPONSES

Interstitial transport of nutrients is impaired in shock, leading to a decline in intracellular high-energy phosphate stores. Mitochondrial dysfunction and uncoupling of oxidative phosphorylation are the most likely causes for decreased amounts of adenosine triphosphate (ATP). As a consequence, there is an accumulation of hydrogen ions, lactate, reactive oxygen species, and other products of anaerobic metabolism. As shock progresses, these vasodilator metabolites override vasomotor tone, causing further hypotension and hypoperfusion. Dysfunction of cell membranes is thought to represent a common end-stage pathophysiologic pathway in the various forms of shock. Normal cellular transmembrane potential falls, and there is an associated increase in intracellular sodium and water, leading to cell swelling that interferes further with microvascular perfusion. In a preterminal event, homeostasis of calcium via membrane channels is lost with flooding of calcium into the cytosol and concomitant extracellular hypocalcemia. There is also evidence for a widespread but selective apoptotic (programmed cell death) loss of cells, contributing to organ and immune failure.

NEUROENDOCRINE RESPONSE

Hypovolemia, hypotension, and hypoxia are sensed by baroreceptors and chemoreceptors that contribute to an autonomic response that attempts to restore blood volume, maintain central perfusion, and mobilize metabolic substrates. Hypotension disinhibits the vasomotor center, resulting in increased adrenergic output and reduced vagal activity. Release of norepinephrine from adrenergic neurons induces significant peripheral and splanchnic vasoconstriction, a major contributor to the maintenance of central organ perfusion, while reduced vagal activity increases the heart rate and cardiac output. Loss of vagal activity is also recognized to upregulate the innate immune inflammatory response. The effects of circulating epinephrine released by the adrenal medulla in shock are largely metabolic, causing increased glycogenolysis and gluconeogenesis and reduced pancreatic insulin release. However, epinephrine also inhibits production and release of inflammatory mediators through stimulation of β-adrenergic receptors on innate immune cells.

Severe pain or other stresses cause the hypothalamic release of adrenocorticotropic hormone (ACTH). This stimulates cortisol secretion that contributes to decreased peripheral uptake of glucose and amino acids, enhances lipolysis, and increases gluconeogenesis. Increased pancreatic secretion of glucagon during stress accelerates hepatic gluconeogenesis and further elevates blood glucose concentration. These hormonal actions act synergistically to increase blood glucose for both selective tissue metabolism and the maintenance of blood volume. Many critically ill patients have recently been shown to exhibit low plasma cortisol levels and an impaired response to ACTH stimulation, which is linked to a decrease in survival. The importance of the cortisol response to stress is illustrated by the profound circulatory collapse that occurs in patients with adrenocortical insufficiency (Chap. 406).

Renin release is increased in response to adrenergic discharge and reduced perfusion of the juxtaglomerular apparatus in the kidney. Renin induces the formation of angiotensin I that is then converted to angiotensin II by the angiotensin converting enzyme; angiotensin II is an extremely potent vasoconstrictor and stimulator of aldosterone release by the adrenal cortex and of vasopressin by the posterior pituitary. Aldosterone contributes to the maintenance of intravascular