CHAPTER 15

Hypotensive Agents

KEY CONCEPTS

1. Clinical trials have shown that inhaled nitric oxide is a selective pulmonary vasodilator that is beneficial in the treatment of reversible pulmonary hypertension. By improving perfusion only in ventilated areas of the lung, inhaled nitric oxide may improve oxygenation in patients with acute respiratory distress syndrome or during one-lung ventilation.
2. Acute cyanide toxicity is characterized by metabolic acidosis, cardiac arrhythmias, and increased venous oxygen content (as a result of the inability to utilize oxygen). Another early sign of cyanide toxicity is the acute resistance to the hypotensive effects of increasing doses of sodium nitroprusside (tachyphylaxis).
3. By dilating pulmonary vessels, sodium nitroprusside may prevent the normal vasoconstrictive response of the pulmonary vasculature to hypoxia (hypoxic pulmonary vasoconstriction).
4. Preload reduction makes nitroglycerin an excellent drug for the relief of cardiogenic pulmonary edema.
5. Hydralazine relaxes arteriolar smooth muscle, causing dilatation of precapillary resistance vessels via increased cyclic guanosine 3′,5′-monophosphate.
6. The body reacts to a hydralazine-induced fall in blood pressure by increasing heart rate, myocardial contractility, and cardiac output. These compensatory responses can be detrimental to patients with coronary artery disease and are minimized by the concurrent administration of a β-adrenergic antagonist.
7. Fenoldopam mesylate (infusion rates studied in clinical trials range from 0.01–1.6 mcg/kg/min) reduces systolic and diastolic blood pressure in patients with malignant hypertension to an extent comparable to nitroprusside.
8. Dihydropyridine calcium channel blockers preferentially dilate arterial vessels, often preserving or increasing cardiac output.

A multitude of drugs are capable of lowering blood pressure, including volatile anesthetics, sympathetic antagonists and agonists, calcium channel blockers, β-blockers, and angiotensin-converting enzyme inhibitors. This chapter examines agents that may be useful to the anesthesiologist for intraoperative control of arterial blood pressure.

Patients with an increasing "vascular age" routinely present for anesthesia and surgery. As patients chronologically age, so too does their vasculature. When a pulse wave is generated by ventricular contraction, it is propagated through the arterial system. At branch points of the aorta, the wave is reflected back toward the heart. In patients

of young vascular age, the reflected wave tends to augment diastole, improving diastolic pressure. In patients with "older" vasculature, the wave arrives sooner, being conducted back by the noncompliant vasculature during late systole, which causes an increase in cardiac workload and a decrease in diastolic pressure (Figure 15–1). Thus, older patients develop increased systolic pressure and decreased diastolic pressure.

Widened pulse pressures (the difference between systolic and diastolic pressures) have been associated with both increased incidence of postoperative renal dysfunction and increased risk of cerebral events in patients undergoing coronary bypass

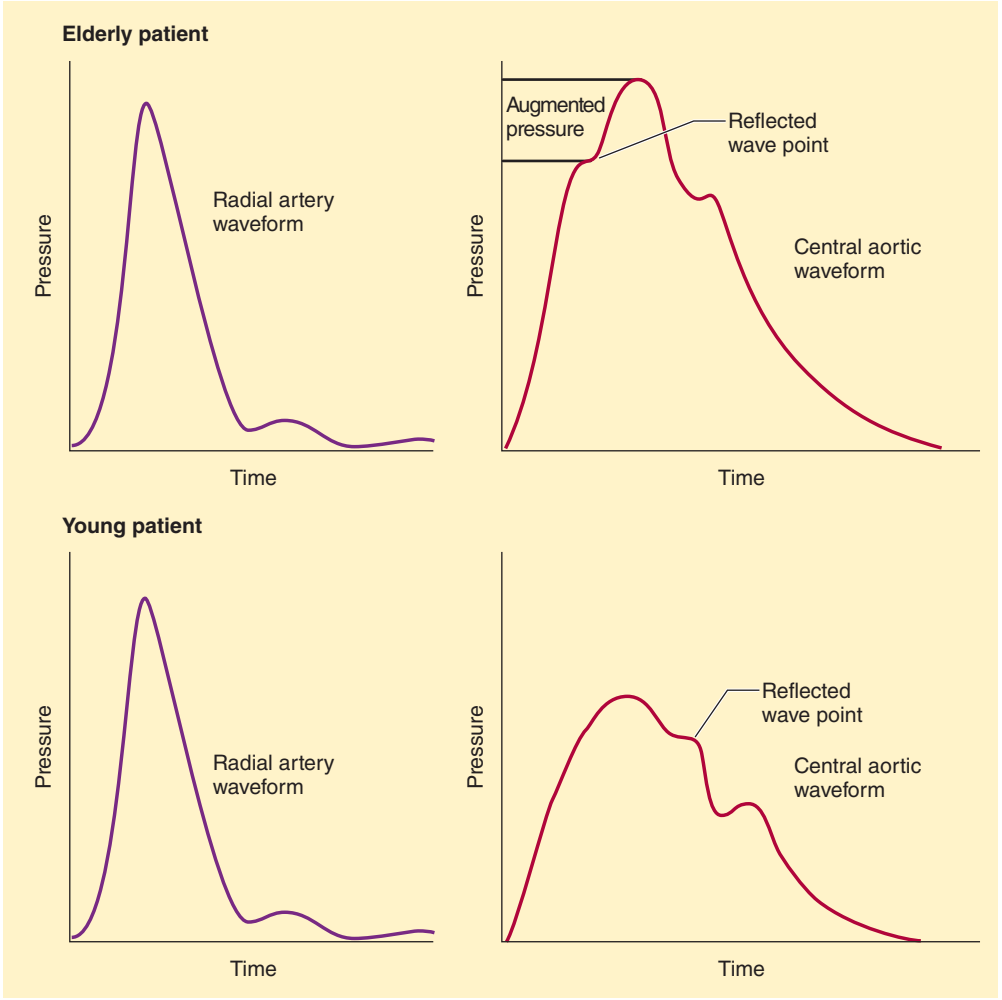

FIGURE 15–1 Illustration of the influence of increased vascular stiffness on peripheral (radial) and central (aortic) pressures. Note the similarity of peripheral radial pressures in individuals with normal (lower left panel) and increased (upper left panel) vascular stiffness. In young individuals with normal vascular stiffness, central aortic pressures are lower than radial pressures (lower panels). In contrast, in older individuals with increased vascular stiffness, central aortic pressures are increased and can approach or equal peripheral pressures as a result of wave reflection and central wave augmentation during systole (top panels). (Reproduced, with permission, from Barodka V, Joshi B, Berkowitz D, Hogue CW Jr, Nyhan D: Implications of vascular aging. Anesth Analg 2011;112:1048.)

surgery. Consequently, control of blood pressure is essential to mitigate postoperative morbidity, especially as patients of advanced vascular age present for surgery.

β-Blocker therapy should be maintained perioperatively in patients who are being treated with β-blockers as a part of their routine medical regimen. Furthermore, according to the American College of Cardiology, β-blockers are also of potential benefit to patients with more than one cardiac risk factor, especially those who are undergoing vascular surgery. However, the routine administration of high-dose β-blocker therapy may, in the absence of dose titration, be harmful in patients not taking β-blockers. The American College of Cardiology/American Heart Association guidelines for β-blocker use perioperatively should be closely followed. Adherence to such guidelines is used by third parties as a "quality" performance indicator for anesthesia delivery. Thus, anesthesia providers should periodically review recommendations regarding β-blocker therapy, as guidelines evolve as new evidence becomes available and older evidence is refuted. β-Blockers (esmolol, metoprolol, and others) were previously discussed for the treatment of transient perioperative hypertension and are routinely used by anesthesia providers. This chapter discusses antihypertensive agents other than β-blockers that are used perioperatively.

Along with increased vascular age, diastolic dysfunction is often underestimated in patients, as it can present in individuals with preserved systolic function. Acute diastolic heart failure can develop in the perioperative period secondary to hypertensive crisis. Diastolic dysfunction occurs due to the inability of the heart to relax effectively. Failure to actively sequester calcium ion into the sarcoplasmic reticulum (an energy-dependent process) impedes relaxation. Acute hypertension can produce diastolic dysfunction perioperatively, leading to elevated left ventricular end-diastolic pressures, myocardial ischemia, and pulmonary edema. Consequently, as increasing numbers of patients have diastolic dysfunction, tight control of blood pressure perioperatively is essential for safe anesthetic practice.

Blood pressure is essentially the product of cardiac output and systemic vascular resistance. Agents that lower blood pressure either reduce the force of myocardial contraction and/or produce vasodilatation of the arterial and venous capacitance vessels. Agents used to lower blood pressure include nitrovasodilators, calcium antagonists, dopamine agonists, anesthetic agents, and angiotensin-converting enzyme inhibitors. β-Blockers have been previously discussed.

Nitrovasodilators

SODIUM NITROPRUSSIDE

Mechanism of Action

Sodium nitroprusside and other nitrovasodilators relax both arteriolar and venous smooth muscle. Its primary mechanism of action is shared with other nitrates (eg, hydralazine and nitroglycerin). As these drugs are metabolized, they release **nitric oxide**, which activates guanylyl cyclase. This enzyme is responsible for the synthesis of cyclic guanosine 3',5'-monophosphate (cGMP), which controls the phosphorylation of several proteins, including some involved in the control of free intracellular calcium and smooth muscle contraction.

Nitric oxide, a naturally occurring potent vasodilator released by endothelial cells (endothelium-derived relaxing factor), plays an important role in regulating vascular tone throughout the body. Its ultrashort half-life (<5 s) provides sensitive endogenous control of regional blood flow. 1 Inhaled nitric oxide is a selective pulmonary vasodilator that is beneficial and routinely used in the treatment of reversible pulmonary hypertension.

Clinical Uses

Sodium nitroprusside is a potent and reliable antihypertensive. It is usually diluted to a concentration of 100 mcg/mL and administered as a continuous intravenous infusion (0.5–10 mcg/kg/min). Its extremely rapid onset of action (1–2 min) and fleeting duration of action allow precise titration of arterial blood pressure. A bolus of 1–2 mcg/kg minimizes blood pressure elevation during laryngoscopy but can cause transient hypotension in some patients. The

potency of this drug requires frequent blood pressure measurements—or, preferably, intraarterial monitoring—and the use of mechanical infusion pumps. Solutions of sodium nitroprusside must be protected from light because of photodegradation.

Metabolism

After parenteral injection, sodium nitroprusside enters red blood cells, where it receives an electron from the iron (Fe^{2+}) of oxyhemoglobin. This nonenzymatic electron transfer results in an unstable nitroprusside radical and methemoglobin (Hgb Fe^{3+}). The former moiety spontaneously decomposes into five cyanide ions and the active nitroso (N ═ O) group.

The cyanide ions can be involved in one of three possible reactions: binding to methemoglobin to form **cyanmethemoglobin**; undergoing a reaction in the liver and kidney catalyzed by the enzyme rhodanase (thiosulfate + cyanide → thiocyanate); or binding to tissue cytochrome oxidase, which interferes with normal oxygen utilization (Figure 15–2).

2 The last of these reactions is responsible for the development of **acute cyanide toxicity**, characterized by metabolic acidosis, cardiac arrhythmias, and increased venous oxygen content (as a result of the inability to utilize oxygen). Another early sign of cyanide toxicity is the acute resistance to the hypotensive effects of increasing doses of sodium nitroprusside (tachyphylaxis). It should be noted that tachyphylaxis implies acute tolerance to the drug following multiple rapid injections, as opposed to tolerance, which is caused by more chronic exposure. Cyanide toxicity is more likely if the cumulative dose of sodium nitroprusside is greater than 500 mcg/kg administered at an infusion rate faster than 2 mcg/kg/min. Patients with cyanide toxicity should be mechanically ventilated with 100% oxygen to maximize oxygen availability. The pharmacological treatment of cyanide toxicity depends on increasing the kinetics of the two reactions by administering sodium thiosulfate (150 mg/kg over 15 min) or 3% sodium nitrate (5 mg/kg over 5 min), which oxidizes hemoglobin to methemoglobin. Hydroxocobalamin combines with cyanide to form cyanocobalamin (vitamin B_{12}).

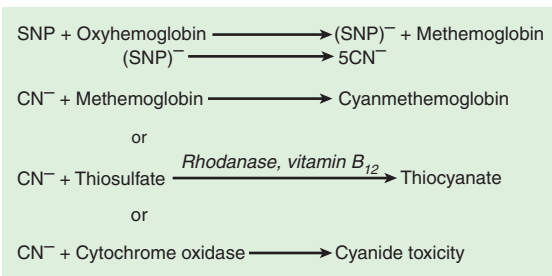

FIGURE 15–2 The metabolism of sodium nitroprusside.

Thiocyanate is slowly cleared by the kidney. Accumulation of large amounts of thiocyanate (eg, in patients with renal failure) may result in a milder toxic reaction that includes thyroid dysfunction, muscle weakness, nausea, hypoxia, and an acute toxic psychosis. The risk of cyanide toxicity is not increased by renal failure, however. Methemoglobinemia from excessive doses of sodium nitroprusside or sodium nitrate can be treated with methylene blue (1–2 mg/kg of a 1% solution over 5 min), which reduces methemoglobin to hemoglobin.

Effects on Organ Systems

The combined dilation of venous and arteriolar vascular beds by sodium nitroprusside results in reductions of preload and afterload. Arterial blood pressure falls due to the decrease in peripheral vascular resistance. Although cardiac output is usually unchanged in normal patients, the reduction in afterload may increase cardiac output in patients with congestive heart failure, mitral regurgitation, or aortic regurgitation. In opposition to any favorable changes in myocardial oxygen requirements are reflex-mediated responses to the fall in arterial blood pressure. These include tachycardia and increased myocardial contractility. In addition, dilation of coronary arterioles by sodium nitroprusside may result in an **intracoronary** steal of blood flow away from ischemic areas that are already maximally dilated.

Sodium nitroprusside dilates cerebral vessels and abolishes cerebral autoregulation. Cerebral blood flow is maintained or increases unless arterial blood pressure is markedly reduced. The resulting increase in cerebral blood volume tends to increase intracranial pressure, particularly in patients with

reduced intracranial compliance (eg, brain tumors). This intracranial hypertension can be minimized by slow administration of sodium nitroprusside and institution of hypocapnia.

The pulmonary vasculature also dilates in response to sodium nitroprusside infusion. Reductions in pulmonary artery pressure may decrease the perfusion of some normally ventilated alveoli, increasing physiological dead space. By dilating pulmonary vessels, sodium nitroprusside may prevent the normal vasoconstrictive response of the pulmonary vasculature to hypoxia (hypoxic pulmonary vasoconstriction). Both of these effects tend to mismatch pulmonary ventilation to perfusion and decrease arterial oxygenation.

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In response to decreased arterial blood pressure, renin and catecholamines are released during administration of nitroprusside. Renal function is fairly well maintained during sodium nitroprusside infusion, despite moderate drops in arterial blood pressure and renal perfusion.

Sodium nitroprusside does not directly interact with neuromuscular blocking agents. Nonetheless, a decrease in muscle blood flow caused by arterial hypotension could indirectly delay the onset and prolong the duration of neuromuscular blockade.

NITROGLYCERIN

Mechanism of Action

Nitroglycerin relaxes vascular smooth muscle, with venous dilation predominating over arterial dilation. Its mechanism of action is presumably similar to that of sodium nitroprusside: metabolism to nitric oxide, which activates guanylyl cyclase, leading to increased cGMP, decreased intracellular calcium, and vascular smooth muscle relaxation.

Clinical Uses

Nitroglycerin relieves myocardial ischemia, hypertension, and ventricular failure. Like sodium nitroprusside, nitroglycerin is commonly diluted to a concentration of 100 mcg/mL and administered as a continuous intravenous infusion (0.5–10 mcg/kg/min). Glass containers and special intravenous tubing are recommended because of the adsorption of nitroglycerin to polyvinylchloride. Nitroglycerin can also be administered by a sublingual (peak effect in 4 min) or transdermal (sustained release for 24 h) route. Some patients seem to require higher than expected doses of nitroglycerin to achieve a given drop in blood pressure, particularly after chronic administration (tolerance). Tolerance may be due to depletion of reactants necessary for nitric oxide formation, compensatory secretion of vasoconstrictive substances, or volume expansion. Dosing regimens that provide for intermittent periods of low or no drug exposure may minimize the development of tolerance.

Metabolism

Nitroglycerin undergoes rapid reductive hydrolysis in the liver and blood by glutathione-organic nitrate reductase. One metabolic product is nitrite, which can convert hemoglobin to methemoglobin. Significant methemoglobinemia is rare and can be treated with intravenous methylene blue (1–2 mg/kg over 5 min).

Nitroglycerin reduces myocardial oxygen demand and increases myocardial oxygen supply by several mechanisms:

- The pooling of blood in the large-capacitance vessels reduces venous return and preload. The accompanying decrease in ventricular end-diastolic pressure reduces myocardial oxygen demand and increases endocardial perfusion.
- Any afterload reduction from arteriolar dilation will decrease both end-systolic pressure and oxygen demand. Of course, a fall in diastolic pressure may lower coronary perfusion pressure and actually decrease myocardial oxygen supply.
- Nitroglycerin redistributes coronary blood flow to ischemic areas of the subendocardium.
- Coronary artery spasm may be relieved.

The beneficial effect of nitroglycerin in patients with coronary artery disease contrasts with the coronary steal phenomenon seen with sodium nitroprusside. Preload reduction makes nitroglycerin an excellent drug for the relief of cardiogenic pulmonary edema. Heart rate is unchanged or minimally increased. Rebound hypertension is

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less likely after discontinuation of nitroglycerin than following discontinuation of sodium nitroprusside. The prophylactic administration of low-dose nitroglycerin (0.5–2.0 mcg/kg/min) during anesthesia of patients at high risk for perioperative myocardial ischemia remains controversial.

The effects of nitroglycerin on cerebral blood flow and intracranial pressure are similar to those of sodium nitroprusside. Headache from dilation of cerebral vessels is a common side effect of nitroglycerin.

In addition to the dilating effects on the pulmonary vasculature (previously described for sodium nitroprusside), nitroglycerin relaxes bronchial smooth muscle.

Nitroglycerin (50–100 mcg boluses) has been demonstrated to be an effective (but transient) uterine relaxant that can be beneficial during certain obstetrical procedures if the placenta is still present in the uterus (eg, retained placenta, uterine inversion, uterine tetany, breech extraction, and external version of the second twin). Nitroglycerin therapy has been shown to diminish platelet aggregation, an effect enhanced by administration of *N*-acetylcysteine.

HYDRALAZINE

5 Hydralazine relaxes arteriolar smooth muscle, causing dilation of precapillary resistance vessels via increased cGMP.

Intraoperative hypertension is usually controlled with an intravenous dose of 5–20 mg of hydralazine. The onset of action is within 15 min, and the antihypertensive effect usually lasts 2–4 hr. Hydralazine can be used to control pregnancy-induced hypertension.

Hydralazine undergoes acetylation and hydroxylation in the liver.

Effects on Organ Systems

6 The lowering of peripheral vascular resistance causes a drop in arterial blood pressure. The body reacts to a hydralazine-induced fall in blood pressure by increasing heart rate, myocardial contractility, and cardiac output. These compensatory responses can be detrimental to patients with coronary artery disease and are minimized by the concurrent administration of a β-adrenergic antagonist. Conversely, the decline in afterload often proves beneficial to patients in congestive heart failure.

Hydralazine is a potent cerebral vasodilator and inhibitor of cerebral blood flow autoregulation. Unless blood pressure is markedly reduced, cerebral blood flow and intracranial pressure will rise.

Renal blood flow is usually maintained or increased by hydralazine.

Non-Nitrovasodilator Hypotensive Agents

FENOLDOPAM

Mechanism of Action

Fenoldopam mesylate causes rapid vasodilation by selectively activating D_1-dopamine receptors. It has also demonstrated moderate affinity for α_2-adrenoceptors. The R-isomer is responsible for the racemic mixture's biological activity due to its much greater receptor affinity, compared with the S-isomer.

Clinical Uses

7 Fenoldopam mesylate (infusion rates studied in clinical trials range from 0.01–1.6 mcg/kg/min) reduces systolic and diastolic blood pressure in patients with malignant hypertension to an extent comparable to nitroprusside. Side effects include headache, flushing, nausea, tachycardia, hypokalemia, and hypotension. The onset of the hypotensive effect occurs within 15 min, and discontinuation of an infusion quickly reverses this effect without rebound hypertension. Some degree of tolerance may develop 48 hr after the infusion. Studies are conflicted as to fenolodopam's ability to "protect" and "maintain" renal function in perioperative patients with hypertension at risk of perioperative kidney injury.

Metabolism

Fenoldopam undergoes conjugation without participation of the cytochrome P-450 enzymes, and its

metabolites are inactive. Clearance of fenoldopam remains unaltered despite the presence of renal or hepatic failure, and no dosage adjustments are necessary for these patients.

Effects on Organ Systems

Fenoldopam decreases systolic and diastolic blood pressure. Heart rate typically increases. Low initial doses (0.03–0.1 mcg/kg/min) titrated slowly have been associated with less reflex tachycardia than higher doses (>0.3 mcg/kg/min). Tachycardia decreases over time but remains substantial at higher doses.

Fenoldopam can lead to rises in intraocular pressure and should be administered with caution or avoided in patients with a history of glaucoma or intraocular hypertension.

As would be expected from a D_1-dopamine receptor agonist, fenoldopam markedly increases renal blood flow. Despite a drop in arterial blood pressure, the glomerular filtration rate is well maintained. Fenoldopam increases urinary flow rate, urinary sodium extraction, and creatinine clearance compared with sodium nitroprusside.

CALCIUM ANTAGONISTS

8 Dihydropyridine calcium channel blockers (nicardipine, clevidipine) are arterial selective vasodilators routinely used for perioperative blood pressure control in patients undergoing cardiothoracic surgery. Clevidipine is a relatively new drug with a short half- life, which facilitates its rapid titration. Unlike verapamil and diltiazem, the dihydropyridine calcium channel blockers have minimal effects on cardiac conduction and ventricular contractility. Calcium channel blockers bind to L-type calcium channel and impair calcium entry into the vascular smooth muscle. These L-type receptors are more prevalent on arterial vessels than venous capacitance vessels. Consequently, cardiac filling and preload is less affected by these agents than nitrates, which might dilate both arterial and venous systems. With preload maintained, cardiac output often increases when vascular tone is reduced by use of dihydropyridine calcium blockers. Nicardipine infusion is titrated to effect (5–15 mg/h).

Other intravenous agents that can produce hypotension perioperatively include the intravenous angiotensin-converting enzyme inhibitor enalaprilat (0.625–1.25 mg). The role of enalaprilat as a nondirect-acting agent in the acute treatment of a hypertensive crisis is limited.

CASE DISCUSSION

Controlled Hypotension

A 59-year-old man is scheduled for total hip arthroplasty under general anesthesia. The surgeon requests a controlled hypotensive technique.

What is controlled hypotension, and what are its advantages?

Controlled hypotension is the elective lowering of arterial blood pressure. The primary advantages of this technique are minimization of surgical blood loss and better surgical visualization.

How is controlled hypotension achieved?

The primary methods of electively lowering blood pressure are proper positioning, positive-pressure ventilation, and the administration of hypotensive drugs. Positioning involves elevation of the surgical site so that the blood pressure at the wound is selectively reduced. The increase in intrathoracic pressure that accompanies positive-pressure ventilation lowers venous return, cardiac output, and mean arterial pressure. Numerous pharmacological agents effectively lower blood pressure: volatile anesthetics, spinal and epidural anesthesia, sympathetic antagonists, calcium channel blockers, and the peripheral vasodilators discussed in this chapter.

What surgical procedures might benefit most from a controlled hypotensive technique?

Controlled hypotension has been successfully used during cerebral aneurysm repair, brain tumor resection, total hip arthroplasty, radical neck

dissection, radical cystectomy, and other operations associated with significant blood loss. Controlled hypotension may allow safer surgery of patients whose religious beliefs prohibit blood transfusions (eg, Jehovah's Witnesses). Decreasing extravasation of blood may improve the result of some plastic surgery procedures.

What are some relative contraindications to controlled hypotension?

Some patients have predisposing illnesses that decrease the margin of safety for adequate organ perfusion: severe anemia, hypovolemia, atherosclerotic cardiovascular disease, renal or hepatic insufficiency, cerebrovascular disease, or uncontrolled glaucoma.

What are the possible complications of controlled hypotension?

As the above list of contraindications suggests, the risks of low arterial blood pressure include cerebral thrombosis, hemiplegia (due to decreased spinal cord perfusion), acute tubular necrosis, massive hepatic necrosis, myocardial infarction, cardiac arrest, and blindness (from retinal artery thrombosis or ischemic optic neuropathy). These complications are more likely in patients with coexisting anemia. Consequently, the use of induced or controlled hypotension continues to decline.

What is a safe level of hypotension?

This depends on the patient. Healthy young individuals tolerate mean arterial pressures as low as 50–60 mm Hg without complications. On the other hand, chronically hypertensive patients have altered autoregulation of cerebral blood flow and may tolerate a mean arterial pressure of no more than 20% to 30% lower than baseline. Patients with a history of transient ischemic attacks may not tolerate any decline in cerebral perfusion.

What special monitoring is indicated during controlled hypotension?

Intraarterial blood pressure monitoring and electrocardiography with ST-segment analysis are strongly recommended. Central venous monitoring and measurement of urinary output by an indwelling catheter are indicated if extensive surgery is anticipated.

GUIDELINES

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