90 mL). Thus, cardiac output depends on the force of myocardial contraction, blood volume, and other factors. Peripheral vascular resistance is determined by local blood flow and the degree of constriction or dilation in arterioles and arteries (vascular tone).

Autoregulation of Blood Flow

Autoregulation is the ability of body tissues to regulate their own blood flow. Local blood flow is regulated mainly by nutritional needs of the tissue, such as lack of oxygen or accumulation of products of cellular metabolism (eg, carbon dioxide, lactic acid). Local tissues can form vasodilating and vasoconstricting substances to regulate local blood flow. Important tissue factors include histamine, bradykinin, serotonin, and prostaglandins.

Histamine is found mainly in mast cells surrounding blood vessels and released when these tissues are injured. In some tissues, such as skeletal muscle, mast cell activity is mediated by the sympathetic nervous system (SNS) and histamine is released when SNS stimulation is blocked or withdrawn. In this case, vasodilation results from increased histamine release and the withdrawal of SNS vasoconstrictor activity. *Bradykinin* is released from a protein in body fluids. Kinins dilate arterioles, increase capillary permeability, and constrict venules. *Serotonin* is released from aggregating platelets during the blood clotting process. It causes vasoconstriction and plays a major role in control of bleeding. *Prostaglandins* are formed in response to tissue injury and include vasodilators (eg, prostacyclin) and vasoconstrictors (eg, thromboxane A_2).

An important component of regulating local blood flow is the production of several vasoactive substances by the endothelial cells that line blood vessels. Vasoconstricting substances, which increase vascular tone and blood pressure, include angiotensin II, endothelin-1, and thromboxane A_2. Vasodilating substances, which decrease vascular tone and blood pressure, include nitric oxide and prostacyclin. Excessive vasoconstrictors or deficient vasodilators may contribute to the development of atherosclerosis, hypertension, and other diseases. Injury to the endothelial lining of blood vessels (eg, by the shear force of blood flow with hypertension or by rupture of atherosclerotic plaque) leads to vasoconstriction, vasospasm, thrombus formation, and thickening of the blood vessel wall. All of these factors make the blood flow through a narrow lumen and increase peripheral vascular resistance.

Overall, regulation of blood pressure involves a complex, interacting, overlapping network of hormonal, neural, and vascular mechanisms, and any condition that affects heart rate, stroke volume, or peripheral vascular resistance affects arterial blood pressure. Many of these mechanisms are compensatory effects that try to restore balance when hypotension or hypertension occurs. The mechanisms are further described in Box 55–1 and referred to in the following discussion of antihypertensive drugs and their actions in lowering high blood pressure.

Response to Hypotension

When hypotension (and decreased tissue perfusion) occurs, the SNS is stimulated, the hormones epinephrine and norepinephrine are secreted by the adrenal medulla, angiotensin II and aldosterone are formed, and the kidneys retain fluid. These compensatory mechanisms raise the blood pressure. Specific effects include:

1. Constriction of arterioles, which increases peripheral vascular resistance
2. Constriction of veins and increased venous tone
3. Stimulation of cardiac beta-adrenergic receptors, which increases heart rate and force of myocardial contraction
4. Activation of the renin–angiotensin–aldosterone mechanism

Response to Hypertension

When arterial blood pressure is elevated, the following sequence of events occurs:

1. Kidneys excrete more fluid (increase urine output).
2. Fluid loss reduces both extracellular fluid volume and blood volume.
3. Decreased blood volume reduces venous blood flow to the heart and therefore decreases cardiac output.
4. Decreased cardiac output reduces arterial blood pressure.
5. The vascular endothelium produces vasodilating substances (eg, nitric oxide, prostacyclin), which reduce blood pressure.

HYPERTENSION

Hypertension is persistently high blood pressure that results from abnormalities in regulatory mechanisms. It is usually defined as a systolic pressure above 140 mm Hg or a diastolic pressure above 90 mm Hg on multiple blood pressure measurements.

Primary or essential hypertension (that for which no cause can be found) makes up 90% to 95% of known cases. Secondary hypertension may result from renal, endocrine, or central nervous system disorders and from drugs that stimulate the SNS or cause retention of sodium and water. Primary hypertension can be controlled with appropriate therapy; secondary hypertension can sometimes be cured by surgical therapy.

The Sixth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure, published in 1997, classified blood pressures in adults (in mm of Hg), as follows:

- Normal = systolic 130 or below; diastolic 85 or below
- High normal = systolic 130 to 139; diastolic 85 to 89
- Stage 1 hypertension (mild) = systolic 140 to 159; diastolic 90 to 99
- Stage 2 hypertension (moderate) = systolic 160 to 179; diastolic 100 to 109