Deliberate Hypotension - Miller

INTRODUCTION

The concept of intentionally decreasing arterial blood pressure to hypotensive levels during surgery was first proposed by Cushing 1 in 1917 for intracranial surgery and was introduced into clinical practice by Gardner 2 in 1946. Deliberate hypotension gained popularity in Great Britain after Griffiths and Gillies 3 advocated the “hypotensive spinal technique” in 1948. In 1950 Enderby 4 introduced ganglionic blockade using pentamethonium to decrease arterial blood pressure. Subsequent techniques included decreasing cardiac output with volatile anesthetics such as halothane 5 and administering vasodilators such as sodium nitroprusside; b-adrenergic receptor blocking drugs, which were initially used with trimethaphan 6 ; or a combination of a- and b-adrenergic receptor blocking drugs. 7 More recently, nitroglycerin, 8 purine derivatives, 9 and isoflurane 10 have also been used.

As early as 1950, Enderby 4 emphasized that bleeding could be controlled not only by decreasing mean arterial blood pressure (MAP) but also by properly positioning the patient **(Ch. 52**). Since that time, the decision to induce hypotension has often been controversial, primarily because of an inability to define the lowest safe MAP with confidence. 11 The terms *controlled hypotension, induced hypotension, deliberate hypotension,* and *hypotensive anesthesia* have all been used. This chapter uses *deliberate hypotension.*

Most studies define deliberate hypotension as a reduction in systolic blood pressure to 80 to 90 mm Hg. According to another definition, deliberate hypotension is a decrease in MAP to 50 to 65 mm Hg in normotensive patients.

The main purpose of deliberately inducing hypotension is to decrease blood loss, thereby improving operating conditions or decreasing the need for blood transfusions. Therefore, benefit to the patient should be the single criterion determining the need for deliberate hypotension. The potential for transmitting disease by blood transfusion has made deliberate hypotension an even more important consideration today than ever before **(Ch. 46**). The possible benefit to the surgeon of improved visibility of the operative field during delicate procedures (e.g., plastic surgery) is a strong incentive, but it is more difficult to quantitate.

This chapter provides a general overview of deliberate hypotension, leaving the discussion of most specific clinical applications to specialty chapters (e.g., neuroanesthesia in **Ch. 52**).

THE ABILITY OF DELIBERATE HYPOTENSION TO REDUCE BLOOD LOSS

Enderby‘s 4 first report demonstrated that of 35 patients, 18 had excellent and 8 had moderate reduction in blood loss during deliberate hypotension, and 9 patients had no reduction. This inconsistency was attributed to differing vascular responsiveness to the hypotensive drugs and, in some cases, inadequate positioning. Enderby emphasized that the absolute MAP may not be as important to bleeding as positioning of the surgical field. He maintained that bleeding at the surgical site would be minimized if the wound were kept uppermost (rather than dependent): arterial vessels would have less pressure, veins would drain more easily, and bleeding at the surgical site would be less.

Deliberate hypotension certainly can decrease blood loss in many surgical procedures. In 1953 Boyan 12 used hexamethonium (C6) to lower systolic blood pressure to 65 to 70 mm Hg in 112 patients undergoing radical cancer surgery. Although the impression of the surgical team was that blood loss was less, no data were provided. Several subsequent reports also claiming a decrease in blood loss noted, however, that some patients continued to bleed during deliberate hypotension and that other patients not undergoing deliberate hypotension had minimal blood loss. Whether these differences can be ascribed to positioning, ventilation, or other factors is unknown.

Assigning importance to the possible influences on blood loss is difficult because few clinicians have actually measured this variable. Also, such studies have had major flaws in experimental design, execution, or data analysis. 13 Usually MAP of 50 to 65 mm Hg is considered a safe range for deliberate hypotension.

Eckenhoff and Rich 14 supplied objective data that deliberate hypotension can indeed decrease blood loss. Blood loss was compared for patients undergoing rhinoplasty, portacaval shunt, or craniotomy for aneurysm or suspected tumor with (n = 115) or without (n = 116) deliberate hypotension. For each of these procedures, blood loss decreased by 50 percent or more with hypotension. Most of the other

studies evaluating different hypotensive agents for a variety of surgical procedures had no control group, and assessment of blood loss was visual. 15, 16, 17, 18

The best documentation that decreasing arterial blood pressure decreases blood loss applies to patients undergoing major orthopedic procedures. Often blood loss is significant during these procedures, and the effect of deliberate hypotension can be documented more readily. For example, a well-controlled study of 55 patients undergoing total hip arthroplasty found that the 38 patients given pentolinium tartrate, halothane, and *d* -tubocurarine for deliberate hypotension had less blood loss. 19 In another study, 25 patients given sodium nitroprusside to lower arterial blood pressure during total hip arthroplasty had significantly less blood loss than the 25 patients not undergoing deliberate hypotension. 20 Operating room time was also slightly lower for the hypotensive group.

Other studies have also had success reducing blood loss during total hip arthroplasty. Thirty patients undergoing this procedure had MAP reduced to 50 mm Hg by administration of sodium nitroprusside (*n* = 12) or high inspired concentrations of halothane (*n* = 9). 21 Nine control patients were normotensive. Blood loss was 1,200 mL for the normotensive controls but only approximately 400 mL for both hypotensive groups. No complications were seen. Another study had similar results—almost a 50 percent reduction in blood loss—when MAP was decreased to 55 mm Hg by sodium nitroprusside. 22 An interesting aspect of the study was the use of hemodilution to determine whether total blood loss could be reduced by this method. Even with hemodilution, patients given sodium nitroprusside had the lowest blood loss. Table 41–1 shows blood losses for a variety of hypotensive techniques during total hip arthroplasty. 19, 20, 21, 22, 23, 24 Another study on primary total hip arthroplasty (under epidural anesthesia) showed that the degree of hypotension significantly influenced blood loss. 25 Intraoperative blood loss was 179 ± 73 ml when MAP was kept at 50 ± 5 mm Hg and 263 ± 98 mL when MAP was kept at 60 ± 5 mm Hg.

TABLE 41–1. Reported Blood Losses for Total Hip Arthroplasty

REPORTED	INTRAOPERATIVE	INVESTIGATORS	HYPOTENSIVE TECHNIQUE	BLOOD
PRESSURE (mm Hg)				**BLOOD LOSS (mL)**
Amaranath et al (1975)23	Halothane, N2O	Normotensive	1,514 ± 273	
Morphine, N2O, trimethaphan	<30% control	884 ± 89		
Morphine, N2O, SNP	<30% control	820 ± 96		
Thompson et al (1978)21	Halothane, N2O	20% control	1,183	
Halothane, N2O	50 MAP	407 ± 102		
Halothane, N2O, SNP	50 MAP	326 ± 42		
Eerola et al (1979)19	Halothane, N2O	>80 systolic	2,336 ± 212	
Halothane, N2O, pentolinium	<80 systolic	730 ± 80		
Vazeery and Lunde (1979)20	N2O, fentanyl	94 MAP	1,038 (500–1,750)	
N2O, fentanyl, SNP	64 MAP	212 (160–350)		
Barbier-Böhm et al (1980)22	Halothane, N2O	Normotensive	900 ± 130	
Halothane, N2O, SNP	55 MAP	320 ± 35		
Qvist et al (1982)24	N2O, fentanyl, droperidol	99 MAP	2,093 ± 1,332	
Halothane, N2O	73 MAP	718 ± 482		
Sharrock et al (1993)25	Epidural anesthesia	50 MAP	179 ± 73	
Epidural anesthesia	60 MAP	263 ± 98		

Abbreviations: **BP, blood pressure; SNP, sodium nitroprusside; MAP, mean arterial blood pressure; N2O, nitrous oxide**

TABLE 41–1. Reported Blood Losses for Total Hip Arthroplasty

Deliberate hypotension has also been used successfully for a variety of other surgical procedures, including head and neck surgery, 26 procedures on the cranium 18 and middle ear, 17 and radical cancer operations. 27 A retrospective study of 37 patients undergoing radical cystectomy for bladder cancer found that the average blood loss was 50 percent less with deliberate hypotension (versus standard normotensive anesthesia). 28 Elsewhere, the use of sodium nitroprusside–induced hypotension reduced blood loss by 50 percent in patients undergoing lienorenal shunts for portal hypertension. 29 When esmolol was compared with sodium nitroprusside for controlled hypotension during orthognathic surgery, the surgeons generally rated bleeding as mild to moderate and the field as

"drier" with esmolol. 26 Furthermore, total measured blood loss with esmolol was 49 percent of that with sodium nitroprusside (436 versus 895 mL, respectively).

Although deliberate hypotension usually decreases surgical blood loss, some exceptions have occurred. For unknown reasons, not all patients respond as predicted. For other patients, the correlation between decrease in arterial blood pressure and blood loss is not linear. 30 Some studies report that deliberate hypotension did not reduce blood loss significantly and that the incidence of postoperative wound hematoma even increased. 31 It is difficult to evaluate these last two studies because of the scant data presented and the imprecision with which blood losses were measured.

Shortly after the introduction of deliberate hypotension, drug therapy focused on keeping arterial blood pressure at the surgical site at 50 to 65 mm Hg, a level believed to decrease blood loss significantly. Because intraoperative measurement of cardiac output was not done routinely, the specific mechanism by which reduction of arterial blood pressure decreased blood loss could not be defined precisely. Didier et al 32 suggested that depression of cardiac output correlated better with a dry field than did MAP. To determine whether a decrease in arterial blood pressure or cardiac output was the primary cause of decreasing blood loss, Sivarajan et al 33 studied 20 healthy subjects undergoing bilateral sagittal osteotomy of the mandible. Cardiac output decreased 37 percent with trimethaphan but increased 27 percent with sodium nitroprusside. Blood loss was similar for both groups, even though cardiac output was two times greater with sodium nitroprusside (Table 41–2). Sivarajan et al concluded that blood pressure, not cardiac output, determined blood loss.

TABLE 41–2. Mean Arterial Blood Pressure Versus Cardiac Output as the Primary Determinant of Blood Loss

In summary, most patients will have less blood loss if MAP is decreased to 50 to 65 mm Hg. Patient positioning and attention to ventilation, both of which influence venous return, play important roles in minimizing blood loss. Clinical experience suggests that blood loss can be decreased with less severe degrees of hypotension and that attention to the surgical field may be a better monitor than the absolute value for MAP. Most clinical studies do not support the belief that deliberate hypotension decreases operating room time.

TABLE 41–2. Mean Arterial Blood Pressure Versus Cardiac Output as the Primary Determinant of Blood Loss

GROUP	HEART RATE (beats/min)	MAP (mm Hg)	CARDIAC OUTPUT (L/min)	TOTAL PERIPHERAL RESISTANCE (dyn/s/cm5)
Control	98 ± 13	76 ± 10	6.4 ± 1.4	835 ± 209
After 30 min of trimethaphan	89 ± 9b	53 ± 5b	4.1 6 0.6b	786 ± 114b
Control	108 ± 14	72 ± 6	6.5 ± 0.7	819 ± 66
After 30 min of SNP	125 ± 18	56 ± 3a	8.3 ± 1.4b	529 ± 103b

Abbreviations: **MAP, mean arterial blood pressure; SNP, sodium nitroprusside**
aTotal blood loss was similar for both trimethaphan (170 ± 102 mL) and SNP (183 ± 92 mL).
bSignificantly different at *P* = .05
(Adapted from Sivarajan et al33)

TECHNIQUES TO INDUCE DELIBERATE HYPOTENSION

Physiologic Techniques

Body positioning, the hemodynamic effects of mechanical ventilation, and changes in heart rate and circulatory volume can be used with drugs to lower blood pressure to the desired level. The appropriate use of physiologic maneuvers helps decrease the dose of potentially toxic drugs needed to produce hypotension.

Pharmacologic Techniques

The ideal agent for inducing hypotension would have ease of administration, a predictable and dose-dependent effect, rapid onset and recovery from effects, quick elimination without the production of toxic metabolites, and minimal effects on blood flow to vital organs. In addition, the ideal agent would not increase brain size or affect cerebral autoregulation during neurosurgery. Although such an agent does not yet exist, many anesthetic and vasoactive drugs have been used successfully to produce deliberate hypotension, including (1) spinal and epidural anesthesia, (2) volatile anesthetics (halothane, enflurane, isoflurane, sevoflurane, desflurane), (3) direct-acting vasodilating drugs (sodium nitroprusside,

nitroglycerin, hydralazine, purine derivatives), (4) autonomic ganglion–blocking drugs (trimethaphan), (5) a-adrenergic receptor blocking drugs (phentolamine, urapidil), (6) b-adrenergic receptor blocking drugs (propranolol, esmolol), (7) combined a- and b-adrenergic receptor blocking drugs (labetalol), (8) calcium channel entry blocking drugs (nicardipine), and (9) prostaglandin E1 (PGE1).

Spinal and Epidural Anesthesia

In 1948 Griffiths and Gillies **3** used subarachnoid block to produce intentional hypotension. In 1952 Greene **34** advocated the use of general anesthesia in which hypotension was induced using a high spinal technique to relieve the distressing symptoms of hypotension. Epidural anesthesia **(Ch. 42)** was introduced in the early 1950s and is now considered an effective method of inducing hypotension. **35**, **36** Pharmacologic sympathectomy with local anesthetics is a very effective way of inducing hypotension. Epidural or spinal anesthesia produces arteriolar and venous dilation and hypotension. These effects are enhanced by a pooling of blood in the venous system that decreases venous return and cardiac output. If the block is extended to the midthoracic region, sympathetic innervation of the heart (T1–T4) is also affected, thereby preventing compensatory tachycardia. **37** The unpredictable degree of hypotension and the necessity for large infusions of fluids are the principal drawbacks of this technique. It was recently demonstrated, however, that if hemodynamic stability is maintained by intravenous infusion of low-dose epinephrine (1–5 mcg/min), this technique can be used safely. **25**, **35** An epidural anesthetic technique is most commonly used to minimize blood loss during lower abdominal or pelvic surgery.

Volatile Anesthetic Drugs

Clearly one can decrease MAP by increasing the inspired concentration of inhaled anesthetic.

Cardiovascular Effects

Hypotension after halothane results primarily from myo-cardial depression that produces a dose-dependent decrease in arterial blood pressure, cardiac output, and stroke volume, plus a dose-dependent increase in right heart filling pressure **(Fig. 41–1)**. Although halothane also dilates vessels in the skin, brain, and viscera, systemic vascular resistance (SVR) does not decrease significantly because skeletal muscle tone increases; in addition, renal vascular resistance increases. **38**
FIGURE 41–1 Effect of increasing concentrations of halothane anesthesia on mean arterial blood pressure (MAP), stroke volume (SV), and systemic vascular resistance (SVR) during the awake state, spontaneous ventilation (SpV), and controlled ventilation (intermittent positive-pressure ventilation, IPPV). Elevation in right arterial pressure (RAP) is evidence of myocardial depression. (From Prys-Roberts et al**38**)

In studies on patients and animals, isoflurane decreased blood pressure by decreasing SVR, whereas cardiac output was maintained constantly at clinically relevant concentrations of the anesthetic. **10**, **39** In another study of 10 patients given isoflurane to reduce MAP to 40 mm Hg, cardiac index showed a small but significant decrease. **40** The two studies on patients **10**, **40** may have different results because the latter study used the awake value as control.

The intravascular volume status of the patient before induction of hypotension affects the degree of reduction in cardiac output during isoflurane anesthesia. In healthy young people, 2 to 3 percent isoflurane decreases MAP by decreasing SVR. In older or chronically hypertensive patients, similar concentrations of isoflurane may also decrease cardiac output. For these individuals, combining a moderate concentration of isoflurane with agents that tend to maintain cardiac output would be more appropriate than using high concentrations of isoflurane alone.

Cerebrovascular Effects

Halothane decreases cerebrovascular resistance and increases cerebral blood flow (CBF) in a concentration-related manner, provided autoregulatory limits are not exceeded. As a result, intracranial pressure (ICP) may increase. Cerebral autoregulation is lost when the concentration of halothane increases. **41**

By increasing the normal production of cerebrospinal fluid, enflurane is also capable of increasing ICP. **42** In addition, enflurane has induced seizure activity in some patients, especially during hypocapnia.

The administration of low concentrations of isoflurane (£1 MAC) produces controllable decreases in MAP and a concentration-related depression of cerebral metabolism while preserving the physiologic

relationships between flow and pressure, and flow and metabolism. With higher concentrations of isoflurane, the direct vasodilatory effects predominate: CBF increases, and autoregulation is impaired. 39, 43 However, even low concentrations of isoflurane may increase ICP in patients who have reduced intracranial compliance. 44 In the presence of cerebral vasodilation, cerebral edema is more likely to occur if systemic blood pressure is allowed to increase. Therefore, the possibility of secondary neurologic injury exists. A recent study on dogs with cryogenic brain lesions showed that brain edema was greater when hypotension was induced with isoflurane than with labetalol. 45 Adenylate kinase, a marker of brain cell injury, was found in the cerebrospinal fluid of patients undergoing isoflurane-induced hypotension for corrective surgery of dentofacial deformities. 46 However, this study did not include a control group. In a subsequent investigation the same authors found that adenylate kinase occurred also in patients after isoflurane anesthesia under normotensive conditions for orthognathic surgery. 47 In conclusion, adverse effects on the brain were found, using a sensitive biochemical method and a battery of psychometric examinations. Arterial hypotension, however, was not shown to have a direct causal relationship to the adverse effects found.

Volatile anesthetics should not be used as the sole agent to induce hypotension in patients who have intracranial disease because the high concentrations that may be required can worsen brain edema. Such a technique may also increase ICP before opening of the dura and may affect autoregulation. The combination of increased ICP and decreased MAP can reduce cerebral perfusion pressure to less than 40 mm Hg, a circumstance that can produce brain ischemia. Recent studies in animals and patients showed that combining isoflurane with either an a-adrenergic receptor blocking drug or a combined a- and b-adrenergic receptor blocking drug attenuated the negative effects of using isoflurane as the sole hypotensive agent. 48, 49 In summary, isoflurane should only be used as an adjuvant drug (and in low concentrations) during induced hypotension. This method has the advantages of decreased cerebral metabolism and preserved pulmonary gas exchange. 50 The profile of hemodynamic changes induced by sevoflurane and desflurane is very similar to that of isoflurane. However, due to the pharmacokinetic properties of these volatile agents, including a low blood/gas solubility, these hemodynamic effects can be better controlled with them as compared with isoflurane. Therefore, sevoflurane and desflurane appear to be superior to isoflurane when used as an agent to facilitate deliberate hypotension. Surprisingly, these drugs have not been investigated yet with respect to their suitability in deliberate hypotension.

Information on the cerebral effects of the newer anesthetic agents is limited. Hypotensive anesthesia with desflurane reduces CBF by 36 percent and reduces CMRO2 by a similar amount, 51 and 4 MAC of sevoflurane has no adverse effects on brain energy metabolism. 52

Intravenous Drugs

Many intravenous drugs have been used to decrease arterial blood pressure acutely. Certainly, drugs that permit moment-to-moment control of blood pressure are the most popular. Most of these drugs are titrated to obtain the desired surgical field or predetermined MAP, or both. The differences in pharmacologic properties among agents suggest that combinations of these drugs may provide a better pharmacologic profile than could be provided by any agent used alone.

Sodium Nitroprusside

Sodium nitroprusside is a vasodilating drug most commonly used to induce hypotension during surgery. Its onset of action is rapid, of short duration, and readily controllable. Sodium nitroprusside acts primarily on arteriolar tone; only 65 to 70 percent of arterial sodium nitroprusside is recovered in venous plasma. 53

Studies on the cardiovascular effects of sodium nitroprusside have yielded contradictory results. Some studies report an increase in heart rate and cardiac output with no change in stroke volume. 54, 55 Yet others report either no change in cardiac output 57, 58, 59 or a decrease. 60, 61 However, sodium nitroprusside clearly has no adverse effect on myocardial contractility. 57, 58

The different results concerning cardiac output and stroke volume probably relate to differences in circulatory volume and cardiac filling pressures before hypotension. Patients with subarachnoid hemorrhage have low circulatory volume, 62 a condition that can decrease preload and cardiac output. 61 Lawson et al 63 found that stroke volume and cardiac output increased during sodium nitroprusside–induced hypotension in deliberately overhydrated patients undergoing orthopedic surgery. The importance of circulatory volume was demonstrated by experiments in dogs in which fluid balance was shown to be an important determinant of the cardiovascular response to sodium nitroprusside. 64

When sodium nitroprusside was given, cardiac output decreased during hypovolemia but not normovolemia.

Because the intact sodium nitroprusside contains five cyanide groups, toxicity is a concern [65] (Fig. 41–2). The breakdown of sodium nitroprusside in the blood produces free cyanide, the concentration of which depends on the quantity of sodium nitroprusside infused. [66] Cyanide diffuses rapidly into the tissue, where it binds with high affinity to cytochrome oxidase. Such binding causes interference with electron transport and produces tissue hypoxia. Some of the cyanide ions diffuse out of the erythrocytes and are metabolized in the liver and kidney to thiocyanate, which is excreted in the urine. Bisset et al [67] challenged the concept that cyanide is released *in vivo,* arguing that any cyanide found in the blood of patients given sodium nitroprusside is caused by photodegradation of the drug *in vitro,* either before infusion or during assay of the samples. These investigators also stated that "it may well be safe to infuse quantities larger than those currently recommended."
FIGURE 41–2 Schematic representation of the breakdown of sodium nitroprusside *in vivo.* The high affinity of cytochrome oxidase for cyanide leads to tissue hypoxia. (Modified from Tinker and Michenfelder[65])

Experiments examining the question of photodegradation concluded that cyanide measured in the blood of patients given sodium nitroprusside did not appear to be an artifact of assay methods. [68] Furthermore, degraded nitroprusside remains biologically active and may be more toxic than intact nitroprusside, as free cyanide is a product of degradation.

Shortly after the widespread use of sodium nitroprusside, reports of toxicity began to appear. [69], [70] In some of the initial reports, large concentrations of sodium nitroprusside had been infused. However, in some individual cases, younger patients appeared to show resistance to the effects of nitroprusside, and the mechanisms were sought. Studies designed to investigate the complex physiologic changes that occur whenever arterial blood pressure is decreased focused, for example, on resetting of baroreflex sensitivity in control of heart rate. [71] The sympathetic nervous system and the renin-angiotensin system are activated. Also, the release of vasopressin increases. [72] Although these increases in vasopressin were greater than the increases in plasma catecholamines or plasma-renin activity during sodium nitroprusside–induced hypotension, the significance of this result remains speculative and will not be resolved until a specific antagonist of the vascular properties of vasopressin is found.

The question of resistance or tachyphylaxis to sodium nitroprusside is complex, and each of the previous possibilities needs further discussion. In one study, normal patients had significant increases in plasma levels of norepinephrine and epinephrine during sodium nitroprusside–induced hypotension. [73] This response does not occur in patients with subarachnoid hemorrhage, possibly because the adrenergic system is already maximally activated before induction of hypotension. Such activation of the adrenergic system could also contribute to the low circulatory volume found in subarachnoid hemorrhage. [62] Consequently, the hemodynamic effects of sodium nitroprusside in patients with subarachnoid hemorrhage will differ from that in normal subjects because of differences in circulatory volume and activity of the sympathetic nervous system. This increase in the plasma catecholamine level may produce resistance to the effects of sodium nitroprusside.

One study on the effect of pretreatment with propranolol 1 day before cerebral aneurysm surgery found that plasma catecholamine levels were significantly lower during surgery (including the time of deliberate hypotension) with propranolol. [74] Similarly, the intraoperative intravenous administration of incremental doses of propranolol reduced heart rate and the amount of sodium nitroprusside necessary to maintain hypotension. [75]

The renin-angiotensin system is also activated when hypotension is induced with sodium nitroprusside. Infusion of sodium nitroprusside increased plasma-renin activity in rats 4-fold. [76] When the production of angiotensin II was inhibited by saralasin, arterial blood pressure decreased further. Subsequently, Khambatta et al [77] reported a 5-fold increase in plasma renin activity in patients made hypotensive with sodium nitroprusside. Because the renin-angiotensin system plays an important role in tachyphylaxis to sodium nitroprusside–induced hypotension, two approaches use this system to circumvent the problem.

The first approach is based on the fact that the renin response was attenuated (but not abolished) when patients were pretreated with propranolol for 1 day before surgery. [78] Furthermore, the dose of sodium nitroprusside necessary to produce hypotension was reduced, and rebound hypertension did not occur on discontinuation of the drug. The second approach tries to inhibit the renin-angiotensin system directly by pretreating patients with a single oral dose of captopril, a drug that prevents conversion of angiotensin I to angiotensin II. [79] The dose of sodium nitroprusside needed to produce the same degree of hypotension was one-fifth that needed for untreated patients. In addition, the desired level of

hypotension was easier to maintain, and rebound hypertension did not occur on discontinuation of sodium nitroprusside. Because of the decreased requirement for sodium nitroprusside, pretreatment with captopril resulted in significantly lower plasma levels of cyanide. Converting-enzyme inhibition can also be done by IV administration of enalaprilat (2.5 mg) 60 minutes before hypotension is started. 80

Investigators have sought other causes of resistance to the effects of sodium nitroprusside. Grayling et al 81 found that free cyanide can cause contraction of an aortic ring after the ring has been contracted by norepinephrine and then relaxed by sodium nitroprusside. If this phenomenon occurs in humans, then as the plasma level of cyanide increases, an increasing dose of sodium nitroprusside would be necessary to produce a comparable degree of relaxation. A potentially lethal cycle could thus begin.

Aging also plays an important role in the response to sodium nitroprusside. Early reports of resistance to sodium nitroprusside involved younger patients. Wood et al 82 studied 16 patients 18 to 76 years of age. The vasodepressor effect of sodium nitroprusside was enhanced in the elderly **(Fig. 41–3)**. Plasma norepinephrine and epinephrine concentrations were similar for both groups. This increased sensitivity to sodium nitroprusside may be owing in part to resistance of cardiac adrenergic receptors to catecholamine stimulation as a consequence of reduced affinity to b-adrenergic receptors.
FIGURE 41–3 Plotting the age of 16 patients against change in mean arterial pressure (BP^{-}) per mg/kg/min dose of sodium nitroprusside (SNP) shows that the elderly need less SNP than the young to produce the same degree of deliberate hypotension. (From Wood et al82)

Because the question of resistance to tachyphylaxis to sodium nitroprusside is so complex, guidelines for the administration of this agent should be followed to prevent toxicity. Simply titrating sodium nitroprusside against arterial blood pressure alone cannot be justified. Accurate knowledge of dose, rate of administration, and total dose given is prerequisite to the use of sodium nitroprusside. The recommended maximum dosages of 1.5 mg/kg for acute administration and 0.5 mg/kg/h (10 mcg/kg/min for 10 min) for chronic administration appear to be safe. 83

Data on the effects of sodium nitroprusside on CBF during controlled hypotension are inconsistent. Some studies reported no change in CBF from baseline. 84, 85, 86 Other studies reported that CBF decreased 87, 88, 89 or, along with ICP, increased (in animals and neurosurgical patients). 90, 91 The reasons for these conflicting results are not easy to determine; differences in species, anesthetic technique, and baseline conditions may play a role. Delayed measurement of CBF after the start of sodium nitroprusside may be the reason that early changes in flow are not observed.

One study showed the importance of the degree of hypotension induced by sodium nitroprusside on cerebral blood flow. 92 Initially, when sodium nitroprusside was given to decrease MAP moderately, CBF also increased. However, as larger doses of sodium nitroprusside were administered to decrease MAP further, CBF remained near its baseline value until MAP reached 65 mm Hg. When MAP fell below this level, the pressure-flow relationship was linear.

In rats the effects of profound hypotension (MAP of 30 mm Hg for 30 minutes), using trimethaphan or sodium nitroprusside CBF on basal cerebral blood flow was investigated. 93 Hypotension induced with nitroprusside caused a smaller reduction in CBF. EEG activity, which indicates continuing neuronal function, was maintained for longer in the nitroprusside group.

Impairment or loss of autoregulation of CBF is a primary concern when hypotensive agents are used in neurosurgical anesthesia. Clearly, sodium nitroprusside impairs autoregulation in normal animals. 92 Impairment of autoregulation by sodium nitroprusside precludes any modulation of CBF in response to acute alterations in systemic arterial blood pressure. Under these circumstances, the intracranial contents not only are subjected to the specific pharmacologic activity of these drugs but will also closely reflect changes in the systemic circulation.

Nitroglycerin

Nitroglycerin directly dilates venous capacitance vessels. 94 It has a short half-life and no clinically significant toxic metabolites. The effect of nitroglycerin on cardiac output is variable. Although most studies suggest that cardiac output does not change, this result may depend on the volume status of the patient. Although both resistance and capacitance vessels are dilated, nitroglycerin has its major effect on the latter. Because capacitance of the venous circulation increases markedly with nitroglycerin, cardiac output may decrease if preload is compromised. 95 However, the effect of reduced preload would be offset by an increase in nervous sympathetic activity, elicited through baroreceptor activity and resulting in increased heart rate and myocardial contractility. 96 The baroreceptor reflex mechanism

would also counteract the decrease in SVR, resulting in a biphasic response (initial arteriolar vasodilation followed by vasoconstriction in the mesenteric, iliac, coronary, and systemic beds). 97

Because the adrenergic response will be partially blocked by anesthesia, the cardiovascular effects of nitroglycerin will be different in anesthetized subjects. 96 Recent research indicates that cardiac index is lower when MAP is decreased to 40 mm Hg with nitroglycerin rather than sodium nitroprusside. 40 Yaster et al 98 studied 14 patients 9 to 14 years of age. Mean arterial blood pressure was reduced to 55 mm Hg or less by infusion of sodium nitroprusside or nitroglycerin. At infusion rates as high as 40 mg/kg/min, nitroglycerin was not able to produce rapid, predictable, and sustained decreases in arterial blood pressure during general anesthesia. Nitroglycerin did not decrease MAP below 60 mm Hg in six of the eight patients studied.

The decrease in blood pressure with sodium nitroprusside is more rapid. Significant differences also seem to exist on discontinuation of the two drugs. Significant rebound hypertension frequently occurs after acute termination of sodium nitroprusside, 77 whereas acute termination of nitroglycerin has produced a prolonged period of vasodilation in animals. 99 As with sodium nitroprusside, low intracranial compliance contraindicates the use of nitroglycerin prior to opening of the dura mater. 100 Even when the dura has been opened, both nitrates incur some risk of increased cerebral blood volume and significant brain swelling. 101 Differences between sodium nitroprusside and nitroglycerin clearly exist. Although both drugs are able to decrease arterial blood pressure, the effect of sodium nitroprusside is more rapid and consistent.

Hydralazine

Hydralazine, a smooth muscle relaxant, effectively induces hypotension when low concentrations of enflurane are administered. 102 Hydralazine significantly reduces SVR without changing cardiac output, pH, or venous admixture. Rebound hypertension does not occur, and ICP increases significantly. 102

Purine Derivatives

A natural substance that produces hypotension would be an attractive alternative to the previously discussed drugs. Both adenosine triphosphate (ATP) and adenosine meet these criteria. 103 Adenosine triphosphate rapidly degrades into adenosine and phosphate, adenosine being the component producing vasodilation. Adenosine is metabolized to uric acid; the amount is in dispute. 104 Hypotension occurs rapidly, owing to marked dilation of resistance vessels, the subsequent hyperkinetic circulation, and an increase in cardiac output. Plasma-renin activity and plasma catecholamines do not increase. 105, 106 Similar degrees of hypotension can be achieved as with sodium nitroprusside, but recovery is more rapid, and no rebound hypertension occurs. 8, 104 Unfortunately, ATP and adenosine dilate cerebral vessels, increase CBF, increase ICP when intracranial compliance is low, and impair cerebral autoregulation 104, 107, 108 (Fig. 41–4).
FIGURE 41–4 Changes in cerebral blood flow (DCBF) after acute increases in mean arterial pressure (MAP) before, during, and after adenosine triphosphate (ATP)–induced hypotension demonstrate that cerebrovascular reactivity is normal before hypotension but impaired during and after hypotension. Specifically, five anesthetized baboons had acute increases in MAP of approximately 20 mm Hg (by means of intravenous administration of angiotensin II amide) at three times: before ATP-induced hypotension; during infusion of ATP, once MAP had decreased to approximately 40 percent of control; and after infusion of ATP, once CBF had returned to control. Mean values ±SD. $*P < .05$; $**P < .01$. (Modified from Van Aken et al104)

Adenosine is a potent coronary vasodilator that can produce an unfavorable redistribution of coronary blood flow, leading to ischemia. Some patients with coronary artery disease have shown signs of ischemia during administration of adenosine. 109 Administration through a central venous catheter is advocated to increase efficacy of the drug. With peripheral administration, partial breakdown of the drug occurs before it can reach the arteriolar vascular smooth muscle. As a result, drug requirements are 40 percent higher. The dose requirement can be reduced by concomitant administration of dipyridamole, which inhibits adenosine uptake, primarily by blocking carrier-mediated diffusion into cells. 105 Another potential disadvantage of adenosine and ATP is their ability to cause heart block. 110

Trimethaphan

Ganglionic blockade has long been the mainstay of deliberate hypotension. Hypotension results from occupation of the receptor sites and stabilization of the postsynaptic membrane, both of which block neural transmission through the autonomic ganglia. Because autonomic ganglion–blocking drugs such as trimethaphan lack selectivity, both parasympathetic and sympathetic activity are depressed.

Parasympathetic depression produces unwanted effects like tachycardia, mydriasis, cycloplegia, reduced gastrointestinal tone and motility, and urinary retention.

Trimethaphan has maintained some popularity because of its short half-life (1–2 minutes), owing to rapid inactivation by plasma cholinesterase with subsequent renal excretion. This characteristic makes it easy to control blood pressure. Potential problems include histamine release (related to the rate of infusion), bronchospasm, tachyphylaxis, and potentiation of succinylcholine-induced myoneural blockade. **111** Trimethaphan seldom increases ICP, as ganglionic blockade generally does not affect the cerebral circulation. However, trimethaphan may increase ICP when rapidly infused during low intracranial compliance (possibly because of histamine release). In addition, cerebral ischemia has occurred in dogs given trimethaphan to induce hypotension to a MAP of 55 mm Hg. **112** These results contrast with the safety of comparable levels of hypotension produced by sodium nitroprusside, nitroglycerin, adenosine, and isoflurane, presumably because these drugs are cerebral vasodilators. It should be noted that dilation of the pupils is a pharmacologic property of trimethaphan caused by blockade of the ciliary ganglion. This effect might erroneously be attributed to cerebral ischemia by those unfamiliar with the drug.

Combined Therapy (Sodium Nitroprusside and Trimethaphan)

Large doses of sodium nitroprusside can produce cyanide toxicity. Large doses of trimethaphan may result in prolonged hypotension. To avoid these problems, the use of a 10:1 mixture of trimethaphan and sodium nitroprusside has been advocated. This ratio was proposed because of the relative potencies of the two agents. The mixture proved to be an efficient and rapid hypotensive agent with the potential for rapid recovery; also, the total dose of sodium nitroprusside could be reduced substantially. **113**

Miller et al **114** compared sodium nitroprusside with a 10:1 trimethaphan-sodium nitroprusside mixture in 20 patients undergoing neurosurgical procedures. Controlled ventilation kept arterial carbon dioxide partial pressure ($PaCO_2$) at 25 to 30 mm Hg. Cardiac output was significantly lower with the mixture than with sodium nitroprusside alone. However, the total dose of sodium nitroprusside needed to produce a similar degree of reduction in blood pressure was five times lower with the mixture. This type of combined therapy might be beneficial for prolonged periods of hypotension.

Phentolamine

Phentolamine decreases MAP by blockade of a-adrenergic receptors within 2 minutes of intravenous administration. Blood pressure returns to control values within 15 minutes. Intracranial pressure does not change significantly, but cerebral perfusion pressure is lower for 10 minutes after drug administration. **115**

Urapidil

Urapidil, an antihypertensive drug not available in the United States, has two mechanisms of action: antagonism of peripheral a-adrenergic receptors and interaction with 5-hydroxytriptamine1A receptors in the brain. This pharmacologic profile explains the vasodilation and lack of significant sympathetic activation observed during administration of urapidil. **116** Intracranial pressure and compliance have not been affected in animals or patients given urapidil. **117**, **118** Cerebral blood flow of baboons did not change when MAP was decreased from 107 ± 13 to 70 ± 13 mm Hg with urapidil. **119** A greater degree of hypotension could not be achieved by increasing the dose. Rebound hypertension did not occur. Urapidil seems to be a suitable agent for the induction of moderate degrees of hypotension (MAP of 70 mm Hg). Administration of urapidil with isoflurane in animals has attenuated the undesirable effects and diminished the required concentration of the volatile anesthetic. **48** This technique is often used in clinical practice in Europe.

Esmolol

Esmolol is a short-acting cardioselective intravenous b-adrenergic receptor-blocking drug having a very rapid onset of action **(Ch. 14)**. **120** It has been used by itself to decrease blood pressure **26**, **121**, **122** or in combination with other drugs. **123** In contrast to sodium nitroprusside–induced hypotension, plasma renin activity decreased slightly during esmolol-induced hypotension. This absence of renin release improved the stability of hypotension. **123**

One study on 30 patients undergoing resection of arterio-venous malformations with deliberate hypotension showed the potential of esmolol to produce marked myocardial depression. **122** Patients were randomly assigned to receive isoflurane (£4%), sodium nitroprusside (£8 mg/kg/min), or esmolol

(£24 mg/min) for a 20 percent reduction in MAP to 60 to 65 mm Hg. Esmolol was associated with a 39 percent decrease in cardiac output, which, because of a 22 percent increase in SVR, far exceeded the reduction in MAP. The increase in SVR occurred despite a 32 percent decrease in plasma-renin activity. In contrast, with sodium nitroprusside or isoflurane, the decrease in MAP was accompanied by a decrease in SVR of similar magnitude but no change in cardiac output **(Fig. 41–5)**. Plasma-renin activity increased 48 percent with sodium nitroprusside and 126 percent with isoflurane. Heart rate increased 13 percent with sodium nitroprusside, did not change with isoflurane, and decreased 23 percent with esmolol. Because of its potential for marked myocardial depression, it seems prudent to combine esmolol with other drugs or to use it when only modest reductions in blood pressure are required.
FIGURE 41–5 Percentage change from baseline for hemodynamic variables and plasma-renin activity (PRA) during hypotension induced by esmolol, sodium nitroprusside, or high-dose isoflurane in 30 patients undergoing resection of intracranial arteriovenous malformations. For mean arterial blood pressure (MAP) and heart rate (HR), $n = 10$ for esmolol and nitroprusside and $n = 9$ for isoflurane. For cardiac output (CO), central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), and systemic vascular resistance (SVR), $n = 9$ for esmolol and isoflurane and $n = 7$ for nitroprusside. For plasma renin activity, $n = 8$ for all groups. *Significantly ($P < .05$) different from the other two groups. (From Ornstein et al**122**)

Labetalol

Labetalol produces hypotension by blocking both alpha1 - and beta1 -receptors **(Ch. 14)**. Labetalol also blocks b2 -receptors. As a result of decreases in cardiac output and peripheral vascular resistance, blood pressure decreases promptly after intravenous administration of labetalol. Although the peak effect of intravenous labetalol occurs within 5 minutes, its half-life is relatively long (4 hours) compared with that of sodium nitroprusside or nitroglycerin. **124**

Hypotension induced with labetalol produces only minimal increase in intrapulmonary shunting and no increase in heart rate, whereas both variables increase significantly with sodium nitroprusside. **124** Combining labetalol with inhalation agents such as halothane and isoflurane produces a remarkable hypotensive synergism; labetalol is less potent in this regard when combined with intravenous anesthetics. **125** An important advantage of labetalol is the absence of any increase in ICP, even when intracranial compliance is reduced. **126** Experiments in rats showed that blood flow to vital organs was significantly better when the hypotensive agent was isoflurane combined with labetalol rather than isoflurane alone. **127** A study on patients also confirmed that preservation of renal blood flow was superior with labetalol. **49** The same investigators also showed that hypotension induced by labetalol with isoflurane anesthesia did not cause more impairment of mental functions than normotensive general anesthesia. **128** However, clinicians should be aware that labetalol masks the adrenergic response to acute blood loss. Because of the relatively long half-life of labetalol, this effect lasts through the early postoperative period.

Nicardipine

Nicardipine is a calcium channel blocking drug that dilates peripheral, coronary, and cerebral vessels while maintaining myocardial contractility and cardiac output without tachycardia. **129** Careful titration of nicardipine infusions (10–250 mcg/kg/h) is mandatory because nicardipine-induced hypotension resists conventional treatment such as phenylephrine. **130**, **131**

Prostaglandin E1

Prostaglandin E1 (PGE1) is another naturally occurring substance that has been evaluated as a possible hypotensive drug. One study of 14 mastectomy patients given PGE1 reported that all but two had a decrease of approximately 40 mm Hg in arterial blood pressure, which returned to control values on termination of the drug. **132** None of these patients complained of abdominal pain, diarrhea, or other known side effects of prostaglandin infusion after recovery from general anesthesia. Renal blood flow increased, and no arrhythmias were noted. Other studies reported that local CBF and carbon dioxide reactivity were well maintained during PGE1 -induced hypotension for cerebral aneurysm surgery. **133**, **134** PGE1 appears to be a mildly hypotensive agent that may not be able to produce profound hypotension in all patients.

EFFECT OF HYPOTENSION ON ORGAN FUNCTION

Deliberate hypotension decreases arterial blood pressure by decreasing cardiac output or SVR, or both. However, a reduction in cardiac output may not be the most appropriate method because keeping

cardiac output stable is crucial for maintaining blood flow to the tissues. Cardiac output should remain sufficiently high not only to provide adequate oxygen and energy substrates but also to remove metabolic waste products before their accumulation causes tissue damage. The final effect of hypotensive anesthesia on cardiac output depends on the balance of its effects on afterload, preload, myocardial contractility, and heart rate. These effects interact with homeostatic mechanisms. Other important factors include the physical state of the patient, the administration of additional drugs, and the pattern of ventilation used intraoperatively. Because deliberate hypotension is clearly designed to decrease arterial blood pressure but still preserve organ blood flow and function, it must be emphasized that decreasing blood pressure by hemorrhage also decreases organ blood flow. The use of deliberate hypotension requires constant assessment of intravascular fluid volume throughout surgery, to ensure optimal organ function.

The effects of hypotension on various organ beds are complex, depending on the drugs used and the magnitude and length of hypotension. Differences in species may also be important when evaluating the many animal studies on organ function during deliberate hypotension.

Central Nervous System

Because ischemia of the brain and myocardium are the principal hazards of deliberate hypotension, the effects of arterial hypotension on the cerebral circulation (Chs. **19** and **52**) are particularly important. The adequacy of cerebral perfusion during induced hypotension has been studied using clearance of radioactive xenon, electroencephalographic monitoring, and measurement of jugular venous oxygen content. **135**, **136**, **137** Although these tools are relatively crude measurements of cerebral function, all have shown that deliberate hypotension does not produce permanent changes in cerebral hemodynamics. Furthermore, the performance of elderly patients on psychologic tests given several days after total hip arthroplasty with deliberate hypotension did not differ from their performance before surgery. **21** The current rationale for setting the "safe" lower limit for MAP at 50 to 55 mm Hg in normothermic patients is based on the belief that this range represents the lowest MAP at which autoregulation of CBF is still in force. **136** Once MAP falls below this limit, CBF decreases in parallel with pressure. For chronically hypertensive patients, the curve for autoregulation (CBF versus MAP) shifts to the right, that is, the lowest blood pressure at which autoregulation of CBF is still in force is higher for these patients than for normotensive patients **138** **(Fig. 41–6)**. With effective antihypertensive therapy, however, the curve for autoregulation moves back to its normal position. **139** Sharrock et al **35** showed that induced hypotension is a safe technique for patients with medically controlled hypertension.

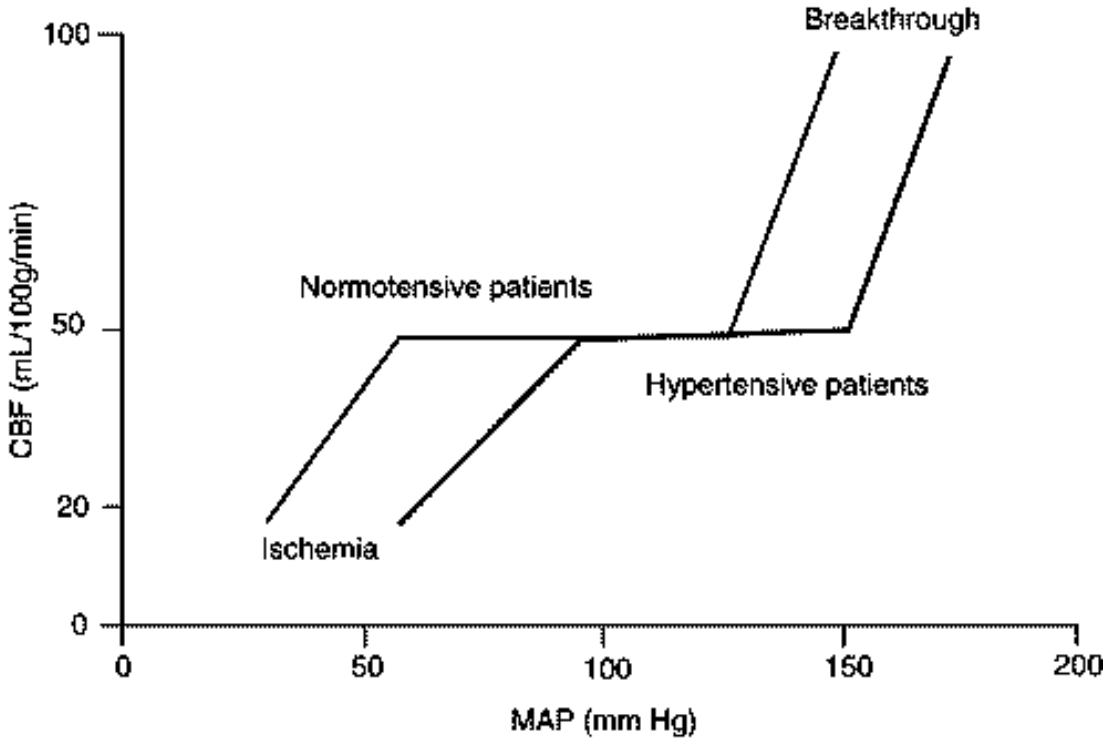

FIGURE 41–6 The curve for autoregulation of cerebral blood flow (CBF); that is, CBF versus mean arterial blood pressure (MAP) shifts to the right for chronically hypertensive patients. The lowest MAP at which autoregulation of CBF is still in force is higher for these patients than for normotensive patients. "Breakthrough" refers to the upper limit, in normotensive and hypertensive individuals, of autoregulation

of CBF beyond which CBF suddenly increases, this upper limit being displaced toward higher pressures in hypertensive patients.138

The factor most important to cerebral autoregulation is cerebral perfusion pressure and not blood pressure as such. Perfusion pressure is the difference between arterial input and venous outflow pressures. Because pressure in the cerebral venous system approximates ICP, cerebral perfusion pressure is usually calculated as MAP – ICP. An important consequence is that patients with increased ICP should never undergo deliberate hypotension before the dura is opened unless measurement of ICP is available before the surgical procedure. According to several investigators, normal cerebral oxygen metabolism can continue with a reduction in CBF to a value as low as 18 mL/100 g/min. A "normal" man has CBF this low when cerebral perfusion pressure decreases to 30 to 40 mm Hg. Children are able to tolerate even lower levels. When the skull is opened, cerebral perfusion pressure corresponds to MAP of approximately 30 to 40 mm Hg, measured at the level of the internal carotid artery. When such extreme hypotension is applied, the use of brain retractors should be avoided, blood oxygenation should be optimal, and the margin for error is zero. In our opinion, this situation creates an unjustifiably high risk for the patient. We believe that deliberate hypotension should not be pushed to this limit. Higher cerebral perfusion pressure is required for patients with chronic hypertension and altered cerebral autoregulation. Autoregulation may be absent in the tissue surrounding brain tumors, 140 in the acute phase of a subarachnoid hemorrhage, 141 and after brain trauma. 142

Pinaud et al 143 studied the consequences of this very low level of hypotension in nine adults undergoing repair of cerebral aneurysms. MAP was decreased to 40 mm Hg with sodium nitroprusside. Intraoperative CBF and the cerebral metabolic rate for oxygen were measured before, during, and after hypotension. This reduction in MAP seemed to be safe for the area of the brain studied. In poorly perfused regions, however, the occurrence of local brain and cerebrospinal fluid lactic acidosis, especially in the retracted areas, might increase risk at such low pressures. Unfortunately, the study technique did not allow such a determination.

PaCO2 is an important consideration during deliberate hypotension. During normotension, CBF changes linearly with PaCO2 when PaCO2 is 20 to 70 mm Hg. An increase of 1 mm Hg in PaCO2 produces a 2.65 percent increase in CBF. However, when a progressive degree of hypotension is induced, this relationship becomes progressively flatter, so that when the MAP falls below 50 mm Hg, CBF no longer responds to changes in PaCO2144 **(Fig. 41–7)**. A partial exception may be sodium nitroprusside–induced hypotension: in one study, hypocapnia did not further reduce CBF during trimethaphan hypotension but did so with sodium nitroprusside. 145 It must be emphasized that hypocapnia reduces CBF only at moderate levels of hypotension, and that at very low blood pressures (deep hypotension) PaCO2 no longer influences CBF.

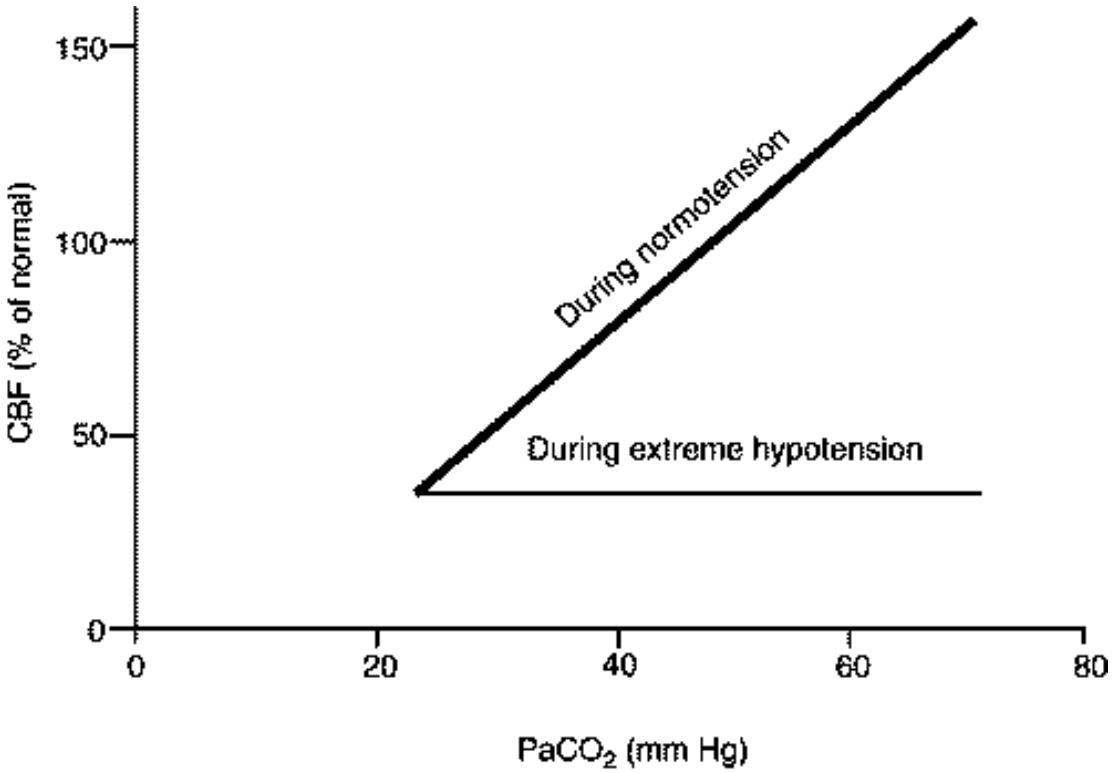

FIGURE 41–7 The relationship between cerebral blood flow (CBF) and arterial carbon dioxide partial pressure (PaCO2) at normal blood pressure and during extreme hypotension (mean arterial blood pressure of 35 mm Hg). The complete relationship between CO2 and CBF at normotension is sigmoid in shape, but the relationship between CBF and PaCO2 values in the range of 20 to 70 mm Hg is virtually linear. (Modified from Harper et al[144])

Whether one drug is better than another in preserving CBF is often debated. Stoyka and Schutz [84] examined the effects of sodium nitroprusside and trimethaphan in dogs subjected to a cerebral perfusion pressure of 80 to 30 mm Hg. With trimethaphan, autoregulation was lost below 60 mm Hg and CBF decreased as cerebral perfusion pressure decreased. However, with sodium nitroprusside, CBF remained at a stable level despite the decrease in cerebral perfusion pressure **(Fig. 41–8)**. Similarly, another study demonstrated that the normal ionic gradients established across cell membranes were depressed by hypotension, more so with trimethaphan than with nitroprusside. [146] Ishikawa et al [147] used Evans blue dye to examine the blood-brain barrier in dogs. Dysfunction of the blood-brain barrier was more pronounced with sodium nitroprusside than with trimethaphan. Because each of these studies used extreme degrees of hypotension, their results cannot be applied automatically to the usual clinical practice of decreasing MAP to 50 to 65 mm Hg. This level of MAP appears to keep CBF at rates adequate for the needs of the brain. For the moderate degrees of hypotension used routinely, both sodium nitroprusside and trimethaphan are equally effective. At deeper levels of hypotension, sodium nitroprusside may be preferable.
FIGURE 41–8 Change in cerebral blood flow (DCBF) in dogs subjected to varying degrees of hypotension induced by trimethaphan or sodium nitroprusside. When cerebral perfusion pressure (CPP, which is systemic arterial blood pressure minus cerebrospinal fluid pressure) was decreased incrementally from 80 to 30 mm Hg, CBF decreased with trimethaphan but not SNP. (Modified from Stoyka and Schutz[84])

The use of isoflurane alone to induce hypotension has gained popularity. For normocapnic dogs, isoflurane appeared to offer certain advantages over other techniques commonly used to induce hypotension. [148] At low cerebral perfusion pressures (<30 mm Hg), the cerebral metabolic rate for oxygen was better preserved, suggesting cerebral protection. Isoflurane also favorably influenced the global cerebral oxygen supply/demand ratio in humans having a MAP of 50 mm Hg [149] **(Fig. 41–9)**.
FIGURE 41–9 The changes in cerebral blood flow and cerebral metabolic rate for oxygen (CMRO2) in 12 patients before, during, and after decrease in mean arterial blood pressure induced by isoflurane. *P < .25 compared with prehypotension value. (From Newman et al[149])

The data of Seyde and Longnecker [150] in rats indicate that isoflurane is not harmful to the central nervous system during hypotension. When MAP was decreased to 40 mm Hg with sodium

nitroprusside, adenosine, or deep levels of isoflurane anesthesia and tissue oxygen pressures were measured, the lowest incidence of low values for tissue oxygen occurred with deep isoflurane. Again, current data suggest that either isoflurane or sodium nitroprusside is safe to use for deliberate hypotension.

Heart

Clinical and experimental studies demonstrate that cardiac function is better preserved with isoflurane than with equihypotensive doses of halothane or enflurane **(Ch. 16)**. **10**, **38**, **151**, **152** Investigators believe that isoflurane is the volatile anesthetic most suitable for healthy patients undergoing deliberate hypotension. Experimental data indicate that the cardiovascular effects of the newly developed volatile anesthetics sevoflurane and desflurane are comparable to those of isoflurane. **153**, **154** Although the low blood solubility of these drugs would allow even more rapid control of blood pressure, **155** further clinical experience and studies on potential side effects are required.

Recent clinical reports describe the successful use of continuous infusion of propofol to produce deliberate hypotension. **156** The cardiovascular effects of anesthetic doses of propofol are very similar to those of isoflurane: arterial blood pressure decreases primarily because of venodilation and a reduction of SVR. **157** However, using the cardiovascular side effects of anesthetic drugs to produce arterial hypotension may entail excessive doses that increase the risk of cardiac depression **152**, **158**, **159** and toxic side effects. For this reason, a technique combining anesthetic drugs with specific vasodilating drugs has recently gained popularity.

During deliberate hypotension, maintenance of an oxygen supply sufficient for the metabolic needs of the myo-cardium is of primary importance. The intact coronary circulation undergoes a high degree of pressure-flow autoregulation that is mildly disrupted by volatile anesthetic agents. **160** However, progressive systemic hypotension gradually depletes coronary vasodilatory reserve and diminishes the ability of the heart to cope with stresses that increase myocardial oxygen demand. **161** Arterial hypotension obtained with direct vasodilating drugs such as sodium nitroprusside and with the calcium channel blocker nicardipine frequently incurs reflex tachycardia. **60**, **162** In addition to increasing myocardial metabolism, tachycardia shortens diastole and may thus reduce myocardial perfusion. **161**

Many drugs have been used to suppress tachycardia. The cardioselective b1 -receptor antagonist esmolol decreases heart rate but has profound negative inotropic properties. **122** In combination with vasodilating drugs, however, esmolol can be used at lower doses to block reflex tachycardia, thus avoiding excessive cardiac depression. **123** A similar approach using ganglionic blocking drugs to suppress reflex tachycardia induced by nitroprusside has been effective in humans and animals. **114**

Some drugs having a unique pharmacologic profile do not induce reflex tachycardia despite their predominantly vasodilatory action. With labetalol and urapidil, reflex tachycardia in response to a1 -mediated vasodilation is counterbalanced by the drug‘s concomitant b1 -antagonistic and central serotoninergic properties, respectively. **116**, **124** Adenosine, a powerful vasodilator, directly depresses the sinus node and may also cause less tachycardia. **163**

As a compensatory mechanism to preserve myocardial perfusion at rest, the vasodilatory reserve of patients with coronary artery lesions is diminished even at normal coronary perfusion pressure. Under these circumstances, systemic hypotension will directly decrease myocardial perfusion. **164** Whether myocardial ischemia will develop as a result of hypotension depends on the concomitant changes in myocardial metabolic requirements. **165** Drugs that reduce metabolic requirements (e.g., anesthetic agents and b1 -antagonists) may protect the heart from ischemia. **166**, **167** Nitroglycerin can also be advantageous, as it improves perfusion to jeopardized myocardium. **168** In contrast, potent arteriolar coronary vasodilators, such as adenosine and sodium nitroprusside should be avoided unless appropriate monitoring is used because they may redistribute coronary blood flow away from ischemic myocardium, that is, cause coronary steal. **169**, **170**

Controversy still exists over the ability of isoflurane, also an arteriolar vasodilator, to cause coronary steal. Clinical and experimental studies indicate that hypotension induced by isoflurane causes more regional myocardial ischemia than halothane. **171**, **172**, **173** Other experimental studies, however, provide evidence against this hypothesis. **169**, **174** That is, the vasodilating properties of isoflurane are weak and probably offset by the concomitant reduction in metabolic requirements. Isoflurane may even favor collateral myocardial perfusion. **175**, **176**

As a general rule, however, patients with known or suspected ischemic heart disease should not undergo deliberate hypotension unless appropriate monitoring is used. For these patients, other techniques that can partially replace the use of systemic hypotension for a given indication (e.g., reduction of blood loss) must be considered.

Finally, considerable interest has developed in the combined use of deliberate hypotension and normovolemic hemodilution to reduce the requirements for perioperative autologous blood transfusion. Preliminary data from animals, however, indicate that hemodilution reduces coronary vasodilatory reserve and the tolerance to myocardial ischemia during hypotension, even in the intact coronary circulation. 177

Lungs

Eckenhoff et al 178 noted a higher than normal carbon dioxide tension in the blood during hypotension induced with either pentolinium or trimethaphan. Measuring physiologic dead space in 25 patients, they concluded that hypotension combined with increased mean airway pressure, head-up tilt, and surgery may all lead to increased dead space. Khambatta et al 179 measured dead space in patients undergoing hypotensive anesthesia with sodium nitroprusside. They concluded that if cardiac output were maintained by replacement of intravascular fluids during induced hypotension, physiologic dead space would not increase. This conclusion is supported by Suwa et al 180 who earlier demonstrated that a decrease in cardiac output would increase dead space; this result may explain the findings of Eckenhoff et al. 178

Oxygenation may also change during deliberate hypotension (Ch. 15). In one study, arterial oxygenation decreased markedly with infusion of sodium nitroprusside. 181 In another study, normal subjects had a similar decrease in oxygenation and an increase in shunt fraction when sodium nitroprusside was infused. 182 For patients with chronic obstructive pulmonary disease whose shunt fractions were already increased, no change in shunt fraction could be demonstrated. The response to infusion of nitroglycerin in both normal patients and those with chronic obstructive pulmonary disease was similar to the response to sodium nitroprusside. A third study compared hypotension induced with sodium nitroprusside versus isoflurane in 16 patients undergoing total hip arthroplasty. 183 Pulmonary shunt fraction increased with sodium nitroprusside but not isoflurane. Animal data support this clinical observation. 184

Other effects of hypotensive agents on pulmonary function have been minimal. Trimethaphan caused a slight increase in respiratory rate and a mild degree of alveolar hyperventilation. 185 Lung mechanics did not change. Because of changes in oxygenation and possibly carbon dioxide elimination, controlled ventilation is preferable for patients undergoing deliberate hypotension.

Kidneys

Renal blood flow normally equals 20 to 25 percent of cardiac output (Ch. 18). The renal circulation is characterized by a well-functioning autoregulatory mechanism. Renal arterioles have low resting vascular tone and therefore limited ability to dilate further in response to hypotensive drugs. The glomerular filtration rate is maintained until MAP falls below 75 mm Hg. 186 At this level, perfusion is still sufficient to meet the metabolic needs of the kidney cells, although oliguria may ensue. Because most clinical studies have demonstrated that normovolemic patients have rapid recovery of urine production on discontinuation of induced hypotension, strict maintenance of urine production during deliberate hypotension is unnecessary. 187, 188, 189

Thompson et al 21 could find no significant changes in serum creatinine, blood urea nitrogen, or serum or urinary electrolytes for 30 patients having deliberate hypotension. Because renal dysfunction is not a frequent complication of deliberate hypotension, short periods of decreased renal flow are apparently not detrimental.

Recently Toivonen et al 49 demonstrated that kidney function is better preserved during hypotension induced with a combination of labetalol and isoflurane than with deep levels of isoflurane anesthesia alone (Table 41–3).

TABLE 41–3. Effect of Induced Hypotension on Kidney Functiona

HYPOTENSIVE DRUG(S)		
VARIABLE	**DEEP ISOFLURANEb**	**LABETALOL AND ISOFLURANEc**
UF (mL/min)		
Before	0.58 ± 0.12	0.56 ± 0.17
During	0.07 ± 0.02d	0.25 ± 0.10
After	1.28 ± 0.17e	0.56 ± 0.06
CCreat (mL/min)		
Before	78 ± 14	78 ± 11
During	8 ± 1d,f	33 ± 8d
After	110 ± 17	120 ± 17
UOsm (mOsm/kg/H2O)		
Before	530 ± 27	611 ± 65
During	369 ± 53d	568 ± 97
After	470 ± 27g	598 ± 43
FENa (%)		
Before	0.28 ± 0.10	0.23 ± 0.05
During	0.16 ± 0.03	0.13 ± 0.04
After	0.58 ± 0.14d	0.18 ± 0.04

Mean values (±SEM) for urinary flow rate (UF), creatinine clearance (CCreat), urine osmolality (UOsm), and fractional excretion of sodium (FENa) for 10 patients in two hypotensive groups. Variables were determined during anesthesia, before the start of hypotension (before); during hypotension (during); and after anesthesia (after).
bIsoflurane, 1.4 ± 0.2 vol percent
cLabetalol, 0.5 mg/kg, and isoflurane, 0.7 ± 0.1 vol percent
d,eSignificantly different at *P* <.01 and *P* <.05, respectively, when compared with the corresponding "before" value
f,gSignificantly different at *P* <.01 and *P* <.05, respectively, when compared with the labetalol/isoflurane group
(From Toivonen et al49)

TABLE 41–3. Effect of Induced Hypotension on Kidney Function

Splanchnic Circulation

Because pressure-flow autoregulation is limited in the hepatic arterial bed and probably absent in the portal venous circulation, profound changes in liver perfusion may occur during deliberate hypotension. 190 Consequently, preference should be given to drugs that preserve cardiac output during systemic hypotension. Extrinsic control of hepatic blood flow occurs primarily through alpha 1 -mediated vasoconstriction. 191 Baroreflex activation, surgical stress, or exogenous vasopressors will therefore decrease hepatic blood flow. 191 Autoregulation in the intestine is less pronounced than in the kidney or brain, and the circulatory control of splanchnic perfusion is poorly understood. Again, increased sympathetic nervous outflow following baroreflex stimulation induces splanchnic vasoconstriction. 192

Clinical monitoring of the splanchnic circulation is extremely difficult. In addition, only a few animal studies provide data on splanchnic perfusion during systemic hypotension. Chronically instrumented dogs had better preservation of hepatic oxygen supply with isoflurane than with halothane or enflurane. 193, 194 Also, using a combination of intravenous adjuvants with isoflurane to induce hypotension was better at preserving hepatic blood flow than using isoflurane alone. 48 Whether some hypotensive adjuvant drugs offer advantages over others regarding homeostasis of splanchnic circulation is unknown. Finally, the combination of hemodilution and isoflurane-induced hypotension adversely affected hepatic perfusion, oxygenation, and function in acutely instrumented laparotomized pigs. 195

Eye

Intraocular pressure consists of the combined pressure of blood and aqueous humor within the eye (Ch. 63). When arterial blood pressure decreases, intraocular pressure also decreases. The eye has two separate systems of blood vessels: the retinal and the uveal. The uveal vessels are peculiar in possessing both precapillary sphincters and, hence, having a steady blood flow. Because the uveal system carries most of the blood supplying the eye, sudden decreases in MAP are transmitted to the eye as decreases in intraocular pressure. 196 The effect of hypotension on blood flow to the eye accounts for some of the complications of deliberate hypotension, including blurring of vision and, on

rare occasion, blindness. Therefore, proper positioning with special attention to local pressure on the eyes is extremely important.

Skin and Muscle

Measurement of blood flow to skin and muscle has relied on microsphere studies in animals. As relative blood flow to skin and muscle is small, this method is suspect. Hoffman et al **197** found that blood flow to the skin of rats decreased with sodium nitroprusside, nitroglycerin, and 2 percent enflurane, whereas blood flow to skeletal muscle increased. In another study, 20 patients given sodium nitroprusside or trimethaphan to induce hypotension for middle-ear surgery had no change in lactate, pyruvate, or standard bicarbonate with either drug. **198** Extensive clinical experience with a variety of hypotensive drugs seems to support the claim that deliberate hypotension is not injurious to these tissues, as myoglobinuria, skin necrosis, and muscle weakness do not occur.

However, experimental studies report differences between sodium nitroprusside and nitroglycerin regarding oxygen pressure in muscle. Hauss et al **199** found that the oxygen pressure in canine skeletal muscle decreased markedly with sodium nitroprusside but not nitroglycerin. These investigators suggested that sodium nitroprusside but not nitroglycerin severely impairs autoregulation of the microcirculation. This study used a surface technique and generation of a histogram to assess oxygen pressure in tissue. Some investigators believed this method is too crude and, because of the size of the electrode used, does not give an accurate estimate of tissue oxygenation.

When Endrich et al **200** used more complex methods to compare the effects of sodium nitroprusside versus nitroglycerin on striated hamster muscle, they also found significant differences. Endrich and coworkers not only examined tissue oxygenation but also measured microvascular pressures, vascular diameters and density, and blood cell velocity, in addition to visualizing the microvasculature directly. Although both sodium nitroprusside and nitroglycerin affected resistance vessels similarly, venous capillaries dilated only in response to nitroglycerin. Accordingly, the pressure difference between the arterioles and the venules, which determines capillary perfusion, did not change with nitroglycerin but decreased significantly with sodium nitroprusside **(Fig. 41–10)**. Furthermore, a significant amount of blood was diverted through arteriovenous shunts during sodium nitroprusside–induced hypotension. This mechanism probably explains why tissue oxygenation decreased with sodium nitroprusside but not with nitroglycerin. Endrich et al **200** concluded that nitroglycerin has a distinct advantage over sodium nitroprusside. Unfortunately, the desired degree of hypotension cannot always be achieved with nitroglycerin.

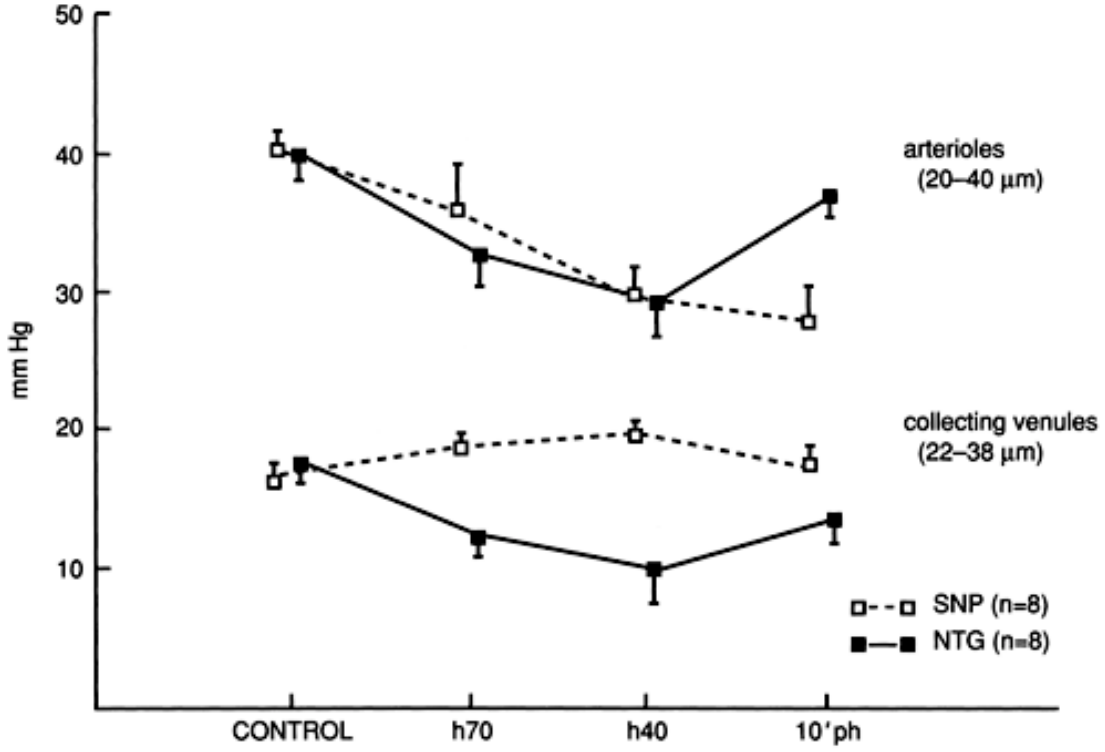

FIGURE 41–10 The pressure in arterioles and collecting venules of hamsters before, during, and after hypotension was induced with either sodium nitroprusside (SNP) or nitroglycerin (NTG). Numbers in parentheses indicate the diameters of the vessels studied. h70 and h40, mean arterial blood pressure of 70 and 40 mm Hg, respectively; 10´ ph, 10 minutes after hypotension. (From Endrich et al[200])

CLINICAL CONSIDERATIONS

When considering the many facets of deliberate hypotension, the concern of the anesthesiologist should be directed toward not only selection of the most appropriate hypotensive drug but also the type of surgery, length of procedure, need to decrease blood loss, and patient suitability.

Indications and Contraindications

Many circumstances and conditions indicate the possible need for deliberate hypotension: neurosurgery, large orthopedic procedures such as total hip arthroplasty or complicated back surgery, surgery on large tumors, surgery of the head and neck, and a variety of plastic surgical procedures. Deliberate hypotension has also been used when religious beliefs preclude blood transfusion. [201] As mentioned, positioning the patient may be as important in controlling bleeding as decreasing arterial blood pressure. Before beginning a surgical procedure, the logistics of patient positioning should be discussed by the anesthesiologist and surgeon.

The contraindications to deliberate hypotension have relaxed over the years. Better drugs and monitoring and more experience with the technique have permitted more patients to benefit from deliberate hypotension during surgery. Even when a clear indication for deliberate hypotension exists, several relative contraindications must be considered. For example, a history of cerebrovascular disease, renal dysfunction, liver dysfunction, or severe peripheral claudication suggests that the patient is less likely to have good organ perfusion during hypotension. Similarly, patients with hypovolemia or severe anemia would not be suitable candidates, as their reserves for adequate organ perfusion are markedly diminished.

The decision to use deliberate hypotension in a patient with long-standing hypertension is more difficult. Strandgaard [202] studied 13 untreated or ineffectively treated hypertensive patients (MAP of 145 mm Hg). Blood pressure was decreased by trimethaphan and head-up tilt. The lower limit of CBF autoregulation was higher for these patients (113 ± 17 mm Hg) than for similarly treated normotensive patients (73 ± 9 mm Hg). The shift in the autoregulatory curve to the right for hypertensive patients puts these patients at higher risk of death and morbidity during deliberate hypotension. Treatment of hypertension returns cerebral autoregulation toward normal. [139], [202] Furthermore, deliberate hypotension seems to be safe for patients with medically controlled hypertension. [35]

The usefulness of deliberate hypotension during clip ligation of cerebral aneurysms is controversial. [203], [204] Because wall stress at any given pressure depends on the thinness of the aneurysm sac, decreasing transmural pressure in the aneurysm during manipulation theoretically decreases the potential for rupture. Therefore, either an increase in MAP or a decrease in ICP prior to opening of the skull will increase transmural pressure (which is equal to MAP – ICP), thereby increasing wall stress and the risk of rupture.

Unfortunately, review of the literature does not produce any firm conclusions regarding the usefulness of deliberate hypotension for preventing rupture of cerebral aneurysms. [203] Furthermore, there is an acceptable alternative that facilitates clipping of a cerebral aneurysm: temporary occlusion of the proximal vessel. [205] In addition, Farrar et al [206] argue that deliberate hypotension increases the incidence of vasospasm, seriously compromises borderline ischemic brain tissue, and impairs cerebral autoregulation. Thus, controlled hypotension may place focal areas and the entire brain at risk of ischemia.

It is also controversial whether patients with myocardial infarction or a history of angina should undergo deliberate hypotension. Our growing knowledge of coronary artery disease and increased ability to monitor these patients more effectively have enabled many more patients with coronary artery disease to undergo induction of deliberate hypotension.

Monitoring During Induced Hypotension

Beat-to-beat measurement of arterial blood pressure is mandatory for patients undergoing clinically significant, deliberate decreases in blood pressure. The usual practice is to insert an arterial catheter for

continuous monitoring of blood pressure. The catheter also allows for intermittent sampling of arterial blood for blood gas analysis. The pressure transducer should be referenced to zero and positioned at the level of the head. Electrocardiographic monitoring is essential for detecting the signs of inadequate myocardial perfusion that indicate excessive hypotension—ectopic beats and changes in the ST segment (Chs. 30, 31, 32).

The correlation between end-respiratory and $PaCO_2$ is unreliable during hypotension. The changes in physiologic dead space, cardiac output, and body metabolism produced by hypotensive anesthesia obscure the interpretation of end-respiratory CO_2 monitoring. Nevertheless, capnography still provides useful information during hypotensive anesthesia. For example, a sudden decrease in end-expiratory PCO_2 may be caused by a sudden decrease in cardiac output (pulmonary embolism) or by disconnection of the breathing system. Capnography may help avoid hyperventilation, which could be harmful, as the decrease in $PaCO_2$ would further reduce CBF during moderate hypotension.

Pulse oximetry and temperature monitoring (especially important because body heat is lost more rapidly from dilated skin vessels) should be used routinely. If large blood loss is anticipated, a central venous line should be inserted. For long procedures, measurement of urinary output is also mandatory. Serum electrolytes, blood gases, and hematocrit level should be measured routinely.

Other monitors that could be used include evoked potentials, the EEG, and tissue pH. 207 These need further evaluation before they are used routinely. Because of the potential problems with deliberate hypotension, monitoring should be optimized for the type and length of surgery performed (Chs. 28 and 35).

COMPLICATIONS

The precise incidence of complications with deliberate hypotension is difficult to determine. In response to a questionnaire circulated during the early 1950s by Hampton and Little, 208 96 deaths were reported for 27,930 responses, for an incidence of 0.34 percent. Of these deaths, 0.24 percent were attributed to anesthesia and hypotension. This initial report almost caused the abolition of deliberate hypotension in the United States. 209 However, in 1961 Enderby 210 reported 9 deaths among 9,107 cases, but only 0.055 percent of the deaths were attributed to anesthesia and hypotension. Table 41–4 summarizes the published mortality rates for various forms of deliberate hypotension. 208, 210, 211, 212, 213, 214 Mortality appears not to differ from that for all anesthetics (0.01 to 0.007%) (Ch. 22).

TABLE 41–4. Mortality in Deliberate Hypotension

INVESTIGATORS (NO. OF PATIENTS)	YEARS	DELIBERATE HYPOTENSION DEATHS (NO. [%])	
Hampton and Little (1953)208	1950–1953	27,930	96 (0.34)
Enderby (1961)210	1950–1960	9,107	9 (0.10)
Larson (1964)211	1958–1964	13,264	113 (0.10)
Enderby (1980)212	1960–1976	9,256	2 (0.02)
Pasch and Huk (1986)213	1977–1984	1,802	1 (0.06)
Enderby (1985)214	1950–1979	20,558	10 (0.04)

TABLE 41–4. Mortality in Deliberate Hypotension

Nonfatal complications, which are more common, were described several decades ago. Hampton and Little 208 reported 908 major and minor complications, for an incidence of 3.3 percent. Complications usually related to the nervous system, such as dizziness, prolonged awakening, and cerebral thrombosis. 215 For Prys-Roberts et al 38 there were two cases of cerebral damage among 15 patients. One 27-year-old patient had hemiplegia after surgery, and a 56-year-old patient who failed to regain consciousness was found to have extensive cerebral and cerebellar infarction. Way and Clarke 216 reported 1 death (cerebral artery thrombosis) among 50 patients undergoing deliberate hypotension. For Linacre, 217 no cerebral complications occurred among 1,000 patients. In another series, retinal thrombosis occurred in 3 of 27,930 patients. 218 Comparable series of patients undergoing present-day techniques to induce hypotension have not been reported. Other potential complications include anuria and oliguria. The more recent literature does not contain reports of these complications, with the exception of postoperative bleeding into the operative site. 31

Current data indicate that hypotension of 50 to 65 mm Hg is safe for young healthy patients. Unfortunately, many of the most appropriate candidates for deliberate hypotension have underlying organ dysfunction that cannot be appreciated easily by routine examination. Certainly these patients are at risk of complications related to hypotension. Thus all candidates for deliberate hypotension should undergo thorough and complete examination before surgery. The decision to use deliberate hypotension should not be made in the operating room without careful consideration of the potential complications.

SUMMARY

Deliberate hypotension is effective in decreasing blood loss and providing better visibility in the surgical field. Many drugs and techniques have been successful in lowering arterial blood pressure. The mechanisms of action of these drugs differ and produce complex changes in reflexes and, subsequently, blood flow to various organs. Because deliberate hypotension is not without risk, the advantages and disadvantages must be considered.

For the healthy young patient, complications are rare. The elderly and those with underlying organ dysfunction are probably at higher risk. Therefore, the anesthesiologist must assess each patient carefully so that the decision to use deliberate hypotension is based on reason. The intelligent use of deliberate hypotension has distinct advantages for certain procedures and may promote surgical success.