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Pharmacology of the Cardiovascular System

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PEARLS

- Clinical acumen and knowledge of physiology is needed to distinguish between the need for an inotropic agent, which is used to increase cardiac contractility, and the need for a vasopressor agent, which is used to increase vascular tone.
- The failing myocardium may need to be supported with an agent that increases contractility and reduces afterload, such as milrinone or dobutamine.
- Interindividual variation in pharmacokinetics and heterogeneity of the pathology seen in critically ill children mandate that response to vasoactive medications be monitored closely and that titration be based on clinical targets rather than on specific dosage levels.

In many pediatric critical care units, disorders of the cardiovascular and respiratory systems are the most frequent reasons for admission. Children with these disorders may require pharmacologic support to maintain adequate end-organ perfusion and oxygenation. The catecholamines are the class of drug most often used for this support; they remain a mainstay of therapy for the pediatric critical care physician, although the role of other agents has expanded. Milrinone, a bipyridine, is used to support patients with hemodynamic compromise of varying etiologies. Vasopressin is employed in the management of patients with vasodilatory shock or after cardiopulmonary bypass. This chapter examines the clinical pharmacology of the five clinically useful catecholamines, vasopressin, the bipyridines, and the venerable cardiac glycosides.

Mechanisms of Response

Pharmacologic manipulation of the cardiovascular system often entails increasing the inotropic state of the myocardium or altering systemic vascular tone to improve perfusion. The final common mediator for both processes is the concentration of calcium in the cytosol. The pathway by which pharmacologic agents affect this parameter is a function of their specific cell surface receptors.

Adrenergic Receptors

Catecholamines modify cellular physiology through their interaction with specific adrenergic receptors. The classic paradigm of α and β classes of adrenergic receptors remains unchanged, although new subtypes and sub-subtypes continue to be identified. Currently, three subtypes of α_1-receptors (A, B, and D), three subtypes of α_2-receptors (A, B, and C) and three subtypes of β-receptors (β_1, β_2, and β_3) are recognized.[1,2] Advances in the biology of the adrenergic receptor have led to a greater understanding of the role of the α-receptor in the heart, adrenergic receptor regulation of cardiac myocyte apoptosis, and the coupling of the β_2-receptor to more than one G protein. The discovery of various genetic polymorphisms for the adrenergic receptors has added even more complexity, but the clinical relevance of many of these polymorphisms and their role in the pathogenesis of disease continue to be elucidated. Despite this increase in our understanding of the adrenergic receptor, the clinical classification of the catecholamines into α and β agents remains functionally unchanged (Table 31.1).

Signal Transduction

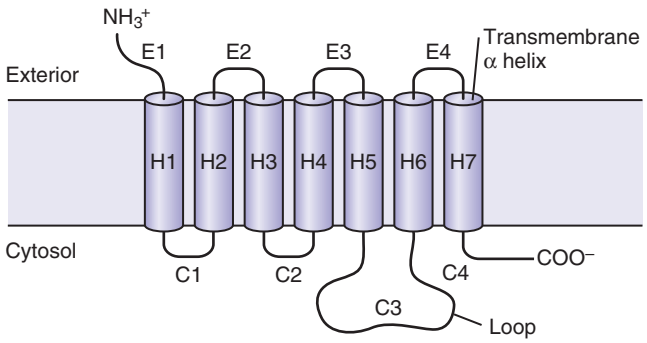
Adrenergic receptors mediate their effects through G proteins; as such, they are classified as G protein–coupled receptors. The adrenergic receptor itself contains seven membrane-spanning α-helical domains, an extracellular N-terminal segment, and a cytosolic C-terminal segment (Fig. 31.1). G proteins are heterotrimeric proteins consisting of α, β, and γ subunits, each of which has multiple subfamilies.[3] The action mediated by a ligand binding to a particular adrenergic receptor is a function of the specific subunits comprising the G protein receptor complex.

Adrenergic receptors typically are coupled to one of three types of G proteins: G_s, G_i, or G_q. G_s proteins produce an increase in adenylate cyclase activity, while G_i proteins inhibit adenylate cyclase activity. G_q protein receptors stimulate phospholipase C to generate diacylglycerol and inositol 1,4,5-triphosphate. Events involving interaction of G proteins, the receptor protein, and

TABLE 31.1 Adrenergic Receptors: Physiologic Responses, Agonist Potency, and Representative Antagonists

Receptor	G Protein	Physiologic Response	Agonist	Antagonist
α_1	G_q	Increase $InsP_3$, 1,2-DG, and intracellular Ca^{2+}; muscle contraction; vasoconstriction; inhibit insulin secretion	E > NE > D	Prazosin
α_2	G_i	Decrease cAMP; inhibit NE release; vasodilation; negative chronotropy	E > NE	Yohimbine
β_1	G_s	Increase cAMP; inotropy, chronotropy; enhance renin secretion	I > E ≥ D ≥ NE	Propranolol, metoprolol
β_2	G_s	Increase cAMP; smooth muscle relaxation; vasodilation; bronchodilation; enhance glucagon secretion; hypokalemia	I ≥ E > D > NE	Propranolol
D_1	G_s	Increase cAMP; smooth muscle relaxation	D	Haloperidol, metoclopramide
D_2	G_i	Decrease cAMP; inhibit prolactin and β-endorphin	D	Domperidone

cAMP, Cyclic adenosine monophosphate; *D,* dopamine; *1,2-DG,* 1,2 diacylglycerol; *E,* epinephrine; *I,* isoproterenol; *InsP3,* inositol 1,4,5-triphosphate; *NE,* norepinephrine.
Modified from Notterman DA. Pharmacologic support of the failing circulation: an approach for infants and children. *Prob Anesth.* 1989;3:288.



• **Fig. 31.1** Typical G protein–coupled receptor with seven membrane spanning regions (H1–H7), cytoplasmic (C1–C4), and extracellular (E1–E4) loops. (From Lodish H, et al: *Molecular Cell Biology,* ed 4. New York, 1999, WH Freeman.)

adenylate cyclase are summarized in Fig. 31.2. In the example of the G_s protein, ligand binding to the coupled receptor causes a conformational change in the G protein, resulting in guanosine diphosphate (GDP) disassociating from the Gsα subunit and guanosine triphosphate (GTP) binding to the α subunit. This GTP-Gα complex then disassociates from the Gβγ subunit and binds to adenylate cyclase, leading to an increase in activity of this enzyme. Adenylate cyclase catalyzes the conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP), thus increasing cellular levels of cAMP. G_i proteins have a different α subunit; when the G_iα GTP complex binds to adenylate cyclase, the enzyme is inactivated. By inhibiting this enzyme, G_i-coupled receptor agonists produce a decrease in the cellular concentration of cAMP. The specific cellular response that follows an alteration in the concentration of cAMP depends on the specialized function of the target cell.[3]

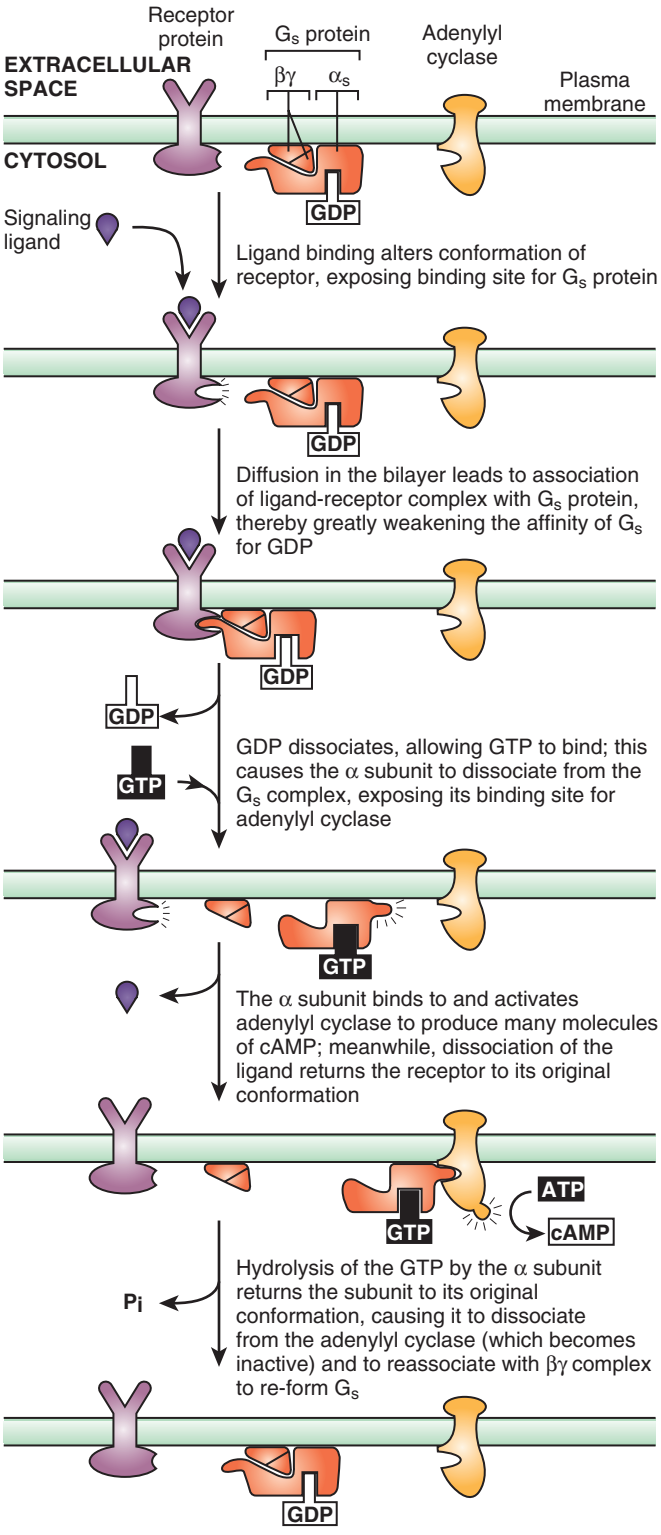
β-Adrenergic Receptors

Myocardial β_1-adrenergic receptors are associated with G_s. When this receptor type is engaged by an agonist agent, the result is enhanced activity of adenylate cyclase and a rise in the concentration of cAMP. This process activates protein kinase A (PKA), which, in turn, phosphorylates voltage-dependent calcium channels, increasing the fraction of channels that can be opened and the probability that these channels are open, producing an increase in intracellular calcium concentration (Fig. 31.3).[4] Calcium then binds to troponin C, allowing for actin-myosin cross-bridge formation and sarcomere contraction. In addition, PKA phosphorylates phospholamban, relieving the disinhibitory effect of the unphosphorylated form on calcium channels in the sarcoplasmic reticulum. The accumulation of calcium by the sarcoplasmic reticulum increases the rate of sarcomere relaxation (lusitropy) and increases the amount of calcium available for the next contraction. This process leads to both enhanced contractility and active diastolic relaxation.

β_2-receptors predominate in vascular smooth muscle.[5] The β_2-receptor is coupled to G_s, thus promoting formation of cAMP. However, the activation of cAMP-dependent protein kinase in vascular smooth muscle stimulates pumps that remove calcium from the cytosol and promotes calcium uptake by the sarcoplasmic reticulum. As cytosolic calcium concentration decreases, smooth muscle relaxes and the blood vessel dilates.

α-Receptors

Vascular smooth muscle contraction is mediated via α_1-adrenergic receptors, of which there are three subtypes: 1A, 1B, and 1D. The individual contributions of each of these subtypes to the control of vascular tone is an active area of investigation. Each subtype may be expressed in all of the vascular beds, but it is thought that one type predominates in any particular bed.[6] α_{1A}- and α_{1B}-receptors are thought to be involved in both the heart and vasculature.[7,8] While α-receptors may have less inotropic effect than β-adrenergic receptors, they do have significant effects in the myocardium. Interestingly, in patients with heart failure, downregulation of β-receptors has been noted while α-receptors are preserved.[9] In fact, data suggest that α_1-receptors may display cardioprotective effects, including activation of adaptive hypertrophy, increased contractility, and prevention of myocyte death.[2,10] The α_1-receptor is coupled to the family of $G_{q/11}$ proteins, which act independently of cAMP. Signal transduction across this receptor is initiated by the activation of phospholipase C, which causes a release of calcium into the cytosol and promotes movement of extracellular calcium into the cell (Fig. 31.4). In vascular smooth muscle, medium light chain kinase is activated and phosphorylates myosin



• **Fig. 31.2** Adrenergic receptor complex. When the receptor is engaged by an appropriate ligand (e.g., isoproterenol for a β_1-receptor), the receptor associates with the α_s polypeptide of the G_s protein. This causes the α_s to extrude GDP and incorporate GTP; α_s then associates with and activates the adenylate cyclase. The process is terminated when GTP is hydrolyzed to GDP and α_s dissociates. *ATP,* Adenosine triphosphate; *cAMP,* cyclic adenosine monophosphate; *GDP,* guanosine diphosphate; *GTP,* guanosine triphosphate. (From Alberts B. *Molecular Biology of the Cell,* ed 3. New York: Garland; 1994.)

light chain 2, leading to smooth muscle contraction.[11] A similar mechanism underlies the inotropic effect of the α_1-receptor in the myocardium.[12] The α_1-receptors also activate calcium influx through voltage-dependent and voltage-independent calcium channels.[13]

Receptor Downregulation

There are numerous sites at which receptor activity of the system can be modified, thereby affecting the sensitivity of target cells to both exogenous and endogenous catecholamines. The best-documented type of modification involves agonist-mediated receptor desensitization. Exposure of receptors to agonists markedly reduces the sensitivity of the target cell to the agonist. Within seconds to minutes after agonist binding, the receptor may be uncoupled as a result of receptor phosphorylation. Agonist-bound receptors may be phosphorylated by PKA or protein kinase C (PKC) or by a member of the family of G receptor kinases (GRKs).[14,15] Sequestration of receptors within the target cell and degradation of sequestered receptors is another mechanism by which receptors are downregulated. The desensitization of α_1-receptors has been extensively reviewed.[16] Homologous desensitization is mediated by GRKs, which are activated by soluble $G\beta\gamma$ subunits and phosphatidylinositol biphosphate. As with the other adrenergic receptors, once phosphorylated, the receptors are internalized into vesicles. The α_1-receptors also demonstrate heterologous desensitization, in which a second messenger kinase, generated as a result of ligand binding, inactivates the receptor and prevents any further signaling. In addition to agonist-mediated desensitization, endotoxin, tumor necrosis factor, and congestive heart failure (CHF) have been implicated in downregulation.[17]

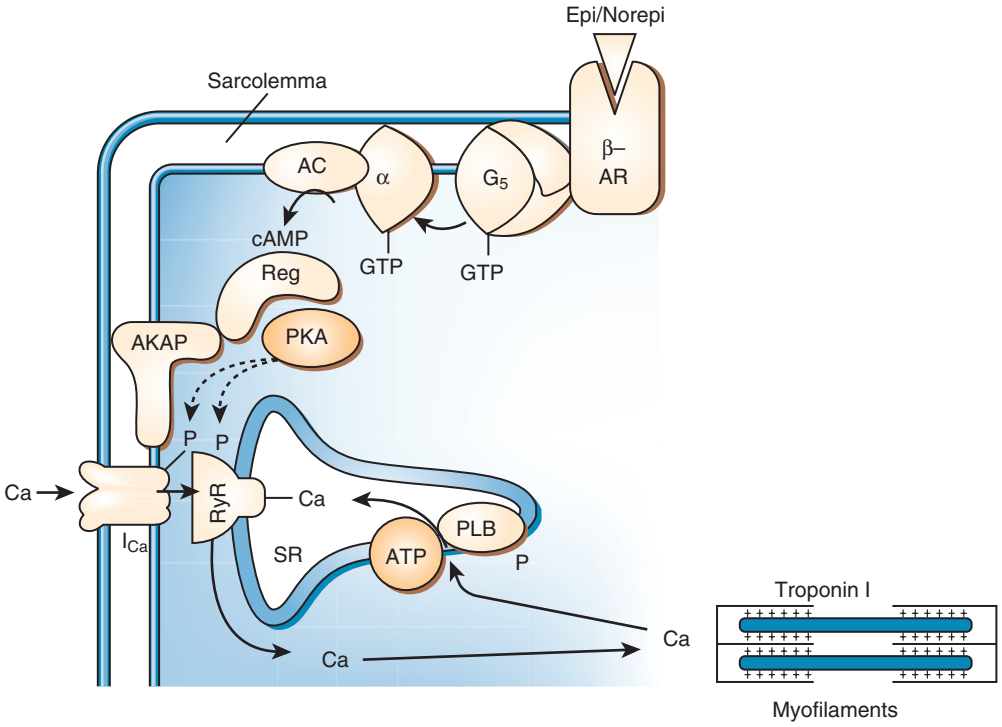
Polymorphisms

Several types of genetic polymorphisms are involved in adrenergic signaling, including single-nucleotide polymorphisms (SNPs), copy number variants (CNVs), and variable number tandem repeats (VNTRs).

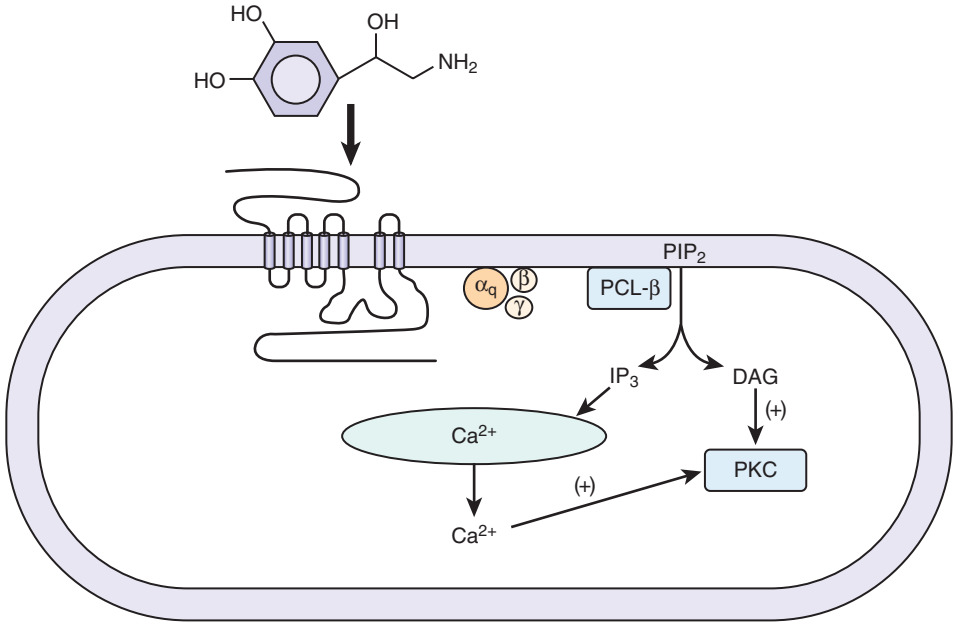
Few examples of functional genetic variants in adrenergic signaling that affect critical illness in children have been documented. Although these variants affect some properties of receptor function, clinical links are still being explored.[41,42,44] The Arg 389 β_1 variant has been shown to moderate the effect of β-blockers on various cardiovascular measures. It may become appropriate to test for this variant when considering therapy with an agent of this class. Interestingly, the Arg 389 β_1 variant has also been associated with increased cAMP generation, poorer prognosis in heart failure, and an increase in the predisposition to hypertension.[18]

Vasopressin Receptors

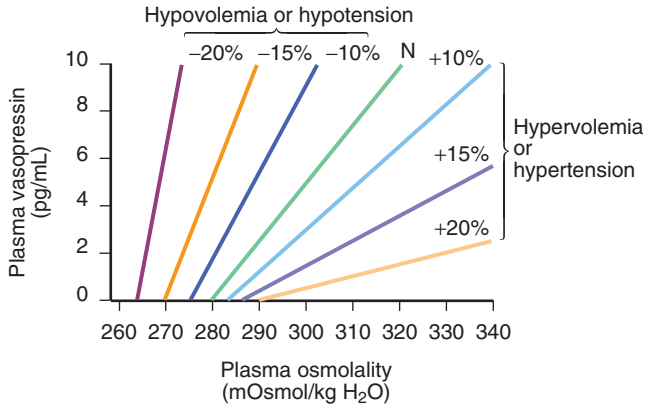
Arginine vasopressin (AVP) is a nonpeptide hormone synthesized in the supraoptic and paraventricular nuclei of the hypothalamus. Three subtypes of vasopressin receptors exist, known as V_1, V_2, and V_3 (or V_{1b}). V_2-receptors are present in the renal collecting duct; V_1-receptors are located in vascular beds, kidney, bladder, spleen, and hepatocytes, among other tissues.[19] Vasopressin is released in response to small increases in plasma osmolality or large decreases in blood pressure or blood volume.[20] The plasma osmolality threshold for release of AVP is 280 mOsm/kg. Above this threshold, there is a steep linear relation between serum osmolality and vasopressin levels.[20] Changes in blood volume of at least 20% are needed to effect a change in vasopressin levels, although levels may then increase by 20- to 30-fold.[20] Hypovolemia also



• **Fig. 31.3** β_1-Adrenergic receptor signaling cascade. Agonist (epinephrine/norepinephrine [Epi/Norepi]) to β-adrenergic receptor (β-AR) results in the α subunit binding to GTP, which activates adenylate cyclase (AC). AC then converts adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP), which binds to regulatory unit (Reg) on protein kinase A (PKA). PKA then promotes an increase in the intracellular concentration of calcium (Ca) by acting on voltage-gated channels (I_{Ca}) and on the sarcoplasmic reticulum (SR). Calcium then promotes sarcomere contraction. *AKAP,* A kinase anchoring protein; *PLB,* phospholamban; *RyR,* ryanodine receptor. (From Bers DM. Cardiac excitation-contraction coupling. *Nature*. 2002;415[6868]:198–205.)



• **Fig. 31.4** α_1-Adrenergic receptor signaling cascade. Binding of an agonist such as norepinephrine to a G protein–coupled receptor activates the $G_{q/11}$ protein, leading to disassociation of the α and βγ subunits. Phospholipase C (PLC-β) is activated in turn and cleaves phosphatidylinositol 4,5-biphosphate (PIP_2) to inositol 1,4,5-triphosphate (IP_3) and diacylglycerol (DAG). IP_3 and DAG promote an increase in intracellular calcium through the sarcoplasmic reticulum and protein kinase C (PKC). (From Zhong H, Minneman KP. Alpha1-adrenoreceptor subtypes. *Eur J Pharm*. 1999;375[1–3]:261–276.)



• **Fig. 31.5** Relationship between plasma vasopressin levels and plasma osmolality. As hypovolemia worsens, vasopressin levels increase for any given plasma osmolality. (Modified from Robertson GL, Athar S, Shelton RL. Osmotic control of vasopressin function. In: Androli TE, Grantham JJ, Rector FC Jr, eds. *Disturbances in Body Fluid Osmolality*. Bethesda, MD: American Physiological Society; 1977.)

shifts the vasopressin response curve to osmolality changes to the left and increases the slope of the curve (Fig. 31.5). Vasopressin can produce vasoconstriction through V_1-receptors in the vascular bed (discussed later), but it also activates V_1-receptors in the central nervous system (CNS), including receptors in the area postrema.[21] This region is responsible for the reflex bradycardia seen with vasopressin infusion, which attenuates the increase in blood pressure that would result from the vasoconstrictor effects of vasopressin.[22,23] In fact, vasopressin causes a greater reduction in heart rate than other vasoconstrictors.[24] If this feedback loop is abolished, vasopressin induces a greater vasopressor response than other agents.[21]

V_1 Receptors

Vasopressin receptors belong to the family of G protein–coupled receptors. V_1-receptors are coupled to G_q and V_2-receptors are coupled to G_s.[20] When vasopressin binds to the V_1-receptor, phospholipase C is activated, with the eventual production of $InsP_3$ and 1,2 DG. These molecules serve to increase the release of calcium from the endoplasmic reticulum as well as increase the entry of calcium through gated channels (Fig. 31.6).[25] The increase in intracellular calcium leads to an increase in the activity of myosin light chain kinase. This kinase acts upon myosin to increase the number of actin-myosin cross-bridges, enhancing contraction of the myocyte. Of note, vasopressin has been shown to produce vasoconstriction in the skin, skeletal muscle, and fat while producing vasodilation in the renal, pulmonary, and cerebral vasculature.[26] This effect may be mediated though nitric oxide or may be a function of the isoform of adenyl cyclase with which the receptor is coupled.[27] Vasopressin also has been shown to augment the pressor effects of catecholamines. V_1-receptors have been demonstrated to have a weakly positive inotropic effect in the heart, although the clinical significance of this effect has not been established.[28]

As with adrenergic receptors, vasopressin receptors undergo downregulation. Vasopressin promotes the phosphorylation of its own receptor immediately after binding. The receptor is removed from the cell surface within 3 minutes after binding.[29] G protein–coupled receptor kinases (GRKs) catalyze the phosphorylation of the receptor. PKC also mediates this reaction and may serve as the means by which other agents downregulate the vasopressin receptor in a heterologous manner.[29]

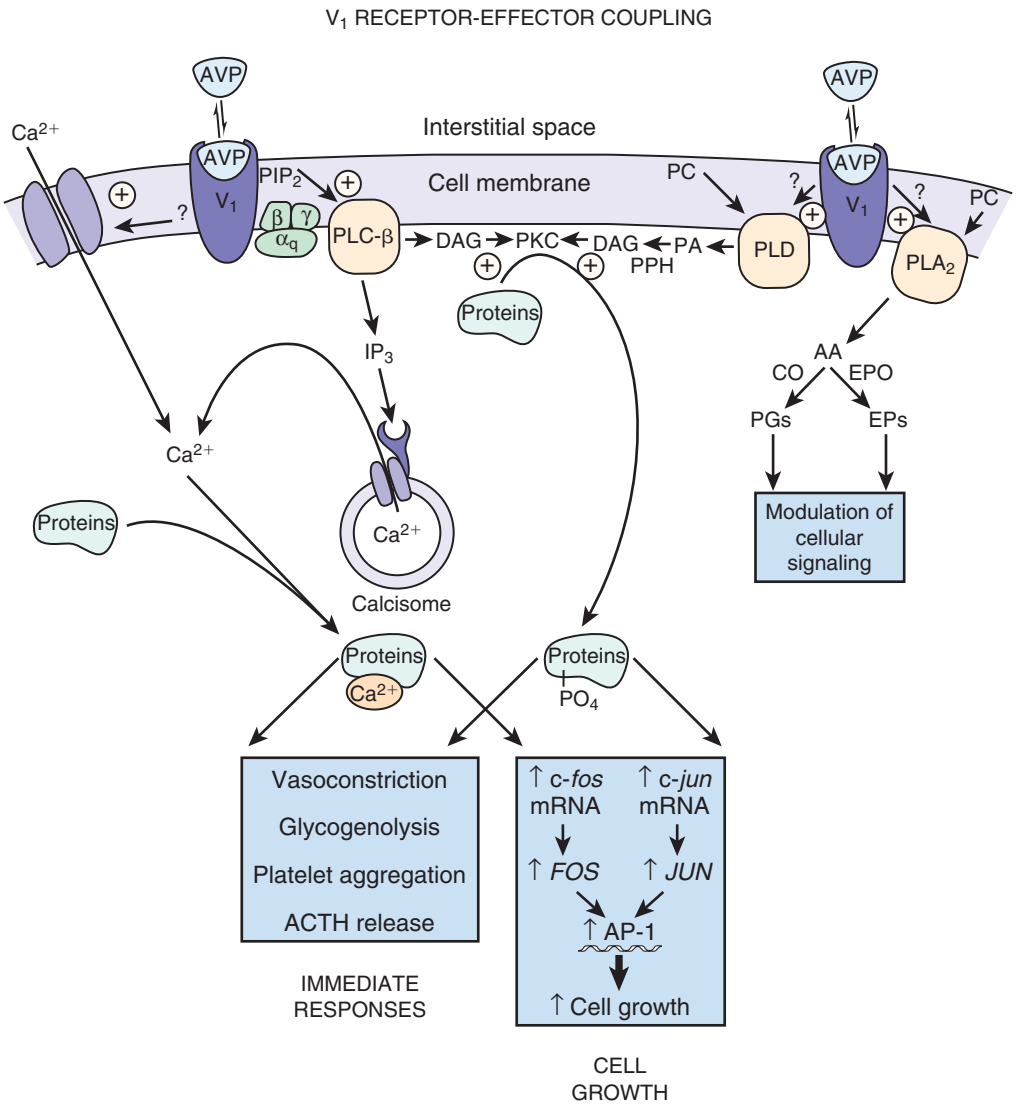
Although numerous mutations in the V_2-receptor have been implicated in nephrogenic diabetes insipidus, much less is known about the V_1-receptor. The molecular basis for individual genetic variation remains an active area of investigation since discoveries in this area may inform risk stratification, prognostic accuracy, and individual response to therapy.

Phosphodiesterase Regulation of Cyclic Adenosine Monophosphate

Phosphodiesterases are a class of enzyme that catalyze the hydrolysis of cAMP and cGMP into AMP and GMP, respectively. These enzymes can downregulate the signals transduced by cAMP, such as PKA activity (discussed previously). Several families of this enzyme exist, each with subtypes. Phosphodiesterase 3 (PDE3) is present in cardiac myocytes, vascular smooth muscle cells, adipocytes, platelets, and pancreatic islet cells and is functionally a cAMP esterase.[30] Different isoforms of PDE3 are present in cardiac (PDE3A1) and vascular smooth muscle cells (PDE3A2) and are localized to different cellular compartments. Thus, they are able to regulate the function of their target enzymes in response to specific cellular signals.[31] The bipyridines, such as milrinone, are competitive inhibitors of PDE3; that is, they bind to PDE3, preventing the enzyme from binding to cAMP.[32,33] Inhibition of PDE3 produces an increase in cAMP, resulting in a positive inotropic effect in the myocardium and vasodilation in the systemic and pulmonary vasculature.[34] In contrast, methylxanthines such as theophylline, which inhibit all phosphodiesterases, cause levels of both cGMP (thought to decrease contractility) and cAMP to increase. This dual increase attenuates the overall inotropic effect. Bipyridines may also enhance contractility by increasing the sensitivity of myofilaments to cytosolic calcium.[35] Milrinone has been shown to enhance the sarcomere uptake of calcium and, thereby, augment left ventricular relaxation (lusitropy).[36] In the peripheral vasculature, PDE3 inhibitors produce vasodilation via a cGMP mechanism.[37] The clinical effect of bipyridine administration is a combination of positive inotropy, lusitropy, and afterload reduction.

ATPase Inhibition

Membrane-bound sodium-potassium adenosine triphosphatase (Na^+/K^+-ATPase) is responsible for maintaining electrochemical gradients across the cellular membrane. It does so by extruding three molecules of sodium from the cell and incorporating two molecules of potassium into the cell, both against their respective concentration gradients. This process occurs at the cost of one molecule of ATP. The enzyme consists of an α and β subunit; there are four subtypes of α and three of β.[38] The β subunit may be involved in the trafficking of the enzyme.[39] The α subunit contains both the binding site and catalytic site. The isoforms expressed are dependent on the type of tissue.[40] Cardiac glycosides (e.g., digoxin) inhibit the Na^+/K^+-ATPase pump, thereby increasing intracellular sodium. The elevation in intracellular sodium alters the transmembrane gradient, thus inhibiting the activity of the voltage-gated sodium/calcium exchange (NCX) pump. This pump exchanges three molecules of extracellular sodium for one molecule of intracellular calcium.[41,42] The net result is a rise in intracellular calcium and, in the cardiac myocyte, enhanced contractility. No evidence exists to suggest the development of tolerance to digoxin with long-term use.[43]



• **Fig. 31.6** V_1-receptor signaling cascade. Binding of arginine vasopressin (AVP) to the V_1 vasopressin receptor (V_1) leads to activation of phospholipase C (PLC-β) via the Gq protein with the production of inositol 1,4,5-triphosphate (IP_3). IP_3 promotes an increase in intracellular calcium, resulting in vasoconstriction. *AA,* Arachidonic acid; *ACTH,* adrenocorticotropic hormone; *AP-1,* transcription factor consisting of heterodimer of FOS and JUN; *CO,* cyclooxygenase; *DAG,* diacylglycerol; *EPO,* epoxygenase; *EPs,* epoxyeicosatrienoic acids; *PA,* phosphatidic acid; *PC,* phosphatidylcholine; *PGs,* prostaglandins; *PIP_2,* phosphatidylinositol 4,5-biphosphate; *PKC,* protein kinase C; *PLA_2,* phospholipase A_2; *PLD,* phospholipase D; *PPH,* phosphatidate phosphohydrolase. *Question mark*s indicate that the mechanism of coupling is unclear. (From Jackson EK. Vasopressin and other agents affecting the renal conservation of water. In: Hardman JG, Limbird LE, eds. *Goodman and Gilman's The Pharmacologic Basis of Therapeutics*, ed 10. New York: McGraw Hill; 2001.)

Developmental Issues

It is often stated that the immature myocardium is less sensitive to inotropic agents than the adult heart. The mechanism responsible for these differences represents an area of active investigation. The majority of studies involve animal models or isolated human tissue.

Age-related differences in the response of the developing myocardium to inotropic agents, receptor regulation, and calcium handling depend on the species studied and model of illness to which the animals are exposed.

Because there are inherent differences between intact healthy animal models and the ill child, as well as pharmacokinetic differences between the infant and adult patient, caution must be exercised when extrapolating laboratory data to the bedside.[44] Nonetheless, a brief review of developmental differences is appropriate.

Structural and ultrastructural differences exist between immature and mature hearts. Reduced ventricular compliance, greater ventricular interdependence, and a reduced ratio of myocardial contractile to noncontractile protein are characteristic of the immature heart. The net effect is that the immature myocardium

neither responds to nor tolerates volume loading as well as the adult heart. In addition to this diminished "preload reserve," the baseline heart rate of infants and children is quite high, which limits the extent to which tachycardia can augment cardiac output before diastolic filling is compromised.

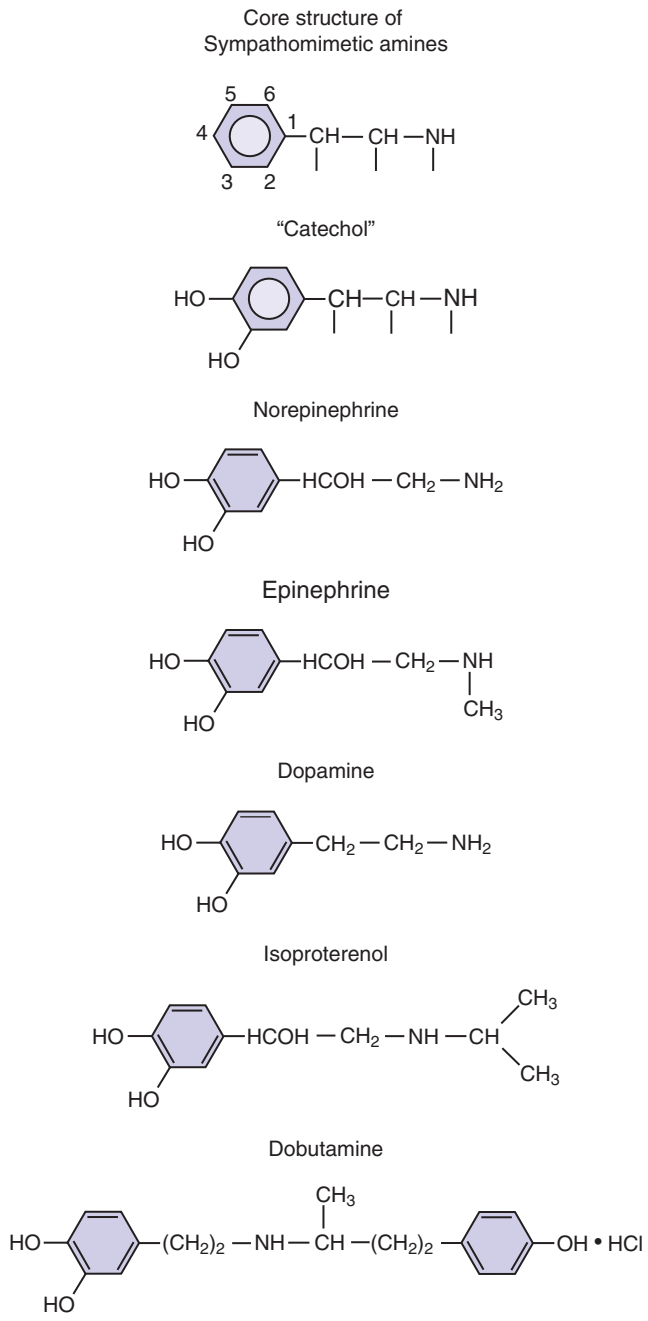
Developmental differences also may exist in the expression of PDE isoforms. In a model of rabbit ventricular myocytes, administration of IBMX (3-isobutyl-1-methylxanthine, a nonselective PDE inhibitor) and rolipram (a PDE4 inhibitor) increased intracellular calcium currents at baseline and in response to isoproterenol in neonatal cells but not in adult cells. In contrast, milrinone (a PDE3 inhibitor) increased intracellular calcium currents at baseline and in response to isoproterenol only in the adult cells.[45] Thus, it would appear that in the neonatal myocardium, PDE4 may be the dominant isoenzyme that regulates intracellular calcium currents.

The combination of impaired preload reserve, limited chronotropic reserve, and reduced sensitivity of the heart and peripheral vasculature to adrenergic agents implies that the response of the immature organism to inotropic and vasopressor agents may differ from the pattern noted in adults.[46,47] Indeed, a meta-review of the use of dobutamine in pediatrics concluded that while there is evidence to support that it improves cardiac output in neonates, animal studies do not adequately define the age-related effects of dobutamine on various physiologic measures or organ systems.[48] This limitation is likely to apply to other agents employed for the treatment of shock. When coupled with the variation in cardiac anatomy due to congenital heart disease, individual differences in response to cardiovascular drugs may be difficult to predict. Therefore, meticulous attention to response is essential for safe administration of these drugs to children.

Sympathomimetic Amines

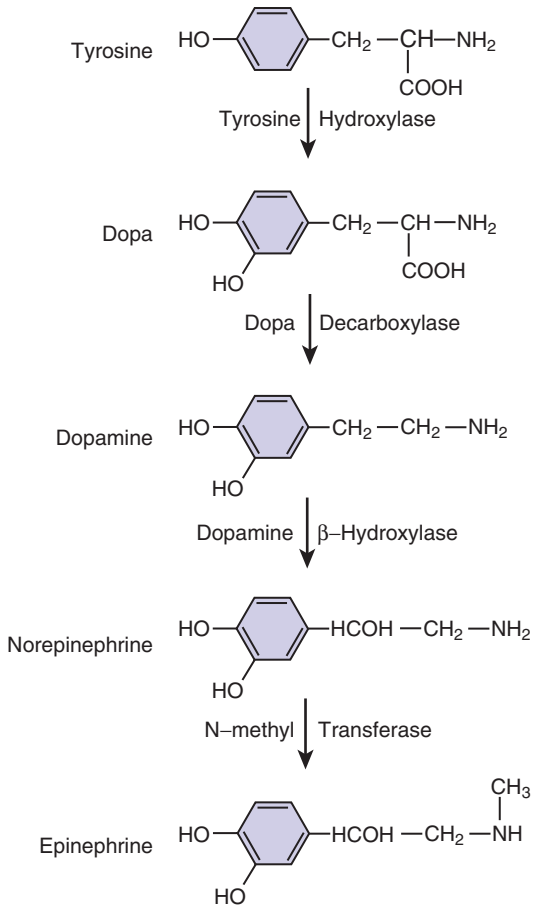
Virtually all sympathomimetics currently used to support hemodynamics are catecholamines. This class includes the endogenous compounds epinephrine, norepinephrine, and dopamine and the synthetic products isoproterenol and dobutamine. Catecholamines have a β-phenylethylamine core with hydroxyl (OH) substituents at the 3 and 4 aromatic ring positions (Fig. 31.7). Minor differences in molecular substitution about the N-terminus or the α or β carbons produce marked differences in activity. Structure-activity relationships are complex for the catecholamines. However, in general, increasing size of the substituent on the amino group enhances β-adrenergic activity, whereas decreasing size is associated with α-adrenergic selectivity.[49] Tyrosine serves as the base compound for the synthesis of catecholamines. Tyrosine hydroxylase catalyzes the conversion of tyrosine to dopa, which undergoes decarboxylation, producing dopamine. Dopamine β-hydroxylase converts dopamine to norepinephrine. In the adrenal medulla, norepinephrine is converted to epinephrine by N-methyltransferase (Fig. 31.8).

Catecholamines are subject to several different elimination processes.[50] For example, a small proportion of dopamine is excreted unchanged in the urine, and it is likely that a proportion undergoes neuronal reuptake. The principal means of elimination appears to be O-methylation by catechol O-methyltransferase (COMT) to form metanephrines, followed by either sulfoconjugation (by phenolsulfotransferase) or by deamination (by monoamine oxidase [MAO]) to homovanillic acid.[51] Substitution at the α carbon determines the rate of deamination by MAO.[52] The contribution of each pathway to total body clearance of



• **Fig. 31.7** Chemical structure of the catecholamines. (Modified from Chernow B, Rainey TG, Lake CR. Endogenous and exogenous catecholamines in critical care medicine. *Crit Care Med.* 1982;10[6]:409–416.)

catecholamines varies with age and the particular drug and circulatory bed involved. In newborn lambs, the lungs accounted for 35% of the total body clearance of norepinephrine and 15% of the clearance of epinephrine. Inhibition of MAO by desipramine decreased pulmonary clearance to near zero and decreased total body clearance of norepinephrine and epinephrine by 51% and 30%, respectively.[53] In adult rabbits, inhibition of COMT and MAO simultaneously decreased pulmonary clearance of norepinephrine, epinephrine, and dopamine but had only minor effects on total body clearance.[54] Inhibition of COMT did not change extracellular levels of catecholamines in the CNS.[55] Furthermore, individual differences in COMT activity are not well correlated



• **Fig. 31.8** Biosynthetic pathways of the endogenous catecholamines. (Modified from Chernow B, Rainey TG, Lake CR. Endogenous and exogenous catecholamines in critical care medicine. *Crit Care Med.* 1982; 10[6]:409–416.)

with dopamine clearance.[56] The liver and gut have been shown to clear between 30% to 52% of the circulating norepinephrine and epinephrine.[57,58] It is likely that processes or drugs that impair organ function and disturb these routes of elimination will decrease the overall metabolic clearance of catecholamines. Liver dysfunction is known to reduce clearance and increase the blood concentration of dopamine during a given infusion rate of the compound.[59]

The properties of catecholamines can be divided into inotropic and vasopressor effects. An inotropic agent increases stroke work at a given preload and afterload. Typically, these agents engage receptors of the β_1-adrenergic class. Agents that stimulate β_1-adrenergic receptors also tend to increase heart rate modestly unless other properties of the drug prevent this increase. Some inotropic agents also activate β_2-receptors, promoting peripheral vasodilation and reflex tachycardia. The improvement in cardiac output produced by these agents may also permit a reflex relaxation of vascular tone and systemic vascular resistance (SVR).

A vasopressor agent increases peripheral vascular tone, elevating SVR and blood pressure. Typically, vasopressors engage α_1-adrenergic receptors, causing contraction of vascular smooth muscle. In principle, the physician will use a vasopressor agent to treat peripheral vasoplegia and an inotropic agent when the major problem is impaired cardiac contractility. In practice, most available agents display a blend of inotropic, chronotropic, and vasopressor activity that is often dose dependent. Norepinephrine has both inotropic and vasopressor effects, although it is most commonly used as a vasopressor agent. Phenylephrine, which is not a catecholamine, has considerable specificity for the α-adrenergic receptor. Thus, it is almost a pure vasopressor. Isoproterenol and dobutamine have little α-adrenergic agonist activity but have considerable activity at the β-receptor; they are mostly used as inotropes. Epinephrine and dopamine have both inotropic and vasopressor activity. At relatively low infusion rates, they enhance myocardial function and increase heart rate (β_1 and β_2). At higher rates, vasopressor activity (α_1) becomes manifest.

Dopamine

Basic Pharmacology

In the enzymatic pathway leading from tyrosine to epinephrine (see Fig. 31.8), decarboxylation transforms L-dopa to dopamine. Dopamine is a central neurotransmitter found in sympathetic nerve terminals and in the adrenal medulla, where it is the immediate precursor of norepinephrine.

Clinical Pharmacology

Dopamine stimulates dopamine (D_1- and D_2-) receptors located in the brain and in vascular beds in the kidney, mesentery, and coronary arteries.[60] It also stimulates α- and β-receptors, although the compound's affinity for these receptors is lower. D_1-receptors are coupled to G_s and thus enhance adenylate cyclase and produce a rise in cAMP, which evokes vasodilation. This increases blood flow to these organs and enhances renal solute and water excretion by the kidney. Dopamine modulates release of aldosterone and prolactin (via D_2-receptors), which also may affect renal solute clearance.[61]

Low infusion rates of dopamine augment renal sodium excretion; intermediate rates (5–10 μg/kg per minute) produce chronotropic and inotropic effects, and still higher infusion rates increase vascular resistance.[62] Renal blood flow, glomerular filtration rate, and sodium excretion are maintained or even increase during dopamine infusion in patients with poor cardiac output.

Research into the dose-physiologic response relationships in patients treated with dopamine have yielded inconsistent results,[63–66] suggesting that a patient's response to a given dose depends on underlying condition, hemodynamics, and adrenergic receptor status, and highlights the importance of titration to individual response when using catecholamines in critically ill patients. Despite these observed variations in dose-response, there is now consensus that the augmentation in urine output seen in patients with poor cardiac output who are started on low-dose, "renal" dopamine results from improved renal blood flow rather than a direct, receptor-mediated diuretic effect on the kidney.

Both the receptor-mediated activity and clinical effects of dopamine depend in part on developmental factors such as age and, in the case of newborns, the degree of prematurity.[67] However, trials in newborns have yielded conflicting results. Nevertheless, dopamine remains one of the most widely used vasoactive medications in the neonatal intensive care unit (ICU) amid ongoing controversies concerning the indications for pharmacologic intervention and specific therapeutic goals (i.e., optimal blood pressure vs. adequate organ perfusion) in this unique population. In addition, uncertainty persists regarding the long-term effects of dopamine on neurologic development in premature infants.[68]

While there is limited evidence to support the observation that the inotropic and peripheral vasoconstrictor effects of dopamine

predominate in the neonatal period,[69] controversies remain regarding the vasodilator effects on the renal, coronary, and cerebral vascular beds.[70] Much of the experimental evidence for diminished sensitivity to dopamine in infants emerged from studies in immature animals, and questions remain as to whether the results can be directly applied to humans. Perez and associates[71] found that in critically ill neonates, infusion rates greater than 20 μg/kg per minute were needed to achieve cardiovascular stability. However, unlike in adults, reductions in urine output or peripheral perfusion were not observed. Bhatt-Mehta and coworkers,[72] found that dopamine at doses as low as 0.5 to 1.0 μg/kg per minute increased cardiac output and stroke volume before heart rate, while increases in SVR did not occur until infusion rates exceeded 8 μg/kg per minute. Seri and colleagues[73] attributed the increase in blood pressure that they observed in critically ill premature infants at doses of 2.5 to 7.5 μg/kg per minute to the enhanced α-adrenergic sensitivity of the immature myocardium, but reduced clearance of dopamine in this age group has also been proposed.[69]

Dopamine crosses the blood-brain barrier in preterm neonates; in one study, Wong et al. demonstrated improved cerebral venous saturations and coupling of cerebral blood flow to cerebral metabolic rate of oxygen consumption.[74]

Pharmacokinetics

Plasma dopamine clearance ranges from 60 to 80 mL/kg per minute in normal adults and is lower in patients with renal or hepatic disease.[59,75] In subjects with normal renal function, the elimination half-life of infused dopamine is approximately 2 minutes.[76] Among critically ill children, the elimination half-life is 26 ± 14 minutes. In neonates, the elimination half-life is 5 to 11 minutes.[77,78] Wide interindividual variations in the rate of dopamine clearance have been reported in critically ill children as well as in healthy adults.[79,80]Age has a striking effect on clearance of dopamine; clearance in children younger than 2 years of age is approximately twice as rapid as it is in older children (82 vs. 46 mL/kg per minute).[59] Allen and colleagues[81] demonstrated that clearance of infused dopamine decreased by almost 50% during the first 20 months of life, while an additional 50% decrease occurs between the ages of 1 and 12 years. Another study did not show a correlation between advancing age and dopamine clearance, although the patients in this study had a mean age of 37 months.[82] Dopamine clearance may also decrease after 24 hours of continuous infusion.[83] Vernon and colleagues[84] studied the pharmacokinetics of dopamine in 15 patients ranging in age from 3 days to 8 years and noted nonlinear behavior; the authors questioned the utility of evaluating total body clearance in this age group. Differences in the rate of sulfoconjugation as a route of elimination also may contribute to the wide variations in the clearance of dopamine in critically ill children.[59,81,82] The effect of coadministration of dobutamine on dopamine clearance has been suggested by some authors. However, an in vitro study showed that, although dopamine and dobutamine both compete for COMT and MAO, the concentrations achieved under clinical conditions are unlikely to produce clinically significant levels of inhibition.[78,85] Pharmacokinetic differences between children and infants, rather than a difference in vascular or myocardial receptor sensitivity, may account for the observation that infants require and tolerate higher infusion rates.

Clinical Role

Dopamine has been shown to be an effective inotropic and vasopressor agent in neonates and infants with a variety of conditions associated with circulatory failure. Fewer data evaluating the efficacy of dopamine in older children are available. Until recently, dopamine was used as a first-line treatment in children with fluid refractory septic shock or distributive shock,[86–89] but updated guidelines for the management of septic shock now recommend norepinephrine or epinephrine as the agent of choice.[90–92] Dopamine may be appropriate for children with mild impairment of myocardial function.[93,94] Severe impairment of vascular tone or cardiac contractility are indications for other agents, and children with primary myocardial disease not complicated by hypotension will benefit from a more selective inotropic agent such as milrinone or dobutamine.[95] Infusion rates of dopamine necessary to improve signs of severe myocardial dysfunction may be associated with tachycardia, dysrhythmia, and increased myocardial oxygen consumption—these adverse effects often outweigh any potential benefit.

Adverse Effects

The clinical signs of dopamine toxicity are mainly cardiovascular: tachycardia, hypertension, and dysrhythmia. However, dopamine is less likely to produce severe tachycardia or dysrhythmias than either epinephrine or isoproterenol.[96] With the possible exception of the bipyridines, all inotropes increase myocardial oxygen consumption because they increase myocardial work. If the resulting increase in oxygen consumption is balanced by improved coronary blood flow, the net effect on oxygen balance is beneficial. The effect of dopamine on myocardial oxygen balance is better than that of isoproterenol but not as good as dobutamine and milrinone.[97] In the setting of cardiogenic shock, the improvement in myocardial contractility with the addition of an inotrope may reduce preload and afterload, improve coronary perfusion pressure, increase myocardial oxygen supply, and prolong diastolic coronary perfusion by reducing heart rate. If the same drug is administered to a patient with normal myocardial contractility, the result may be an increase in cardiac oxygen consumption without an increase in oxygen delivery to the myocardium. Tachycardia, which can both increase oxygen consumption and shorten diastole, is a particular burden.

Dopamine depresses the ventilatory response to hypoxemia and hypercarbia by as much as 60%.[98] β-Agonists, including dopamine, decrease partial pressure of arterial oxygen by interfering with hypoxic vasoconstriction.[99] In one study, dopamine increased intrapulmonary shunting in patients with acute respiratory distress syndrome (ARDS) from 27% to 40%.[98] The effect of dopamine on perfusion to the splanchnic bed is widely debated. Evidence suggests that in patients with sepsis, dopamine may increase splanchnic blood flow, gastric pH, and lead to less lactate production than epinephrine.[101–104] Dopamine may also increase oxygen delivery and reduce oxygen consumption in septic patients.[105,106] On the other hand, experiments in animals suggest that dopamine is capable of modulating cellular immune functions in sepsis and may decrease survival. In a murine model, survival in dopamine-treated septic animals decreased by nearly 40%.[107] An increase in splenocyte apoptosis and decrease in splenocyte proliferation and interleukin-2 (IL-2) release, both of which indicate attenuated immune system function, were also observed.

In infants and children who have undergone cardiac surgery, dopamine may have several endocrinologic effects, including decreases in prolactin and thyrotropin levels as well as a reduction in the pulsatility of growth hormone.[108]

In patients with shock, dopamine can cause limb ischemia, gangrene of distal parts and entire extremities, and extensive loss

of skin.[109] This is owing to release of norepinephrine from synaptic terminals and in vivo conversion to norepinephrine. Hence, it is more often associated with limb ischemia than other adrenergic compounds. Extravasations of dopamine should be treated immediately by local infiltration of phentolamine (5–10 mg in 10 mL of normal saline solution) administered with a fine hypodermic needle.[110]

Preparation and Administration

Dopamine hydrochloride is available as premixed solutions for infusion.[77] The use of standard concentrations and electronic "drip calculators"[111] are encouraged to prevent dosing errors. Dopamine is administered by central vein to avoid the risk of skin injury from extravasation, although it can be given safely through a peripheral intravenous catheter while central access is being secured. Dopamine may also be administered via the intraosseous route.[112] Dopamine is not compatible with some parenteral nutrition solutions or with sodium bicarbonate.[113] Dopamine is stable in solution for 24 to 84 hours.[114,115]

Interactions

Dopamine is metabolized by MAO, and concurrent use of an MAO inhibitor potentiates its effect.[116] Both α-adrenergic blockers and β-adrenergic blockers antagonize the effects of dopamine. Other dopamine antagonists, such as metoclopramide or haloperidol, also may attenuate its effects. An increase in the infusion rate will often overcome the receptor blockade.

Summary

Dopamine has been used to treat mild to moderate cardiogenic or distributive (septic, hypoxic-ischemic) shock associated with hypotension. In the absence of hypotension, acute severe cardiac failure is best treated with dobutamine or milrinone. When septic or cardiogenic shock is complicated by severe hypotension, epinephrine or norepinephrine is preferred, depending on hemodynamics and myocardial function (Table 31.2).

Norepinephrine

Basic Pharmacology

Dopamine is hydroxylated at the β-carbon to produce norepinephrine, the principal neurotransmitter of the sympathetic nervous system (see Figs. 31.7 and 31.8). Because there is no substituent on the N(amino)-terminus, norepinephrine has little β_2 activity and is considerably less potent at that receptor than epinephrine.[116] It is a moderately potent α- and β_1-agonist.

Clinical Pharmacology

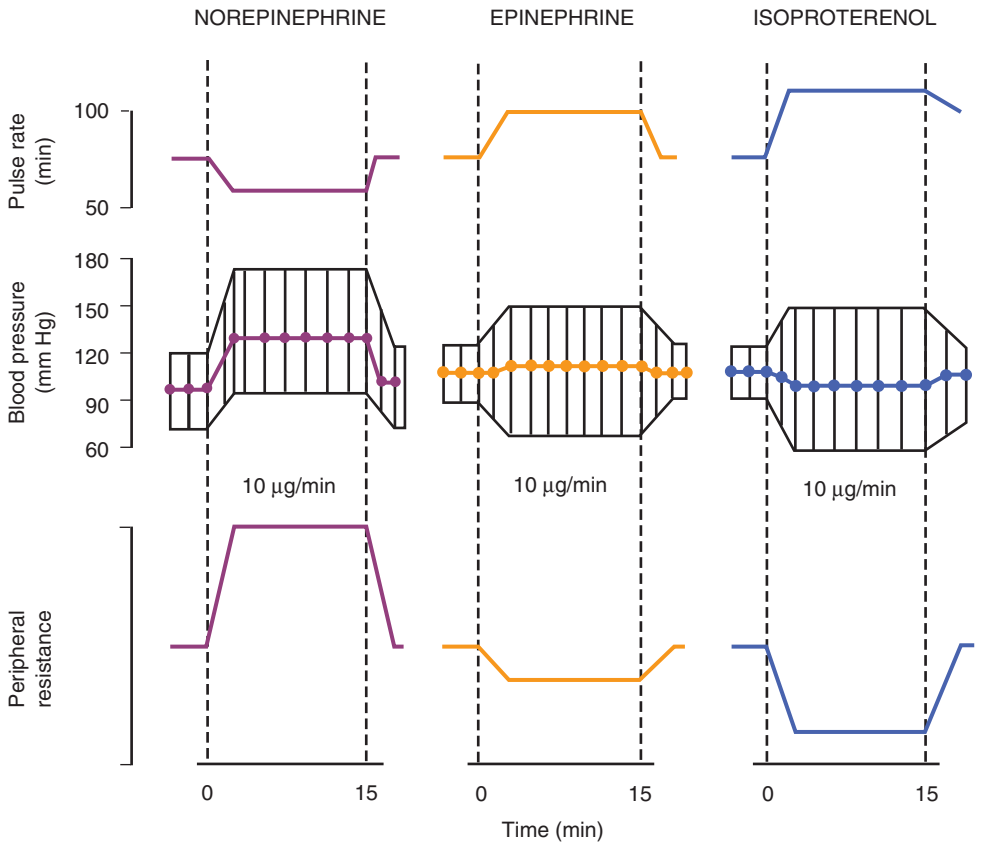
In normal subjects, norepinephrine elevates SVR because α-adrenergic stimulation is not opposed by β_2 stimulation.[116] Reflex vagal activity reduces the rate of sinus node discharge, blunting the expected β_1-chronotropic effect. In normal subjects renal, splanchnic, and hepatic blood flows decrease. The increase in afterload may augment coronary blood flow. This effect may be enhanced by α-adrenergic receptors located in the coronary arteries, although in coronary arteries from explanted human hearts, the vasodilation in response to norepinephrine was mediated via β_2-receptors.[117] Norepinephrine does have inotropic effects on the heart, mediated via α_1- and β_1-receptors. The degree of inotropic response related to α_1 stimulation may be affected by the pressure load on the right ventricle.[118] In the failing heart, the relative contribution from each type of adrenergic receptor appears to be equal.[119] In healthy volunteers, norepinephrine produces a decrease in creatinine clearance because of the effect on renal blood flow. However, in patients with hypotension, the improvement in global perfusion produces an increase in urine output.[120]

The acute hemodynamic effects of norepinephrine are compared with those of epinephrine and isoproterenol in Fig. 31.9. Experience in critically ill children indicates that the hemodynamic responses are not different from those observed in adults. Use of norepinephrine in 18 neonates with persistent pulmonary hypertension–associated heart dysfunction produced significant

TABLE 31.2 Selecting Inotropic and Vasopressor Agents for Specific Hemodynamic Disturbances in Children

	BLOOD PRESSURE OR SVR		
Hemodynamic Pattern	**Normal**	**Decreased**	**Elevated**
Septic Shock			
Stroke index ↑ or ↔		Norepinephrine	
Stroke index ↓	Dobutamine or dopamine	Dopamine or epinephrine (or dobutamine and norepinephrine)	Dobutamine plus vasodilator and/or milrinone
Cardiogenic shock	Dobutamine or dopamine or milrinone	Dopamine or epinephrine	Dobutamine plus vasodilator and/or milrinone
Myocardial dysfunction[a] (complicating critical illness)	Dobutamine or dopamine or milrinone	Dopamine or epinephrine	Dobutamine plus vasodilator and/or milrinone
Congestive heart failure	Dobutamine or dopamine or milrinone		Dobutamine plus vasodilator and/or milrinone
Bradycardia		Isoproterenol	

PDE3, Phosphodiesterase 3; *SVR,* systemic vascular resistance.
[a]For example, acute respiratory distress syndrome or anthracycline therapy.
Modified from Notterman DA. Pharmacologic support of the failing circulation: an approach for infants and children. *Prob Anesth.* 1989;3:288.



• **Fig. 31.9** Effects of intravenous infusion of norepinephrine, epinephrine, and isoproterenol in adult humans. (Modified from Allwood MJ, Cobbold AF, Ginsburg J. Peripheral vascular effects of noradrenaline, isopropylnoradrenaline and dopamine. *Br Med Bull*. 1963;19:132–136.)

increases in systemic blood pressure and left ventricular output, along with improvement in postductal transcutaneous oxygen saturation, pulmonary-to-systemic blood pressure ratio, and an increase in the velocity of pulmonary artery blood flow.[121] In a separate study in 22 neonates with septic shock refractory to fluid support and dopamine or dobutamine, norepinephrine significantly increased mean arterial blood pressure and urine output while decreasing blood lactic acid concentrations.[122]

Pharmacokinetics

There is limited information about the pharmacokinetics of norepinephrine in children. Basal plasma levels of norepinephrine are much higher than basal plasma levels of epinephrine (250–500 vs. 20–60 pg/mL). The minimum concentration at which norepinephrine produces detectable hemodynamic activity is at least 1500 to 2000 pg/mL, suggesting that endogenous plasma norepinephrine simply represents "spillover" from sympathetic activity and that norepinephrine is not a true hormone.[123] The clearance of norepinephrine in healthy adults is 24 to 40 mL/kg per minute, with the half-life averaging 2.0 to 2.5 minutes.[124] The clinical effect of norepinephrine ceases within 2 minutes of the infusion being stopped.[124] Norepinephrine is inactivated by reuptake into nerve terminals, with some elimination occurring by enzymatic degradation in the liver, adrenal glands, and kidney, either by methylation to normetanephrine (by COMT) or by oxidative deamination.[125] 3-Methoxy-4-hydroxymandelic acid is the major metabolite in the urine.[116]

Clinical Role

Norepinephrine improves perfusion in children with distributive or septic shock who are hypotensive but in whom cardiac output is preserved or elevated. Norepinephrine is administered in conjunction with repletion of intravascular volume; titration is best guided by estimates of cardiac output and SVR. The experience in adult patients provides a rationale for using this agent to treat hypotension that is unresponsive to volume repletion[126–129]—norepinephrine is now recommended for warm shock refractory to fluid loading in children.[130–132] A randomized study (in adults) indicates that high-dose norepinephrine is superior to high-dose dopamine for treating hypotension associated with hyperdynamic septic shock.[133] Coronary and renal blood flow increased in lambs at a dose of 0.4 µg/kg per minute while mesenteric blood flow decreased.[134] Thus, titration is important and may entail rapid escalation of dosage. One of several studies in children with septic shock treated with norepinephrine suggested that higher doses might be needed in this population to restore adequate blood pressures and perfusion. A single-center retrospective review of 144 children with septic shock treated with norepinephrine between 2000 and 2010[135] reported a decrease in mortality from 82% to 17% over the study period and an associated increase in norepinephrine use. Mean doses ranged from 0.5 µg/kg per minute to 2.5 µg/kg per minute. The only complications observed were arrhythmias (not requiring treatment) in 2 patients and hypertension, which resolved with lowering of the norepinephrine dose. Notably, the authors reported no complications in

TABLE 31.3 Suggested Infusion Rates for Inotropic and Vasopressor Agents (μg/kg/min)[a]

Agent	CLINICAL INDICATION	
	Inotropic	Pressor
Dopamine	2–15	>12
Epinephrine	0.05–0.5	0.10–1
Norepinephrine		0.05–1
Vasopressin (U/kg/min)		0.0005–0.002[b]
Dobutamine	2.5–20	
Milrinone	0.25–0.75	
Isoproterenol	0.05–1	

[a]Vasopressin is dosed in units or mU/kg/min for shock.
[b]Optimal dosage and infusion rate have not been established in children.

27 patients receiving the drug through a peripheral intravenous catheter for as long as 3 hours.

Norepinephrine is most valuable in the context of tachycardia because, unlike dopamine, at doses required to induce a vasopressor effect, norepinephrine does not elevate and may even lower heart rate through reflex mechanisms. Norepinephrine has also been shown to improve right ventricular performance in adults with hyperdynamic septic shock.[136]

The usual starting dosage for an infusion is 0.05 μg/kg per minute (Table 31.3), with a goal of providing adequate perfusion pressure.[137] Arbitrary values of SVR or blood pressure are not useful end points for therapy. The lowest infusion rate that improves perfusion (skin color and temperature, mental status, urine flow, and reduction in lactate level) should be used.[138]

Other causes of distributive shock (e.g., vasodilator ingestion and intoxication with CNS depressants) also respond to norepinephrine when the predominant hemodynamic problem is low SVR and blood pressure.

Adverse Effects

The increase in afterload that norepinephrine produces can potentially increase myocardial oxygen consumption, but norepinephrine may reflexively decrease heart rate, reducing oxygen consumption and improving diastolic coronary perfusion.[116] Norepinephrine may lead to compromised organ blood flow in the setting of hypovolemia and may elevate blood pressure without improving perfusion. Poor clinical response is usually associated with a low cardiac index, stroke volume, left ventricular stroke work index, and an elevated pulmonary artery occlusion pressure.[126,127] Employing excessive dosages or using norepinephrine to elevate blood pressure without improving perfusion may result in multiple-organ system failure.

Preparation and Administration

Norepinephrine should be diluted in 5% dextrose or 0.9% sodium chloride. Norepinephrine is administered only by central venous catheter, except in extreme emergency. Extravasation of norepinephrine should be treated immediately by local infiltration of phentolamine administered with a fine hypodermic needle.[124,139] As with dopamine, norepinephrine should be administered by a device that permits controlled and precise titration.

Interactions

Tricyclic antidepressants potentiate the action of norepinephrine by reducing neuronal uptake of the compound.[124] MAO inhibitors do not appear to enhance norepinephrine activity. α-Adrenergic blocking agents reduce efficacy of norepinephrine.

Summary

Norepinephrine is the agent of choice in patients with hypotension with low SVR and a normal or high cardiac output after fluid resuscitation (see Table 31.2). Recent septic shock guidelines recommend norepinephrine as the first-choice vasopressor in patients with warm (vasodilatory) shock.[90,132] It is frequently useful in other conditions associated with distributive shock.

Epinephrine

Basic Pharmacology

Epinephrine is synthesized in the adrenal medulla, where it is formed from norepinephrine by addition of a methyl group to the N-terminus.[96] The reaction is catalyzed by N-methyltransferase (see Fig. 31.8). Epinephrine is a hormone; endogenous levels change with the physiologic state of the organism via afferent input to the adrenal medulla. Resting levels are less than 50 pg/mL; heavy exercise produces concentrations of 400 pg/mL or greater.[123] Epinephrine activates α-, β_1-, and β_2-receptors. It is a principal hormone of stress and produces widespread metabolic and hemodynamic effects.[96]

Clinical Pharmacology

Epinephrine activates β_1-receptors in the myocardium and conducting systems at low concentrations, which accelerates phase 4 of the action potential. The heart rate increases, and systolic time intervals are shortened. The inotropic state of the myocardium is also enhanced, producing an increase in force of contraction. Evidence indicates that changes in myocardial oxygen consumption are disproportionate to the increase in force of contraction, thereby decreasing myocardial efficiency.[96] High concentrations of epinephrine or exposure to the compound when the myocardium is sensitized by infarction, operation, or myocarditis may produce serious atrial and ventricular dysrhythmias.[96]

At low plasma concentrations, stimulation of peripheral β_2-receptors promotes relaxation of resistance arterioles; SVR decreases and diastolic blood pressure falls (see Fig. 31.9). The decrease in SVR enhances the direct chronotropic effect of epinephrine. Higher concentrations are associated with activation of vascular α-receptors, and SVR increases. The effect of epinephrine on pulmonary vasculature may also vary with the dosage used.[140] Higher doses are associated with an increase in pulmonary vascular resistance (PVR), both from a direct effect and as a result of increased venous return to the right side of the heart.[96] During infusion of epinephrine, hepatic and splanchnic blood flows increase, while renal blood flow may be reduced.[96]

The thresholds for producing these effects in healthy adults have been examined.[123] Normal basal levels are around 40 pg/mL. As levels increase, the heart rate accelerates first, followed by increases in systolic blood pressure and decreases in diastolic blood pressure. Various metabolic effects (hyperglycemia, cytogenesis, and glycolysis), hypophosphatemia, and hypokalemia may also occur at higher levels. Desensitization to epinephrine occurs rapidly and may be present prior to administration of exogenous catecholamines in the ICU.

Pharmacokinetics

In healthy male volunteers, the plasma clearance of epinephrine is 35 to 89 mL/kg per minute.[141,142] The elimination half-life is approximately 1 minute.[76] Epinephrine is methylated by COMT to metanephrine in the liver and kidneys or deaminated via the action of MAO.[78] It also may be metabolized by extraneuronal uptake.[125] The resulting catabolites are then conjugated to sulfate or glucuronide and excreted in the urine. A wide interindividual variation in clearance is observed in healthy adults. In critically ill children receiving epinephrine at doses from 0.03 to 0.2 μg/kg per minute, plasma concentrations at steady state were linearly related to dose.[143] In this study, wide interindividual variation in clearance was observed.

Clinical Role

Epinephrine is used to treat shock and low cardiac output states associated with myocardial dysfunction. Thus, it is appropriate for treatment of cardiogenic shock or for inotropic support following cardiac surgery.[118] In a model of right ventricular injury, epinephrine increased pulmonary artery blood flow and right ventricular power with greater efficiency than did dopamine or dobutamine.[140] It can also be used to increase pulmonary flow across left to right shunts.[108] Epinephrine is most likely to be useful in patients with sepsis and "cold shock," that is, in the setting of poor perfusion and low cardiac index that does not respond to fluid resuscitation.[144,145] At modest infusion rates (0.05–0.10 μg/kg per minute), SVR decreases slightly; heart rate, cardiac output, and systolic blood pressure increase. At intermediate infusion rates, α_1-adrenergic activation becomes important but is balanced by the improved cardiac output and activation of vascular β_2-receptors. Although epinephrine constricts renal and cutaneous arterioles, renal function and skin perfusion may improve. Very high infusion rates (>1–2 μg/kg per minute) are associated with significant α_1-adrenergic-mediated vasoconstriction; blood flow to individual organs will be compromised and the associated increase in afterload may further impair myocardial function. Studies have shown decreased splanchnic blood flow, decreased oxygen uptake, and increased lactate with epinephrine compared with norepinephrine despite similar increases in global oxygen delivery.[146] Dopamine led to a decrease in lactate and an increase in arterial pH, whereas epinephrine was associated with increases in lactate and metabolic acidosis despite similar increases in cardiac index and oxygen delivery.[147] In newborn piglets, high-dose epinephrine increased SVR, PVR, and lactate while decreasing hepatic blood flow and oxygen delivery.[148] Other studies have shown that the degree of shock also may influence splanchnic blood flow.[149] In a study of adult patients with septic shock, stepwise increases in epinephrine were associated with linear increases in cardiac rate, mean arterial pressure, cardiac index, left ventricular stroke work index, oxygen consumption, and oxygen delivery. Neither PVR nor SVR was affected.[51] Epinephrine is first-line treatment for severe anaphylaxis in both the prehospital and hospital settings, and the case fatality rate from food-related anaphylaxis has declined since the introduction of the epinephrine autoinjector.[150]

Epinephrine has been evaluated in very-low-birth-weight infants with hypotension who did not respond to dopamine at doses as high as 15 μ/kg per minute.[151] Blood pressure and heart rate increased while urine output was maintained. Urine output increased among infants who had been oliguric.

Epinephrine is the most frequently used medication during pediatric cardiopulmonary resuscitation. Bolus injections of epinephrine are used to treat hemodynamically significant bradycardia, asystole, and pulseless arrest. Earlier studies in animals[153,153] demonstrated improved survival after primary cardiac arrest in subjects treated with epinephrine. This was attributed to improved coronary (and therefore myocardial) perfusion from an increase in aortic diastolic pressure. A study in adults following cardiopulmonary arrest attributed to ventricular fibrillation showed that early use of epinephrine was associated with improved survival to hospital discharge, while later initiation of the drug was not.[154,155] The recommended initial dosage is 0.01 mg/kg (10 μg/kg or 0.1 mL/kg of the 1:10,000 solution).[156]

Epinephrine may be given by endotracheal tube; the dosage is 100 μg/kg. Intraosseous administration is appropriate for both bolus and continuous administration of epinephrine. The dosage is the same as for intravenous injection. Epinephrine infusion is also the agent of choice for hypotension following successful treatment of cardiac arrest and, in most cases, of primary cardiogenic shock.

Preparation and Administration

Epinephrine for injection at a concentration of 1:10,000 may be administered undiluted. The 1:1000 injection must be diluted with 0.9% sodium chloride prior to administration. Epinephrine should be infused by a pump capable of precise titration into a central vein, although low-dose infusions may be administered safely via peripheral intravenous catheters if central venous access is not available.

Adverse Effects

Epinephrine produces CNS excitation manifested as anxiety, dread, nausea, and dyspnea.[97] Enhanced automaticity and increased oxygen consumption are the main cardiac toxicities.[96] Extreme tachycardia carries a substantial oxygen penalty, as does hypertension. A severe imbalance of myocardial oxygen delivery and oxygen consumption produces characteristic electrocardiogram changes of ischemia. A subischemic but persistently unfavorable ratio of oxygen delivery to consumption also may be harmful to the myocardium. Epinephrine may be arrhythmogenic. Increases in infusion rate lead to successively more serious events, including atrial and ventricular extrasystoles, atrial and ventricular tachycardia, and, ultimately, ventricular fibrillation. Ventricular dysrhythmias in the pediatric age group are not common but may occur in the presence of myocarditis, hypokalemia, or hypoxemia. Hypokalemia during infusion of epinephrine results from stimulation of β_2-adrenergic receptors, which are linked to Na^+/K^+-ATPase located in skeletal muscle.[157] Hyperglycemia results from β-adrenergic-mediated suppression of insulin release. Increases in blood lactate levels have also been observed.[158] Epinephrine infiltration into local tissues or intraarterial injection can produce severe vasospasm and tissue injury[96] but with less frequency than with norepinephrine, dopamine, or vasopressin.

Epinephrine overdose can be fatal. Several neonates died when inadvertently subjected to oral administration of huge amounts of epinephrine.[159] The syndrome mimicked an epidemic of neonatal sepsis with shock and metabolic acidosis. Intraaortic injection in infants (per umbilical artery) produces tachycardia, hypertension, and renal failure. Intravenous overdose of epinephrine may cause myocardial infarction, ventricular tachycardia, extreme hypertension (up to 400/300 mm Hg), cerebral hemorrhage, seizures, renal failure, and pulmonary edema. Bradycardia also has been observed. Manifestations of acute overdose are treated

symptomatically. β-Receptor antagonists such as propranolol are contraindicated (see later discussion). Hypertension is treated with short-acting antihypertensives (e.g., nitroprusside).

Interactions

Tricyclic antidepressants and antihistamines such as diphenhydramine may potentiate the effects of epinephrine; use of fluorinated anesthetic agents such as halothane may increase the frequency of ventricular dysrhythmia.[96,160–162] Administration of epinephrine with a β-adrenergic antagonist such as propranolol may be dangerous because of residual unopposed α_1 activity. The result can be severe hypertension and bradycardia terminating in asystole. The concomitant use of α- or β-adrenergic antagonists also may antagonize the therapeutic effects of epinephrine.

Summary

Epinephrine is useful in treating shock and low cardiac output states associated with myocardial dysfunction. In critically ill pediatric patients, the most frequent indications for epinephrine infusion are cardiogenic shock, septic shock associated with hypotension and reduced stroke volume, and shock following severe hypoxemia-ischemia (see Table 31.2).

Isoproterenol

Basic Pharmacology

Isoproterenol is the synthetic N-isopropyl derivative of norepinephrine (see Fig. 31.7). The bulky N-terminal substituent confers β_1- and β_2-receptor specificity; the compound does not affect the α-adrenergic receptor. Thus, the principal cardiovascular activities of isoproterenol relate to its inotropic, chronotropic, and peripheral vasodilator effects.[96]

Clinical Pharmacology

Isoproterenol enhances cardiac contractility and heart rate.[96] Peripheral vasodilation produces a fall in SVR, augmenting the direct chronotropic action of the drug. Significant tachycardia ensues. Systolic blood pressure increases while mean and diastolic pressures fall (see Fig. 31.9). Infusion of isoproterenol decreases mesenteric and renal perfusion in healthy patients. However, the increase in cardiac output associated with isoproterenol administration in patients with shock may increase blood flow to these tissues.[96] Isoproterenol increases myocardial demand for oxygen and decreases supply by reducing diastolic coronary filling. Hypotension may complicate initiation of isoproterenol infusion in volume-depleted patients.

Activation of β_2-adrenergic receptors produces bronchodilation and pulmonary vasodilation, respectively.[163] For this reason, isoproterenol by continuous intravenous infusion was employed in the past as adjunctive therapy in children with refractory or rapidly worsening status asthmaticus.[30] Continuously nebulized albuterol and intravenous terbutaline have supplanted isoproterenol for this indication.

Hyperglycemia is not usually observed in patients receiving isoproterenol, although the drug does promote release of free fatty acids. Isoproterenol produces an increase in plasma norepinephrine levels; however, this effect relative to the hemodynamic response to isoproterenol has not been studied.[125]

Pharmacokinetics

Isoproterenol is metabolized by COMT.[96] The plasma elimination half-life of isoproterenol is 1.5 to 4.2 minutes.[164,165] Information about therapeutic isoproterenol concentrations in critically ill patients is not available.

Clinical Role

In the past, isoproterenol was used for a variety of indications, including septic shock and cardiogenic shock associated with myocardial infarction. However, the tachycardia and increased myocardial oxygen consumption, as well as a more sophisticated understanding of the pathophysiology of shock, have limited the use of this compound to only a few specific indications.

Isoproterenol may be used to treat hemodynamically significant bradycardia.[166] However, epinephrine is often preferable.[137] When bradycardia results from heart block, isoproterenol may be used in the acute setting as a bridge to pacemaker placement.

Preparation and Administration

Isoproterenol should be diluted prior to administration.

Adverse Effects

Adverse effects associated with isoproterenol include fear, anxiety, restlessness, insomnia, and blurred vision.[167] Other effects may include headache, dizziness, tinnitus, sweating, flushing, pallor, tremor, nausea, vomiting, and asthenia. Cardiovascular effects may include ventricular tachycardia and other life-threatening ventricular dysrhythmias. Isoproterenol may cause hypertension or severe hypotension.

Interactions

The concomitant administration of a halogenated general anesthetic such as halothane or an intravenous methylxanthine such as aminophylline may potentiate the adverse cardiovascular effects of isoproterenol.[167]

Summary

Isoproterenol is rarely used to treat children or adults. More selective β_2-agonists are safer to use and are preferred. The main indication in the acute setting is for the treatment of symptomatic bradycardia.

Dobutamine

Basic Pharmacology

The structure of dobutamine, a synthetic catecholamine, resembles dopamine in that the β carbon is not hydroxylated. Unlike other catecholamines, there is a large aromatic substituent on the N-terminus. Like isoproterenol, dobutamine is administered as a racemate; (+) dobutamine is a strong β-agonist and an α-antagonist, and (–) dobutamine is an α-agonist and a weak β-agonist.[168] This blend of receptor activities allows dobutamine to deliver significant inotropic and usually trivial chronotropic and vasopressor activity.

Clinical Pharmacology

In adults with CHF, dobutamine increased cardiac index, decreased left ventricular end-diastolic volume, and increased the left ventricular dP/dt (derivative of pressure over time; used as a measure of contractility).[169] Although renal function and urine output may improve as the increase in cardiac output fosters relaxation of sympathetic tone and improved perfusion, dobutamine did not improve indices of renal function compared with dopamine in critically ill patients.[170] Dobutamine improved right ventricular systolic function and decreased PVR in piglets with

right ventricular injury.[140] In healthy children, dobutamine increased left ventricular systolic function and relaxation.[171] In the newborn piglet, dobutamine increased superior mesenteric and renal artery blood flow, increased cardiac index, and decreased SVR.[172] A threshold model with a log-linear dose-response relationship above the threshold has been demonstrated in critically ill term and preterm neonates and in children between 2 months and 14 years of age.[82,173] In one small study, dobutamine infusion was associated with increases in cardiac output, blood pressure, and heart rate. Dobutamine is a relatively selective inotrope with little effect on heart rate at usual infusion rates.[174] Somewhat greater thresholds for improved cardiac output were observed in a second group of children and in infants. However, in all studies, dobutamine improved cardiac contractility without substantially altering heart rate unless high infusion rates were employed.[173,175] In a Cochrane analysis that compared dobutamine with dopamine in premature neonates with low systemic blood flow on the first day of life,[176] dobutamine produced a significantly greater increase in superior vena cava flow whereas dopamine produced a significantly greater increase in mean blood pressure. In addition, dobutamine has been shown to increase cerebral blood flow velocity but not cerebral oxygen consumption in patients with septic shock.[177]

Pharmacokinetics

The plasma elimination half-life of dobutamine in adults is approximately 2 minutes.[76] CHF increases the volume of distribution. Reported clearance values in children have ranged from 32 to 625 mL/kg per minute in one study and from 40 to 130 mL/kg per minute in another.[178,179] The principal route of elimination is methylation by COMT, followed by hepatic glucuronidation and excretion into urine and bile.[96] 3-O-Methyldobutamine also represents a major route of elimination for dobutamine, with up to 33% of the infused drug being eliminated as the sulfoconjugated compound.[180] Dobutamine also is cleared from the plasma by nonneuronal uptake. Some investigators have reported nonlinear elimination kinetics, but other data suggest that dobutamine's kinetics can be adequately described by a simple first-order (linear) model.[82,178,179,181,182]

Clinical Role

In adults, dobutamine produces improvement in a variety of conditions associated with poor myocardial performance, such as cardiomyopathy, atherosclerotic heart disease, and acute myocardial infarction. Dobutamine has been used following surgery for myocardial revascularization, cardiac transplantation, and other procedures associated with postoperative myocardial dysfunction, although undesirable chronotropic effects have also been reported.[183] Dobutamine is not first-line therapy for septic shock unless the primary disturbance is complicated by myocardial dysfunction. Although impaired myocardial performance can be demonstrated early in patients with septic shock, the main problem relates to regulation of vascular tone, and agents that increase SVR are preferred. When ventricular dysfunction complicates clinical management, dobutamine may be a useful adjunct. In this context, dobutamine alone or in combination with dopamine has produced an increase in cardiac output, left ventricular stroke work, and blood pressure.[43] As indicated in Table 31.2, dobutamine can be combined with norepinephrine in treating the patient with myocardial dysfunction associated with hyperdynamic shock (i.e., a child with septic shock who has received cardiotoxic chemotherapy).

Several studies in infants and children demonstrate that dobutamine improves myocardial function in a variety of settings.[82,173,178] Stroke volume and cardiac index improve without a substantial increase in heart rate. SVR and PVR may decrease toward normal.[184] Dobutamine has been evaluated in children following cardiac surgery with cardiopulmonary bypass. In a study by Bohn and colleagues,[44] dobutamine enhanced cardiac output by increasing heart rate, while tachycardia prompted discontinuation of the infusion in several patients. The expected fall in SVR was not observed in children who received the drug after cardiopulmonary bypass. These differences in effectiveness between adults and children following be because myocardial dysfunction and CHF are generally not present in children undergoing repair of congenital heart disease. Rather, the indication for surgery involves abnormalities in cardiac architecture or circulatory anatomy. Berner and associates[185] found that children undergoing mitral valve surgery responded to dobutamine with an increase in stroke volume, whereas children following tetralogy of Fallot repair did not, and their cardiac output increased only through a higher heart rate. A more recent report by the same group indicated that following repair of tetralogy of Fallot, dobutamine did enhance cardiac output when it was combined with atrial pacing to increase heart rate. Isoproterenol without pacing provided a higher cardiac output than either dobutamine alone or dobutamine in combination with pacing.[186] Specific indications for dobutamine in the pediatric age group include low-output CHF and a normal to moderately decreased blood pressure (see Table 31.2). Typical examples include viral myocarditis, anthracycline-associated cardiomyopathy, cyclophosphamide, hemochromatosis (related to hypertransfusion therapy), or myocardial infarction (Kawasaki disease).

Dobutamine is not a first-line agent to treat low-output states that are caused by intracardiac shunt or abnormal cardiac chamber structure. Although dobutamine may be used following corrective or palliative cardiovascular surgery in the child[187] in the context of demonstrated or suspected myocardial dysfunction, milrinone is now the preferred agent for providing inotropy and afterload reduction, despite insufficient evidence of superior effectiveness in a recent meta-analysis.[188] Dobutamine may be of value as adjunctive therapy in treating myocardial dysfunction that complicates ARDS, septic shock, or a hypoxic-ischemic event, but epinephrine is generally preferred.

Preparation and Administration

Dobutamine is available as a premixed solution in a variety of concentrations. Therapeutic dosing ranges between 2.5 and 20.0 μg/kg per minute. However, epinephrine is now generally employed in children requiring doses that exceed 10 μg/kg per minute.

Adverse Effects

Adverse cardiovascular effects include hypertension, tachycardia, and ectopic heart beats. Headache, nausea, vomiting, paresthesia, and dyspnea may also occur. Dobutamine also may decrease serum potassium concentrations.

Dobutamine usually increases myocardial oxygen demand. In subjects with myocardial dysfunction, coronary blood flow and oxygen supply improve with the increase in demand. However, if dobutamine is used when myocardial contractility is normal, oxygen balance will be adversely affected.[189] Tachycardia greatly increases myocardial oxygen consumption and should prompt a reduction in the dosage or use of an alternate agent.

Although dobutamine is less likely than other catecholamines to induce serious atrial and ventricular dysrhythmias, these may occur, particularly in the context of myocarditis, electrolyte imbalance, or high infusion rates.[190] Dobutamine and other inotropes should be administered cautiously to patients with dynamic left ventricular outflow obstruction, as in hypertrophic obstructive cardiomyopathy. Prolonged infusion of dobutamine may inhibit platelet aggregation and, in some adult patients, petechial bleeding has been attributed to dobutamine.[191]

Interactions

The concomitant use of a β-adrenergic antagonist such as propranolol may antagonize the cardiovascular actions of dobutamine.[235] Halogenated anesthetic agents, such as halothane, may potentiate the adverse cardiovascular effects of dobutamine. Dobutamine may increase the insulin requirement in diabetic patients.

Summary

Dobutamine is a positive inotropic agent that may be used to treat poor myocardial contractility. For septic shock and other acute hemodynamic disturbances, dobutamine is an adjunct when the primary problem is complicated by poor myocardial function (see Table 31.2). In this context, concomitant use of a vasopressor such as norepinephrine may be appropriate.

Vasopressin

Basic Pharmacology

Vasopressin is a highly conserved hormone, and vasopressin-like peptides are present in numerous species. Its main function is to preserve fluid balance in the organism. In humans, it is released in response to two main stimuli: increases in plasma osmolality and decreases in effective circulating volume or blood pressure. Although vasopressin has long been used for the treatment of diabetes insipidus, its name derives from its vasopressor effect. Vasopressin also acts as a neurotransmitter in the CNS, has a role regulating adrenocorticotropin hormone release, and is involved in thermoregulation, platelet aggregation, and smooth muscle contraction in the uterus and gastrointestinal tract.[20,24]

Clinical Pharmacology

The response patterns differ for the two stimuli for vasopressin release. An increase in plasma osmolality above 280 mOsm/kg leads to a dramatic increase in the release of vasopressin from the posterior pituitary. The hormone exerts its effect by increasing water reabsorption in the renal collecting duct. The dose-response curve is so steep that when osmolality is 290 mOsm/kg, vasopressin levels exceed those that produce maximal urinary concentration. In contrast, the threshold for release in response to hypovolemia or hypotension is much higher, with decreases of greater than 20% of the circulating volume required. However, once the threshold is reached, plasma levels rise twentyfold to thirtyfold (far exceeding levels seen with hyperosmolality).[20] Vasopressin exerts its hemodynamic effects via the V_{1a}-receptor, which is coupled to G_q. In the peripheral vasculature, intracellular calcium is increased, enhancing contraction and restoring systemic vascular tone. Vasopressin also inhibits potassium channels, further increasing intracellular calcium.[192,193] Baroreceptors in the left atrium, left ventricle, and pulmonary veins sense changes in volume while baroreceptors in the carotid sinus and aorta sense changes in arterial pressure.[20] Decreased pressure leads to a reduced rate of firing and release of the tonic inhibition of vasopressin release.[24]

Vasopressin is a potent vasoconstrictor when present in the plasma at high concentrations. At the lower concentrations associated with the vasopressin response to hyperosmolality, it actually induces vasodilation in the pulmonary, renal, and cerebral circulation via the V_2-receptor or oxytocin-mediated nitric oxide release.[194] It does not elevate blood pressure because an associated decrease in heart rate offsets the increase in SVR. For this reason, vasopressin was not originally considered to be a clinically useful agent to treat hypotension.[195] Landry and colleagues[196]measured plasma vasopressin levels in patients with shock who were receiving catecholamine support. Surprisingly, plasma levels of vasopressin were not elevated in patients with septic shock as compared with those with cardiogenic shock, whose plasma levels were nearly 10 times greater. Vasopressin infusion in patients with septic shock who were receiving catecholamines produced an increase in SVR and mean arterial pressure and a decrease in cardiac index. Plasma vasopressin levels are inappropriately low in patients with vasodilatory septic shock, possibly due to impaired baroreflex-mediated secretion. The authors hypothesized that this phenomenon contributes to the hypotension of vasodilatory septic shock.

It appears that in the early stages of septic shock, vasopressin levels are higher than normal but decrease to relatively low levels as shock persists.[197] This pattern has also been demonstrated in a model of hemorrhagic shock[198] in which neurohypophysis stores of vasopressin were depleted. In three patients with septic shock and low levels of vasopressin, the high-intensity signal from the posterior pituitary on T1-weighted magnetic resonance imaging was lost, suggesting depletion of vasopressin.[197] Hence, vasopressin deficiency may occur early in vasodilatory shock and contribute to its pathogenesis.

Pharmacokinetics

Vasopressin circulates as a free peptide and does not exhibit any protein binding.[26] It is degraded rapidly in the kidneys and liver, with 5% to 15% of an intravenous dose eliminated unchanged in the urine.[199] The normal elimination half-life is 10 to 20 minutes.[199] Renal failure or hepatic insufficiency can prolong the elimination half-life.[200,201]

Clinical Role

The original report by Landry and colleagues[196] generated intense investigation into the clinical applications of vasopressin in the setting of vasodilatory shock. The same group prospectively evaluated vasopressin in patients with vasodilatory shock after placement of a left ventricular assist device.[202] At a dose of 0.1 U/min, vasopressin increased mean arterial pressure and SVR but not cardiac index. Among patients with a high level of endogenous vasopressin, the increase in blood pressure tended to be less. A rapid response to vasopressin was noted in all patients, allowing for the dose to be decreased to as low as 0.01 U/min. This group also published experience with vasopressin in children after cardiac surgery.[203,204] Vasopressin was used to treat 11 children with hypotension on epinephrine infusions following cardiac surgery. At vasopressin doses ranging from 0.0003 to 0.002 U/kg per minute, blood pressure increased within 1 hour and the epinephrine infusion could be decreased in 5 of 8 patients. Two patients who had echocardiographic evidence of poor function died. The remaining nine patients with vasodilatory shock survived and were discharged from the ICU. The authors cautioned against the

use of vasopressin in patients with cardiogenic shock in view of the potential effect on cardiac index. Vasopressin levels were measured in three patients; two had an absolute deficiency and one had a relative deficiency. In adults, vasopressin deficiency (relative or absolute) was associated with shock following cardiopulmonary bypass. Hemodynamic function improved with vasopressin, and the need for other vasopressors decreased.[205] In a prospective, randomized study, the combination of vasopressin at a dose of 0.06 U/min and norepinephrine was compared with norepinephrine alone in patients with catecholamine-resistant vasodilatory shock.[206] The patients in the vasopressin-norepinephrine arm had a lower heart rate and higher blood pressure, SVR, and cardiac index. They also had reduced requirements for norepinephrine and a lower rate of new-onset dysrhythmias. Gastric perfusion also was better preserved in the vasopressin group.

In summary, in studies of patients with vasodilatory shock, vasopressin has been shown to improve blood pressure, increase SVR, lessen the need for catecholamines, improve markers of myocardial ischemia, and improve urine output.[77,207–210] Published experience in pediatric patients with septic shock or following cardiac surgery is still limited. Liedel and colleagues[211] published their experience with 5 patients, ranging in age from 2 weeks (a 23-week premature infant) to 14 years. In 4 patients, blood pressure increased and catecholamine support could be decreased. In three patients, urine output improved. In a multicenter, randomized trial involving 69 pediatric patients with vasodilatory shock,[212] vasopressin (0.0005–0.002 U/kg per minute) or placebo was added to open-label vasoactive agents. There was no difference in the primary end point of time to vasoactive-free hemodynamic stability or in any of the secondary outcomes, which included mortality, ventilator-free days, length of critical care unit stay, and adverse events. Ten deaths occurred in the vasopressin group and five in the placebo group (no statistical significance). It was concluded that low-dose vasopressin did not demonstrate any added benefit. Vasopressin also has been used in children undergoing evaluation for brain death.[213] At a dose of 0.04 U/kg per hour, blood pressure increased and α-agonist support was decreased. No deleterious effect on organ function was noted.

Prior to the 2015 guidelines, vasopressin was added to the Advanced Cardiac Life Support protocol for ventricular fibrillation in adults.[93] However, there is insufficient evidence to make a recommendation either for or against its use in children who sustain a cardiac arrest.[214,215] Mann and colleagues[214] published their experience with vasopressin during cardiopulmonary resuscitation in pediatric patients in a retrospective case series. In six events involving four patients, vasopressin was given after conventional therapy had failed to achieve return of spontaneous circulation (ROSC). In all six events, pulseless electrical activity was the initial rhythm, while at the time vasopressin was given, events were asystole, pulseless ventricular tachycardia, and ventricular fibrillation. In four cases, ROSC was achieved for more than 60 minutes and one patient survived to discharge in a condition close to her neurologic baseline. A review of the American Heart Association National Registry of Cardiopulmonary Resuscitation in children suggested a lower rate of ROSC and longer arrest duration in patients who received vasopressin during in-hospital resuscitation.[216] The authors emphasize that this result should be interpreted with caution, however, because vasopressin was only administered in 64 (5%) of the 1293 cases reviewed, and all of these patients had longer arrest times and were also pretreated with epinephrine.

Dosing and Administration

No standards for pediatric dosing currently exist. The American Heart Association guidelines for pediatric advanced life support[214] suggest a bolus dose of 0.5 U/kg. Standard dosing for vasopressin in vasodilatory shock has not been determined, but the dose used in a recent pediatric study ranged from 0.0005 to 0.002 U/kg per minute. The current guidelines for the management of severe sepsis and septic shock in adults suggest that vasopressin (0.03 U/min) may be added to norepinephrine to raise mean arterial pressure to target or to decrease norepinephrine dose but that it should not be used as the initial vasopressor.[131]

Adverse Effects

Few adverse events have been reported with the use of vasopressin in the setting of vasodilatory shock. Elevation of liver enzymes and total bilirubin, with a decrease in platelet count, have been noted, and one series in adults noted 6 cardiac arrests among 50 patients receiving vasopressin for hemodynamic support.[208,217] All six patients had "severe refractory shock" and five were receiving a vasopressin dose greater than 0.05 U/min. In 30% of patients receiving vasopressin, ischemic skin lesions of the distal limbs, trunk, or tongue were noted. Preexisting peripheral arterial occlusive disease and the presence of septic shock were identified as risk factors.[217] Extravasation of vasopressin from a peripheral intravenous catheter was associated with skin necrosis.[218] Treatment with vasopressin at doses used to augment blood pressures and improve hemodynamics may cause hyponatremia that, in most cases, resolves with discontinuation of the drug.[219] Yet, in a case series involving 10 neonates with severe persistent pulmonary hypertension of the newborn who were treated with vasopressin, no significant decrease in serum sodium was observed.[220] The effect on sodium level may be a function of patient selection, dose, and duration of treatment.

Interactions

The antidiuretic effect of vasopressin may be antagonized with the concomitant administration of epinephrine, heparin, lithium, or demeclocycline.[199] The tricyclic agents chlorpropamide, carbamazepine, clofibrate, phenformin, and fludrocortisone may exert additive antidiuretic effects when used in combination with vasopressin. Concomitant use of vasopressin with a ganglionic blocking agent can enhance the vasopressor effect of vasopressin.

Summary

Vasopressin has been added to the pediatric intensive care unit (PICU) practitioner's armamentarium for the treatment of decreased SVR. Its use may elevate blood pressure and urine output and, although it is not recommended as routine, first-line treatment, a low-dose infusion may be considered as rescue therapy in patients with catecholamine and steroid refractory vasodilatory shock.[132] Its major advantage is in the lack of dependence on adrenergic receptors, which are known to be downregulated in septic shock. Studies to date in adults and children have not shown a benefit in reducing mortality or in decreasing intensive care mortality or ICU length of stay.[132] Vasopressin should not be used in settings in which impaired myocardial function is the principal problem. Thus far, there is insufficient evidence to make a recommendation for or against the routine use of vasopressin in children during cardiopulmonary resuscitation from cardiac arrest.

Bipyridines

Inamrinone (formerly known as amrinone), milrinone, enoximone, and piroximone are nonsympathomimetic inotropic agents. The structure of milrinone is shown in Fig. 31.10. Inamrinone, the earliest formulation to be introduced, was associated with an increased risk of thrombocytopenia in both adults and children[221,222] and potentially fatal hypotension.[223] Thus, it is no longer available in the United States. Neither of these complications has been observed with milrinone, the current bipyridine of choice.

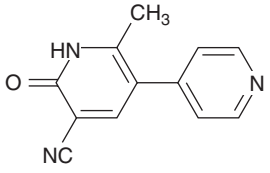
The pharmacologic effects of the bipyridines result from selective inhibition of PDE3 and not from interaction with adrenergic receptors or inhibition of Na^+/K^+-ATPase.[33] These agents augment inotropy and lusitropy as well as relaxation of vascular smooth muscle. They improve myocardial contractility and decrease ventricular afterload.

Milrinone

Clinical Pharmacology

In both adults and children, milrinone acts as an inotrope and vasodilator, producing a direct reduction in preload and afterload.[33,224] Administration to subjects with CHF results in increased cardiac index and reduced SVR, central venous pressure, and pulmonary capillary occlusion pressure,[225] while heart rate is not affected. Systemic hypertension is also reduced.[34,226,227] Patients experience a greater reduction in left and right heart filling pressures and SVR with milrinone than with dobutamine, even at equivalent contractility dosing.[228] Improvement in global hemodynamic function is associated with a more favorable ratio of myocardial oxygen delivery to consumption.[229] Blood pressure is usually maintained, even in the face of reduced SVR, because of the associated improvement in contractility and stroke volume. Increasing doses of milrinone have been shown to correlate with increasing mixed venous oxygen saturation.[230] Milrinone may improve contractility in patients who fail to respond to catecholamines and may further augment cardiac index in patients being treated with dobutamine. Caution is advised when administering milrinone to patients who are intravascularly volume depleted or in whom improvement in cardiac output does not occur, as hypotension may result.[231]

Animal models suggest that phosphodiesterase inhibitors are direct pulmonary vasodilators even at doses lower than those that increase cardiac output.[232] Milrinone reduces PVR in children with intracardiac left-to-right shunts and elevated PVR, while in children with normal pulmonary pressure, a decrease in SVR but not PVR is observed.[233] PDE3 inhibitors provide effective adjunctive therapy in the child with elevated PVR and reduced pulmonary blood flow. Patients given milrinone perioperatively demonstrated improved splanchnic oxygenation and decreased systemic levels of endotoxin and IL-6 following coronary artery bypass grafting.[234]



• **Fig. 31.10** Structure of milrinone.

Several studies have evaluated milrinone in children following surgery for congenital heart disease. In one study, a loading dose of 50 μg/kg followed by a continuous infusion of 0.5 μg/kg per minute was associated with mild tachycardia and a slight decrease in systemic blood pressure.[235] Cardiac index increased while SVR and PVR decreased. In a double-blind, placebo-controlled trial, high-dose milrinone (75 μg/kg bolus followed by continuous infusion at 0.75 μg/kg per minute) was associated with a decreased incidence of low cardiac output syndrome.[236] Length of hospital stay was similar among the treatment groups, but stay greater than 15 days was more common in the placebo arm. In yet another study, three different infusion-dose regimens (0.375, 0.50, and 0.75 μg/kg per minute) after the same loading dose of 50 μg/kg per minute were compared in postoperative pediatric patients with pulmonary hypertension secondary to congenital cardiac disease.[187] While ICU length of stay and duration of mechanical ventilation did not differ between groups, 70% of patients receiving high-dose milrinone required inotropic support to treat hypotension. Milrinone has also been shown to increase cardiac index and decrease SVR after the Fontan procedure.[236]

In a double-blind crossover study of children with nonhyperdynamic septic shock (i.e., normal to low cardiac index and normal to elevated SVR), milrinone increased cardiac index, stroke volume index, and oxygen delivery while decreasing SVR.[237] No differences in blood pressure or PVR were seen when milrinone was given at a dose of 0.5 μg/kg per minute as a continuous infusion after a bolus dose of 50 μg/kg.

Pharmacokinetics

Milrinone is approximately 70% bound to plasma proteins, with approximately 85% renal elimination.[238] Hepatic glucuronidation accounts for a minor elimination pathway. Both renal dysfunction and CHF affect the elimination profile of milrinone, doubling the elimination half-life from approximately 1 to 2 hours.[239,240] In infants and young children undergoing cardiac surgery, the weight-adjusted clearance of milrinone was shown to increase significantly with age.[241–242] Importantly, the milrinone clearance values for both infants and children were significantly higher than those reported in adults following cardiac surgery.[243] In children with septic shock, the median half-life of milrinone was 1.5 hours.[244] Plasma levels did not correlate with changes in cardiac index or SVR. Milrinone clearance is significantly reduced in patients with acute renal dysfunction.[245] When exposed to the same dose, a patient with acute renal failure may have an eightfold higher serum level of milrinone than patients with normal renal function.

Clinical Role

Milrinone augments cardiac contractility and may prevent low cardiac output syndrome (LCOS) in children following cardiac surgery and improves perfusion in patients with cold shock. Patients who respond with excessive vasodilation may be started on a low-dose catecholamine infusion to maintain target blood pressures. Milrinone's properties as a pulmonary vasodilator have made it a useful adjunct in the treatment of pulmonary hypertension.[246]

Preparation and Administration

Milrinone lactate is available in single-dose vials and as premixed solutions.[247,248] A loading dose of 50 μg/kg is generally used in children[239,241] and may be administered undiluted over 15 minutes. Maintenance infusion rates are generally initiated at 0.5 μg/kg per minute and titrated to clinical response.[249] In patients not given a loading dose of milrinone, changes in

cardiac index and plasma levels of milrinone after 3 hours were similar to those seen in patients who received a loading dose.[249] Milrinone is not physically compatible compatible with furosemide but is compatible with many drugs used in the PICU, including dopamine, epinephrine, fentanyl, and vecuronium.[250,251] Milrinone may be administered safely through a peripheral intravenous catheter.

Adverse Effects

In a large pediatric study, serial measurements showed no difference in platelet count over time by treatment arm, and there was no difference in the incidence of thrombocytopenia (platelet count <50,000) during the study infusion.[236] As previously stated, milrinone may cause hypotension in patients with intravascular volume depletion and in patients with renal dysfunction in whom drug clearance is reduced. Milrinone has been cited as a risk factor for early postoperative tachyarrhythmias in patients following congenital cardiac surgery. In one single-center prospective observational study of 603 patients following surgery for congenital heart disease, the incidence of early postoperative tachyarrhythmias was 50%.[252] Identified risk factors included age, cardiopulmonary bypass and aortic cross-clamp time, and the use of milrinone at the time of admission to the cardiac ICU.

Summary

Milrinone offers an attractive combination of positive inotropy with decreased SVR. It is useful in the short-term management of the infant and child with myocardial disease. Milrinone has an established role in the management of impaired cardiac contractility following cardiopulmonary bypass and is the only agent currently approved for use as prophylaxis against LCOS in children following cardiac surgery. Its role in other settings has not been conclusively established by randomized trials.

Digitalis Glycosides

The role of digoxin in the acute care of critically ill children has always been limited by a narrow therapeutic index, slow onset of action, and the potential for life-threatening adverse effects. With the advent of new therapies for both the acute and chronic management of CHF and myocardial dysfunction, its role has further decreased. The PICU practitioner may still encounter patients receiving the drug, particularly for control of dysrhythmias. As is true for the catecholamines and other drugs discussed in this chapter, digoxin exerts its inotropic effects by increasing intracellular calcium.

Basic Pharmacology

Cardiac glycosides consist of a steroid moiety with one to four sugar molecules attached.[253] The number and composition of the associated sugar molecules affect the pharmacokinetics of the specific glycoside; all digitalis glycosides have similar pharmacodynamic properties. Glycosides bind to and inhibit Na^+/K^+-ATPase. Binding of digoxin to ATPase is affected by serum potassium. Hyperkalemia depresses digoxin binding, whereas hypokalemia has the opposite effect, accounting in part for potentiation of digoxin-induced dysrhythmias during hypokalemia.[254] As described earlier in this chapter, inhibition of ATPase produces an increase in intracellular calcium and enhances the inotropic state of the myocardium.

Clinical Pharmacology

In patients with CHF, the positive inotropic action of digoxin leads to increased cardiac output and reductions in filling pressures, edema, and sinus node rate. When CHF is due to obstructive lesions or left-to-right shunts, it is more difficult to demonstrate benefit than when CHF is due to myocardial failure.

In patients with CHF who have a sinus rhythm, administration of digoxin produces a decrease in heart rate, likely because of improved inotropy and resolution of compensatory sympathetic activity. Digoxin enhances vagal tone by increasing baroceptor sensitivity and by directly stimulating central vagal centers,[254] which leads to direct slowing of heart rate, augmenting that produced by improved function. Another effect of digoxin-mediated enhanced vagal tone is slowed conduction of atrial impulses through the atrioventricular node to the ventricle. This property is exploited in use of digoxin to control or treat supraventricular tachycardia and atrial flutter or fibrillation. This aspect of digitalis pharmacology is reviewed in Chapter 33.

Use of digoxin in the PICU is further complicated by the large number of pharmacokinetic and pharmacodynamic interactions between digoxin and other drugs used in critical care.[255] For example, carvedilol (a β-blocker) has been shown to decrease the elimination of digoxin in children, necessitating a reduction in digoxin dosage.[256] Toxicity-related adverse effects are major limiting factors in administering digitalis glycosides to critically ill patients. The most serious are disturbances in cardiac rhythm.[8,253] In adults and older children, the dominant manifestations of digoxin toxicity are tachydysrhythmias, such as premature ventricular contractions, ventricular tachycardia, and ventricular fibrillation. Atrial tachycardia and junctional tachycardia may also occur. Bradycardia and atrioventricular conduction block are manifestations of acute, profound intoxication, which are also seen in infants with enhanced vagal tone and diminished sympathetic activity.

The risk of digitalis toxicity increases with increased myocardial irritability, as in myocarditis, ischemia, hypoxemia, or when administered with catecholamines. Hypokalemia and alkalosis also potentiate digoxin-induced dysrhythmias. Treatment of digoxin toxicity is supportive and requires correction of electrolyte disturbances.[257] Specific pharmacologic support (e.g., with atropine, lidocaine, phenytoin, or magnesium sulfate) may be necessary but is frequently unsuccessful. Life-threatening toxicity is treated with digoxin-specific Fab antibody.[258]

Pharmacokinetics

The dosage of digoxin for young children and infants is much higher than for older children and adults. In the past, this disparity was ascribed to the incorrect belief that developmental immaturity was associated with decreased myocardial sensitivity to digitalis. It is now understood that neonates eliminate digoxin more rapidly.[8] Clearance is dependent on age, although there is wide interindividual variation during the first year of life.[255] Thus, infants may require higher loading ("digitalizing") and maintenance dosages to achieve therapeutically effective plasma concentrations. Distribution of digoxin is relatively slow; therefore, plasma levels will be misleadingly elevated if determined sooner than 6 hours following administration of a dose. In the nonacutely ill child, the half-life of digoxin is 36 hours with a clearance of 8.6 L/h.[259] Digoxin is eliminated by the kidney through glomerular filtration and renal tubular secretion as well as through renal tubular mechanisms, including an efflux pump.

Elimination is strongly affected by renal dysfunction, complicating use of the agent in the critically ill child.

Clinical Role

The indications for digoxin in the care of the critically ill pediatric patient are limited. Its role as an inotropic agent in the acute setting has been supplanted by other drugs with a more favorable pharmacodynamic profile (e.g., milrinone). It is used primarily now to control dysrhythmias.[260] Because digoxin does not produce β-adrenergic receptor desensitization and has beneficial effects by virtue of decreased sympathetic activity, it remains an option in the outpatient management of pediatric CHF.

Preparation and Administration

Digoxin is available in both parenteral and oral formulations. The injectable form must be diluted to avoid precipitation.

Adverse Effects

Cardiovascular adverse effects may include sinus bradycardia, atrioventricular block, ventricular tachycardia, and other dysrhythmias.[255] Gastrointestinal adverse effects include nausea, vomiting, anorexia, diarrhea, constipation, abdominal pain, and abdominal distension. Visual disturbances, photophobia, headache, muscle weakness, fatigue, drowsiness, dizziness, vertigo, seizures, and neuropsychiatric abnormalities may occur.

Interactions

The adverse cardiovascular effects of digoxin may be potentiated by agents that lower serum potassium or magnesium concentrations, such as thiazide diuretics, loop diuretics, amphotericin B, corticosteroids, polystyrene sodium sulfonate, and glucagon.[255] The administration of digoxin with intravenous calcium results in additive or synergistic inotropic and adverse cardiovascular effects. β-Adrenergic antagonists can cause complete heart block when administered with digoxin. Using digoxin with succinylcholine or sympathomimetics increases the risk of dysrhythmias. Digoxin has a narrow therapeutic index; serum digoxin concentrations are increased with concomitant administration of amiodarone, flecainide, quinidine, propafenone, verapamil, captopril, itraconazole, and indomethacin.

Summary

Digitalis glycosides are inotropic agents that have the added benefit of slowing rather than accelerating heart rate. Given its narrow therapeutic window, long half-life, and with the emergence of newer medications, there is rarely a role for digoxin in the acute setting.

Conclusion

Significant advances have been made in our understanding of the mechanisms underlying adrenergic receptor signaling, the control of vascular tone, and the influence of genetic polymorphisms on the pathways involved in these processes. Despite this broader fund of knowledge, the therapeutic options for supporting the patient with impaired end-organ perfusion remain essentially unchanged. The catecholamines comprise the mainstay of therapy for patients in need of inotropic or vasopressor support. Although dopamine is still used, epinephrine and norepinephrine are now preferred for patients with poor cardiac performance or decreased systemic vascular tone, respectively.

Milrinone or dobutamine can be used to increase myocardial contractility in the absence of hypotension. Milrinone is particularly useful after cardiac surgery. Vasopressin has emerged as an option for vasodilatory shock that is resistant to catecholamine therapy. Often, the clinical picture is mixed, and the patient may require both inotropic and vasopressor support. Careful attention to hemodynamics and end-organ perfusion and a thorough understanding of cardiovascular pharmacology are necessary in order to select the agent(s) that will provide the optimal results in critically ill patients.

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Abstract: Cardiovascular dysfunction is a cardinal manifestation of critical illness in children. Pediatric intensivists must have a solid understanding of the basic science and practice aspects of drugs used to treat these disorders. Therefore, a thorough understanding of cardiovascular pharmacology—including the indications, clinical effects, pharmacokinetics, pharmacodynamics, adverse reactions, and drug interactions—is essential to ensure optimal outcomes with minimal risk. This chapter offers an overview of the clinical pharmacology of the five catecholamines, two noncatecholamine agents, and the venerable cardiac glycosides most commonly used to support critically ill children.

Key words: Shock, vasoactive drugs, adrenergic receptors, catecholamines, epinephrine, norepinephrine, inotropes, bipyridines, milrinone, phosphodiesterase inhibitor, vasopressin