Acute postoperative hypertension: A review of therapeutic options

CURTIS E. HAAS AND JACLYN M. LEBlANC

Acute postoperative hypertension (APH) is a common occurrence after surgery that has important implications for care provided on the postanesthesia unit, the intensive care unit, and the surgical floor. APH has been defined as a significant elevation in arterial blood pressure (BP) during the immediate postoperative period that may lead to serious neurologic, cardiovascular, or surgical-site complications and therefore requires intervention and management. Despite the widespread and long-standing recognition of APH, there is no agreement in the literature on a more precise, quantitative definition. APH has an early onset, being observed within 2 hours after surgery in most cases, and is typically of short duration, with most patients requiring treatment for 6 hours or less. Occasionally, APH may persist for 24–48 hours. Postoperative complications of APH may include hemorrhagic stroke, cerebral ischemia, encephalopathy, myocardial ischemia, myocardial infarction, cardiac arrhythmia, congestive heart failure with pulmonary edema, failure of vascular anastomoses, and bleeding at the surgical site. For some complications, it is unclear whether the BP elevation precedes the development of the complication or is a sequela of the complication.

Although APH may occur following any major surgery, it is most commonly associated with cardiothoracic, vascular, head and neck, and neurosurgical procedures. The reported frequency of APH is quite variable and depends on the quantitative definition of APH being used. In one study of 94 patients undergoing radical neck dissection, the fre-

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Purpose. The pathophysiology and treatment of acute postoperative hypertension (APH) are discussed.

Summary. APH is a significant elevation in arterial blood pressure (BP) during the immediate postoperative period. The predominant underlying mechanism appears to be sympathetic activation. APH may lead to serious neurologic, cardiovascular, or surgical-site complications and often requires intervention and management. Postoperative hypertension lasts less than six hours in most patients. Reversible or treatable causes of hypertension, including pain, anxiety, hypothermia, and hypoxemia, should be considered and treated before the implementation of antihypertensive therapy. The ideal agent for treating APH is intravenously administered, is fast acting, and has a short duration of action, allowing the rapid and safe adjustment of therapy to achieve a targeted BP range. Sodium nitroprusside has long been considered the standard therapy and has many of the ideal characteristics. However, because of the need for invasive hemodynamic monitoring and concerns about toxicity in patients given sodium nitroprusside, several newer agents may be preferable in routine clinical practice. Labetalol, nicardipine, and nitroglycerin have been widely studied or used. Hydralazine, esmolol, fenoldopam, angiotensin-converting-enzyme inhibitors, and clonidine may also be useful treatment options.

Conclusion. When treatment of APH is necessary, therapy should be individualized for the patient. No one agent is preferred, but effective options include sodium nitroprusside, nitroglycerin, labetalol, and nicardipine.

Index terms: Angiotensin-converting-enzyme inhibitors; Clonidine; Esmolol; Fenoldopam; Hydralazine; Hypertension; Hypotensive agents; Labetalol; Nicardipine; Nitroglycerin; Sodium nitroprusside; Surgery; Toxicity; Vasodilating agents

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frequency of APH increased from 9.6% to 25.5% as less stringent criteria for the definition of APH were used. Other factors that may affect the frequency of APH include the surgical technique, the method of anesthesia, patient characteristics, and the pain management strategy.32 Table 1 lists surgical procedures commonly associated with APH and the reported frequencies of APH. Most of the data come from studies conducted 20–30 years ago; advances in anesthesia, surgical methods, intraoperative fluid management, and pain control have probably reduced rates of APH, although there is little direct evidence to support this.

This article discusses the pathophysiology and treatment of APH.

Pathophysiology

The pathophysiologic mechanism underlying APH is uncertain and may vary with the surgical procedure and other factors, however, the final common pathway leading to hypertension appears to be activation of the sympathetic nervous system, as evidenced by elevated plasma catecholamine concentrations in patients with APH.8,22,23,32,33 At the time of development of postoperative hypertension, plasma catecholamine concentrations are significantly greater than in normotensive postoperative patients. Activation of the renin–angiotensin–aldosterone system may also contribute to APH;3 however, plasma renin, angiotensin II, and aldosterone activity are not significantly different between hypertensive and normotensive patients in all studies,8 suggesting that the predominant mechanism in APH is sympathetic activation. Wallach et al.8 reported significant correlations between mean arterial pressure (MAP) and both plasma epinephrine (r = 0.59, p < 0.01) and norepinephrine (r = 0.58, p < 0.01) concentrations after coronary artery bypass grafting.

The primary hemodynamic alteration observed in APH is an increase in afterload (systemic vascular resistance [SVR], systolic blood pressure [SBP], and diastolic blood pressure [DBP]), with or without tachycardia; there is no difference in cardiac index, left ventricular stroke volume, or left atrial pressure compared with normotensive patients.8,26,34,35 These findings are consistent with a predominant sympathetic-mediated rise in MAP secondary to vasoconstriction.

Many preoperative patient characteristics and operative factors may be associated with an increased risk of APH, and several postoperative factors may precipitate increased sympathetic activity and therefore cause or aggravate APH. Table 2 lists some of the factors that should be considered when assessing patients with a marked increase in BP during the immediate postoperative period.

Treatment

For most noncardiac types of surgery, there is a lack of agreement about when and how aggressively to treat APH. Debated are the significance of transient postoperative increases in BP, the definition of APH, treatment goals, and the potential adverse effects of vasodilators. Prospective studies showing clinical benefits of aggressive BP control in the postoperative period are lacking. The treatment thresholds used in clinical trials of APH have included either a fixed BP value (e.g., SBP of >160 mm Hg, DBP of >90 mm Hg, or MAP of >110 mm Hg)30,37–40 or a relative change from baseline (e.g., an increase in SBP or DBP of ≥20%).28,29 There is no consensus concerning the ideal treatment threshold for the

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**Table 1.**

**Frequency of Acute Postoperative Hypertension (APH) by Surgical Procedure**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Frequency of APH (%)</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid endarterectomy</td>
<td>9–64</td>
<td>2, 4, 6, 7, 11, 13–15, 19</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>22–54</td>
<td>8, 17, 23–26</td>
</tr>
<tr>
<td>Abdominal aortic surgery</td>
<td>33–75</td>
<td>22</td>
</tr>
<tr>
<td>Radical neck dissection</td>
<td>10–20</td>
<td>3, 27</td>
</tr>
<tr>
<td>Intracranial neurosurgery</td>
<td>57–91</td>
<td>16, 28, 29</td>
</tr>
<tr>
<td>Elective general surgery</td>
<td>3–9</td>
<td>5, 20, 25</td>
</tr>
<tr>
<td>Elective surgery (noncardiac)</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>Release of flexion contractures</td>
<td>46</td>
<td>31</td>
</tr>
</tbody>
</table>

*Includes a mix of general, orthopedic, urologic, gynecologic, obstetric, neurologic, otolaryngologic, and minor vascular surgeries.

**Table 2.**

**Factors Associated with Acute Postoperative Hypertension**

<table>
<thead>
<tr>
<th>Preoperative factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (especially if poorly controlled)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Extent of vascular disease</td>
</tr>
<tr>
<td>Advanced age</td>
</tr>
<tr>
<td>Renal disease</td>
</tr>
<tr>
<td>Operative factors</td>
</tr>
<tr>
<td>Type of surgery</td>
</tr>
<tr>
<td>Vascular</td>
</tr>
<tr>
<td>Cardiothoracic</td>
</tr>
<tr>
<td>Neurosurgery</td>
</tr>
<tr>
<td>Head and neck</td>
</tr>
<tr>
<td>Anesthesia technique</td>
</tr>
<tr>
<td>Anesthesia agents</td>
</tr>
<tr>
<td>Pancuronium</td>
</tr>
<tr>
<td>Acetylcholinesterase inhibitors</td>
</tr>
<tr>
<td>Opiate antagonists</td>
</tr>
<tr>
<td>Operative technique</td>
</tr>
<tr>
<td>Duration of procedure</td>
</tr>
<tr>
<td>Postoperative factors</td>
</tr>
<tr>
<td>Pain</td>
</tr>
<tr>
<td>Anxiety</td>
</tr>
<tr>
<td>Hypothermia, shivering</td>
</tr>
<tr>
<td>Anemia emergence, excitement</td>
</tr>
<tr>
<td>Hypoxia</td>
</tr>
<tr>
<td>Hypercarbia</td>
</tr>
<tr>
<td>Endotracheal tube placement</td>
</tr>
<tr>
<td>Bladder distention</td>
</tr>
<tr>
<td>Antihypertensive withdrawal</td>
</tr>
<tr>
<td>Hypervolemia</td>
</tr>
<tr>
<td>Hypovolemia</td>
</tr>
<tr>
<td>Myocardial ischemia</td>
</tr>
<tr>
<td>Drug interactions</td>
</tr>
<tr>
<td>Increased intracranial pressure</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Vasopressor therapy</td>
</tr>
<tr>
<td>Bronchodilators</td>
</tr>
</tbody>
</table>
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Clinical management of noncardiac surgery patients with APH; treatment is frequently a bedside decision by the anesthesiologist or surgeon that takes into consideration the patient's baseline BP, concomitant diseases, and the perceived risk of complications.

In contrast, it is generally well accepted in cardiothoracic surgery that BP elevations may be associated with significant postoperative complications and that aggressive treatment with intravenous vasodilators is indicated. The most commonly quoted thresholds for the treatment of hypertension in cardiac surgery are a BP of >140/90 mm Hg or a MAP of at least 105 mm Hg, although there is no consensus.

The first step in the management of APH is a careful assessment of the patient to identify postoperative hypertension secondary to potentially reversible or treatable causes (Table 2). Pain and anxiety are common contributors to BP elevations shortly after surgery and should be ruled out or treated before administering antihypertensive therapy. Other potentially reversible causes of APH include hypothermia with shivering, hypoxemia, inadequate ventilation leading to hypercarbia, and bladder distention.

Emergence from anesthesia with excitement is another common cause of transient APH that is usually managed by eliminating potential causes, providing analgesia and sedation as appropriate, and giving supportive care. Both intravascular hypervolemia and hypovolemia can cause acute elevations in BP and should be managed with loop diuretics or fluid administration, as appropriate. The endotracheal tube may cause discomfort, contribute to anxiety and agitation, and increase sympathetic activity; therefore, the patient should be extubated as early as is deemed safe or provided adequate analgesia and sedation.

To minimize the risk of APH, preoperative antihypertensive therapy should be continued until surgery. If antihypertensive withdrawal syndrome is suspected as a cause of APH, the preferred treatment is reestablishment of preoperative antihypertensive medications if possible. Acute myocardial ischemia can elevate BP, as well as be a result of APH. If there is diagnostic or clinical evidence of myocardial ischemia, treatment should be directed primarily toward relieving the ischemia, preferably with agents that will also contribute to management of the elevated BP. Less common causes of postoperative hypertension that should be considered are increased intracranial pressure, pulmonary embolism, sympathomimetic drugs, anticholinergic agents, monoamine oxidase inhibitors, and, rarely, pheochromocytoma.

Short-term administration of antihypertensive drugs is recommended when there is no identifiable, treatable cause of the hypertension. This recommendation is primarily intuitive, since there are no controlled, prospective trials demonstrating that aggressive management of APH improves clinical outcomes or reduces the likelihood of postoperative complications. Intravenous agents are commonly recommended, since in most cases APH occurs shortly after the completion of surgery, while the patient remains intubated or otherwise unable to tolerate oral medications and is being monitored. Oral agents may be considered for patients who are outside the postanesthesia care unit or intensive care unit, but the use of oral agents does not obviate the need for careful monitoring. The ideal agent should have a rapid but smooth onset of action and a short duration of action to allow careful adjustment of the dosage and easy termination of effect. In addition, the agent should have minimal effects on heart rate, cardiac function, and myocardial oxygen demand and have an otherwise benign adverse-effect profile. No agent meets this profile; the choice of drug therapy is dependent on the clinical presentation, patient characteristics, the environment of care, the properties of the drug, and the clinician’s experience. Table 3 lists the agents commonly used in the management of APH and their important characteristics. Drugs of primarily historical relevance (e.g., diazoxide and trimethaphan camsylate) are not included in this review.

Sodium nitroprusside

Sodium nitroprusside is a direct-acting, potent nitrovasodilator that affects both the venous and arterial vasculature. It is metabolized by the blood vessels to nitric oxide, leading to vasodilation via the guanylic cyclase–cyclic guanosine monophosphate (GMP) pathway. The nitric oxide generation pathway responsible for the metabolism of sodium nitroprusside is different from that of nitroglycerin, accounting for the differences in hemodynamic effects and the lack of tolerance. The primary advantages of sodium nitroprusside are its very quick onset of action, short duration of action, minimal effects on heart rate, and lack of detrimental effects on cardiac function.

Sodium nitroprusside has long been considered the standard against which other i.v. antihypertensive agents are compared. Because of its short duration of action, it is administered by continuous i.v. infusion, with the dosage adjusted to achieve the desired hemodynamic response. Sodium nitroprusside is commonly recommended as the drug of choice for APH, especially after cardiac surgery.

As suggested by its pharmacology, sodium nitroprusside reduces SVR, MAP, pulmonary vascular resistance, and left ventricular filling pressure (or other measures of preload) and maintains or increases cardiac output and stroke volume. Mild to moderate increases in heart rate (10-15%) are commonly observed, but overall there is an improvement in...
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Table 3.
Agents Commonly Used To Treat Acute Postoperative Hypertension

<table>
<thead>
<tr>
<th>Agent</th>
<th>Typical Dosage</th>
<th>Time to Onset of Action</th>
<th>Duration of Action</th>
<th>Potential Adverse Events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium nitroprusside</td>
<td>0.5–5 ( \mu )g/kg/min (maximum, 10 ( \mu )g/kg/min)</td>
<td>&lt;1 min</td>
<td>1–3 min</td>
<td>Tachycardia, precipitous reductions in BP, myocardial ischemia, cyanide and thiocyanate toxicity, pulmonary ( \text{V/Q} ) mismatch, rebound hypertension, restlessness, nausea, vomiting</td>
<td>Requires continuous monitoring. Sodium thiosulfate (10:1) prevents cyanide toxicity.</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>5–300 ( \mu )g/min</td>
<td>&lt;1 min</td>
<td>5–10 min</td>
<td>Tachycardia, headache, hypotension, nausea, vomiting</td>
<td>Tolerance develops. Good choice with myocardial ischemia.</td>
</tr>
<tr>
<td>Labetalol</td>
<td>Bolus dose: 10–20 mg, then 10–40 mg q 10 min. Infusion: 0.5–4 mg/min (maximum, 300 mg)</td>
<td>&lt;5–10 min</td>
<td>3–5 hr</td>
<td>Bradycardia, bronchospasm, left ventricular dysfunction, prolonged hypotensive effect</td>
<td>Usual precautions for nonselective ( \beta )-blockers.</td>
</tr>
<tr>
<td>Esmolol</td>
<td>Bolus: 500 ( \mu )g/kg. Infusion: 25–200 ( \mu )g/kg/min</td>
<td>&lt;6–10 min</td>
<td>&lt;20 min</td>
<td>Bradycardia, bronchospasm, left ventricular dysfunction</td>
<td></td>
</tr>
<tr>
<td>Nicardipine</td>
<td>10 mg/hr initially, increased by 2.5 mg/hr q 5–15 min to a maximum of 15 mg/hr. Maintenance: start at 3 mg/hr initially</td>
<td>10–15 min</td>
<td>15–20 min</td>
<td>Tachycardia, hypotension, nausea, vomiting</td>
<td>Use caution with loading infusion as opposed to maintenance infusion dose.</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>5–20 mg q 6 hr</td>
<td>15–30 min</td>
<td>4–6 hr</td>
<td>Tachycardia, hypotension, headache, nausea, flushing, cardiac ischemia</td>
<td>Not routinely recommended.</td>
</tr>
<tr>
<td>Fenoldopam</td>
<td>0.1 ( \mu )g/kg/min initially, increased by 0.05–0.1 ( \mu )g/kg/min q 15–20 min. Maximum, 1.6 ( \mu )g/kg/min</td>
<td>20–40 min</td>
<td>15–30 min</td>
<td>Hypotension, tachycardia, headache, flushing, dizziness, bradycardia, electroencephalographic changes, elevated intraocular pressure</td>
<td>Avoid in patients with glaucoma or high intraocular pressure.</td>
</tr>
<tr>
<td>Enalaprilat</td>
<td>0.625–1.25 mg (repeat if needed)</td>
<td>15–20 min</td>
<td>&gt;4 hr</td>
<td>Hypotension, renal dysfunction, hyperkalemia, angioedema</td>
<td>Contraindicated in patients with bilateral renal artery stenosis.</td>
</tr>
<tr>
<td>Clonidine</td>
<td>0.1–0.2 mg (p.o. or s.i.), repeat q 1 hr to a total dose of 0.8 mg</td>
<td>30–60 min</td>
<td>&gt;4 hr</td>
<td>Central-nervous-system depression, bradycardia, hypotension</td>
<td>Not well studied in APH. Slow onset and long duration may limit value.</td>
</tr>
<tr>
<td>Captopril</td>
<td>12.5–25 mg (p.o. or s.i.), repeat after 30–60 min</td>
<td>30–60 min</td>
<td>&gt;4 hr</td>
<td>Hypotension, renal dysfunction, hyperkalemia, angioedema</td>
<td>Contraindicated in patients with bilateral renal artery stenosis.</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>10 mg, repeat after 30–60 min</td>
<td>20–30 min</td>
<td>&gt;4 hr</td>
<td>Precipitous reduction in BP, cerebral hypoperfusion, tachycardia, myocardial ischemia</td>
<td>No longer recommended. Never give sublingually.</td>
</tr>
</tbody>
</table>

\( \text{BP} = \text{blood pressure}, \text{V/Q} = \text{ventilation:perfusion ratio}, \text{APH} = \text{acute postoperative hypertension}. \)
myocardial oxygen balance.17,26,42,44,45,47 Fremes et al.17 reported that, after cardiac bypass surgery, reductions in MAP to 90–100 mm Hg resulted in favorable effects on hemodynamics and myocardial metabolism; however, further reductions in MAP to the normotensive level (~80 mm Hg) led to net myocardial lactate production suggestive of ischemic metabolism. This study highlights the importance of selecting a proper MAP or hemodynamic target for the management of APH when using a potent mixed vasodilator like sodium nitroprusside.

Sodium nitroprusside is highly effective for the management of APH. The usual starting dosage is 0.25–0.5 μg/kg/min, increased by 0.5–1 μg/kg/min every 5–10 minutes until the desired BP response is achieved. Although the maximum recommended dosage is 10 μg/kg/min, the dosage should not exceed 5 μg/kg/min for more than a few minutes because of the risk of acute cyanide toxicity.45 As a general rule, the lowest possible dosage should be used for the shortest possible period. In uncontrolled studies, sodium nitroprusside has been universally effective in achieving the desired reduction in MAP in patients with APH after cardiac surgery.17,26,42 In one prospective study, 88% of cardiac and noncardiac surgery patients randomly assigned to sodium nitroprusside achieved the therapeutic goal.44 The most common reasons for treatment failure were tachycardia, hypotension, nausea, and vomiting. Sodium nitroprusside has been shown in prospective studies to be as effective and safe as nitroglycerin,47-49 labetalol,24,37 nicardipine,44 and fenoldopam50 for the management of APH. In the setting of documented or suspected myocardial ischemia, alternative agents are preferred because of the risk of decreased coronary perfusion and coronary steal syndrome.46-48

The most common adverse effects of sodium nitroprusside are excessive reductions in BP, tachycardia, myocardial ischemia, cyanide and thiocyanate toxicity, and worsening of hypoxemia secondary to a reversal of hypoxic pulmonary vasoconstriction.44 Because of its potent and labile reduction in BP, sodium nitroprusside should be used only in a well-monitored environment with continuous BP monitoring, preferably with an arterial catheter. Myocardial ischemia may occur secondary to excessive reductions in BP, with a loss of coronary perfusion pressure, reflex tachycardia with a resulting increase in myocardial oxygen demand, or a redistribution of coronary blood flow away from areas of ischemia (coronary steal syndrome).17,45,47

One molecule of sodium nitroprusside is metabolized by combination with hemoglobin to produce one molecule of cyanmethemoglobin and four cyanide radicals. Cyanide radicals are detoxified by reacting with thiosulfate to form thiocyanate, which is then eliminated in the urine (half-life, about three days). The formation of thiocyanate is catalyzed by rhodanase, a mitochondrial enzyme. This reaction is rate limited by the availability of sulfur donors, especially thiosulfate, cystine, and cysteine. When thiosulfate is being provided by usual physiological processes, the conversion of cyanide to thiocyanate occurs at a rate of approximately 1 μg/kg/min, equivalent to a sodium nitroprusside infusion of slightly more than 2 μg/kg/min. When cyanide production exceeds the capacity of this system, excess cyanide can be buffered by combination with methemoglobin. A patient with physiological methemoglobin levels and a normal red-blood-cell mass can buffer approximately 175 μg of cyanide per kilogram, equivalent to approximately 500 μg of sodium nitroprusside per kilogram.51 Therefore, in a 70-kg patient receiving an infusion at 5 μg/kg/min, the red-blood-cell-buffering capacity would be exceeded and cyanide accumulation could occur after 2–2.5 hours. In acutely ill patients with a decreased red-blood-cell mass and depletion of sulfur donors, the onset of cyanide accumulation and toxicity may occur earlier and at lower dosages.52

The signs and symptoms of acute cyanide toxicity include progressive central-nervous-system dysfunction, with headache, anxiety, confusion, lethargy, and coma; cardiovascular instability, with cardiac ischemia, arrhythmia, atrioventricular block, and cardiovascular collapse; and changes in oxygenation and pH, with venous hyperoxemia and lactic acidosis. Other manifestations may include nausea, vomiting, abdominal pain, increased salivation, and tachyphylaxis to the effects of sodium nitroprusside.45,51-54 The accumulation of cyanide and resulting toxicity can be prevented by coadministering sodium thiosulfate in the same infusion, typically in a 10:1 ratio.45,54,55 Sodium thiosulfate provides the substrate necessary to detoxify cyanide, does not interfere with the antihypertensive effects of sodium nitroprusside, and is inexpensive.54,55 Although thiocyanate accumulation and the risk of thiocyanate toxicity are possible, they should not be a concern with short-term administration for the management of APH, and the adverse effects of thiocyanate accumulation are much less concerning than cyanide toxicity.45,54

In patients with acute or chronic hypoxemia, sodium nitroprusside can reverse pulmonary hypoxic vasoconstriction and worsen ventilation-to-perfusion matching, leading to increased hypoxemia.45 Potent vasodilators like sodium nitroprusside should be used cautiously in patients with compromised oxygenation due to chronic lung disease, acute respiratory distress syndrome, or severe pneumonia. This agent may also cause an abrupt increase in intracranial pressure in patients with already elevated intracranial pressure and should be
Nitroglycerin exerts its antihypertensive effects primarily through marked venous relaxation, resulting in decreased ventricular preload and increased venous capacitance. This drug is denitrated in the vascular smooth muscle cell, releasing a free nitrite ion, with a second enzymatic reaction releasing nitric oxide—the more potent vasodilator. Nitric oxide activates guanylyl cyclase and increases cyclic GMP, which promotes relaxation of vascular smooth muscle. The inactive glucuronide metabolites of nitroglycerin are excreted primarily by the kidneys.56

Despite nitroglycerin’s widespread clinical use and recommendations that it be used for the treatment of APH, few formal studies support such use. The trials that exist primarily involved small patient populations after cardiac surgery and often had a crossover design, raising concern about their validity because of a potential carryover effect from the prior treatment and because nitroglycerin therapy was typically continued for 20 minutes or less. Two trials comparing nitroglycerin with sodium nitroprusside found similar decreases in MAP and nonsignificant increases in heart rate.47,48 Excessive hypotension was not reported in either trial; however, these were both small crossover studies primarily intended to compare the hemodynamic response between the two agents after cardiac surgery, not overall clinical efficacy in treating APH. The hemodynamic variables differing most between the two trials were cardiac output and preload. One study found a decrease in cardiac output and preload with both agents,47 while the other observed an increase in cardiac output (significant only for nitroglycerin) and no difference in preload.48 The patients in the second study were receiving intravascular volume expanders, which probably explains the differences in hemodynamic responses between the two studies. Nitroglycerin also benefitted myocardial metabolism compared with sodium nitroprusside, yielding greater decreases in left ventricular stroke work, minute work index, and myocardial oxygen consumption and demand.47

Another trial randomized 12 cardiac surgery patients to nitroglycerin, sodium nitroprusside, or i.v. prostacyclin to achieve a MAP between 75 and 80 mm Hg.49 There were no significant differences in heart rate or oxygen consumption among the three groups. Sodium nitroprusside increased cardiac output and stroke volume and decreased vascular resistance to a greater extent than nitroglycerin; there was no difference in preload.49 Nitroglycerin appeared to have fewer negative effects on oxygenation and intrapulmonary shunt than either sodium nitroprusside or prostacyclin.48,49

Although there are no specific nitroglycerin dosage guidelines for APH, the infusion is usually initiated at 5–10 µg/min (0.075–0.15 µg/kg/min) and increased by 5–10 µg/min every three to five minutes to achieve the goal MAP. The mean ± S.D. dosage in one study was 111 ± 116 µg/min, although there was a considerable range (8–292 µg/min).48 Like sodium nitroprusside, nitroglycerin has a rapid onset of action and a short duration of action, making it attractive for use in the management of APH. Close monitoring of BP and heart rate during the initiation and dosage adjustment of the nitroglycerin infusion is recommended. Nitroglycerin is relatively inexpensive compared with other alternatives.

The main disadvantage of nitroglycerin is the development of tolerance to the vasodilatory effects after 48–72 hours of infusion. This is postulated to be secondary to compensatory mechanisms evoked by baroreceptor-mediated responses and hormones produced in response to the decreased arterial pressure and to a decrease in tissue sulfhydryl donors necessary for the metabolism of nitrates to nitric oxide.56 However, because of the typically short duration of APH, nitrate tolerance is not an important limitation of the use of nitroglycerin in most patients. Primary adverse effects associated with nitroglycerin infusions are headache and reflex tachycardia. There is also the possibility that free nitrite ions can react with hemoglobin to produce methemoglobinemia; this is of greatest concern with the use of prolonged, high-dose infusions and may result in pseudocyanosis, tissue hypoxia, and death.56

Nitroglycerin has several favorable properties as an option in the treatment of APH, especially for the patient with concurrent cardiac ischemia, since the drug has been shown to have beneficial effects on myocardial oxygen supply and demand. However, an increase in heart rate with the administration of nitroglycerin may offset these beneficial effects. Depending on the patient’s fluid status, the effects of nitroglycerin on preload may decrease cardiac output; therefore, it should be used cautiously in patients with moderate to severe left ventricular dysfunction. In addition, patients with critical aortic stenosis are preload dependent and may tolerate nitroglycerin poorly. The drug should be avoided or used very cautiously in these patients. For a patient with compromised oxygenation, nitroglycerin may be better tolerated than sodium nitroprusside because of less effect on hypoxic pulmonary vasoconstriction and a smaller increase in pulmonary shunting.

Labetalol

Labetalol is a racemic mixture of four diastereomers that all have unique effects at α1- and β-adrenergic...
receptors, with a net effect of $\alpha_1$-receptor and nonselective $\beta$-receptor antagonism. The drug also demonstrates some $\beta_2$-receptor agonism, which may contribute to vasodilation and inhibition of the neuronal uptake of norepinephrine (a cocaine-like effect). After i.v. administration, the potency for $\beta$-receptor blockade is about 5–10 times higher than that for $\alpha_1$-receptor blockade. The route of administration affects the drug’s pharmacologic effects, since the different isomers have variable degrees of presystemic metabolism and resulting bioavailability.\textsuperscript{57} Labetalol is an attractive option for the management of APH because it potentially combines vasodilation secondary to $\alpha_1$-receptor antagonism, reversing the increases in afterload observed during APH, with $\beta$-receptor blockade to prevent reflex tachycardia.

Hemodynamic studies of labetalol in the treatment of APH have shown that the drug’s predominant effect is a reduction in SBP, MAP, heart rate, and cardiac output, with no significant change in SVR. Right ventricular filling pressures remained unchanged or were slightly increased.\textsuperscript{24,34,40} This suggests that the predominant effect on MAP is secondary to the nonselective $\beta$-blocking effects on the heart; however, the $\alpha_1$-receptor antagonism appears to prevent an increase in SVR that is commonly observed after the administration of purely nonselective $\beta$-receptor antagonists.\textsuperscript{34} Orlowski et al.\textsuperscript{39} reported a reduction in SVR and an increase in cardiac output and left ventricular stroke volume when labetalol was administered for APH following major vascular surgery; this contradicted the results of other hemodynamic studies. The disagreement may reflect differences in the patient population (major vascular surgery, and the definition of APH was an SBP of $\geq$200 mm Hg or a DBP of $\geq$100 mm Hg) or the method of administering labetalol.\textsuperscript{24,34,39,40} Although formal myocardial metabolism studies in the setting of APH have not been reported, labetalol reduces indicators of myocardial oxygen demand while maintaining or improving indicators of myocardial oxygen supply.\textsuperscript{24,34} This apparent beneficial effect on myocardial metabolism may make labetalol a preferred agent for suspected or documented myocardial ischemia. In addition, labetalol does not affect intracranial pressure or cerebrovascular blood flow and is therefore often a preferred agent for BP control in neurosurgery patients.\textsuperscript{28,58,59}

Labetalol has been evaluated for the treatment of APH following cardiac,\textsuperscript{24,34} vascular,\textsuperscript{37,39,40} intracranial neurologic,\textsuperscript{28,58} and general\textsuperscript{28,38} surgery and has been found to be a safe and effective option, producing overall response rates of 85–100%. Labetalol has also compared favorably with sodium nitroprusside,\textsuperscript{24,37} and esmolol\textsuperscript{34} for the control of APH; however, the hemodynamic mechanisms leading to a reduction in MAP differ. Onset of action is within minutes after i.v. administration, with peak effects observed within 5–10 minutes. The drug has an elimination half-life of up to eight hours and therefore has a relatively long duration of action.\textsuperscript{57}

Labetalol has been administered as individual bolus doses, by continuous i.v. infusion, or as a combination of bolus and infusion therapy for the management of APH, with little agreement concerning dosage, duration, or method of administration.\textsuperscript{24,28,30,34,37,40,58} Since APH is generally short-lived and labetalol has a relatively long duration of action, small bolus doses adjusted to achieve the desired MAP are recommended. An initial dosage of 10–20 mg administered over 2 minutes can be followed by repeat doses every 10 minutes that are increased sequentially to up to 40 mg until the desired BP goal is achieved. The patient may be given subsequent bolus doses of labetalol if needed to maintain BP within the desired range. Alternatively, the drug may be continuously infused at 0.5–4 mg/min until the goal BP is achieved and then stopped because of the long duration of action. Supplemental bolus doses of 10–20 mg may be given every 10 minutes early during the infusion to achieve more rapid BP control. BP should be carefully monitored during dosage adjustment, but invasive monitoring is generally not required. The FDA-labeled maximum dosage is 300 mg over 24 hours; higher dosages may be well tolerated, provided that the patient is properly monitored.\textsuperscript{59}

All of the usual precautions and contraindications applying to the use of a nonselective $\beta$-adrenergic receptor antagonist should be observed. Patients with impaired left ventricular function, defined as an ejection fraction of <40% or a cardiac index of <2.5 L/min/m$^2$, should receive alternative agents for APH.\textsuperscript{34} Patients with bronchospastic lung disease, impaired cardiac conduction, or resting bradycardia should not receive i.v. labetalol for APH. The most common adverse effects of labetalol are excessive reductions in BP, bradycardia, conduction delays, left ventricular dysfunction, and bronchospasm.

**Esmolol**

Esmolol is a cardioselective $\beta$-receptor antagonist with a very short duration of action. The elimination half-life is about 8 minutes because of inactivation by erythrocyte-mediated ester hydrolysis. Peak hemodynamic effects are generally seen within 6–10 minutes after bolus dose administration, and the effects dissipate approximately 20 minutes after discontinuation of the infusion.\textsuperscript{57,60}

The hemodynamic response to esmolol is predicted by its pharmacology. The reduction in SBP and MAP after administration is due to the drug’s $\beta$-receptor-blocking effects, with a reduction in heart rate, cardiac output, and stroke volume. There are slight increases in preload and
SVR. Left ventricular stroke work, an indicator of myocardial oxygen demand, is significantly decreased. Compared with sodium nitroprusside, esmolol produces a similar reduction in MAP after cardiac surgery, but it does so through opposite effects on hemodynamics: Sodium nitroprusside reduces vascular resistance and increases in cardiac function, while esmolol reduces cardiac function and has minimal effects on vascular resistance. 60

A few studies have suggested that esmolol may be an effective option for the management of APH after cardiac and neurologic surgery, but only small numbers of patients were studied. 28,29,60 In the treatment of persistent hypertension after cardiac surgery, esmolol provided a reduction in MAP similar to that caused by sodium nitroprusside, without the reduction in oxygenation variables observed for nitroprusside. 60 Esmolol and labetalol have been found to be equally effective for managing APH during emergence from anesthesia after intracranial neurosurgery. 28

The recommended dosage of esmolol in the treatment of APH is a bolus injection of 500 μg/kg given over one minute followed by an i.v. infusion of 50 μg/kg/min. Every five minutes, the bolus dose can be repeated and the infusion increased by 50 μg/kg/min as needed to achieve the desired BP response, up to a maximum infusion rate of 300 μg/kg/min. 28,60 The most common adverse effects are bradycardia, conduction delays, left ventricular dysfunction, bronchospasm, and excessive reductions in BP. Esmolol should not be administered to patients with baseline poor cardiac function or bronchospastic disease.

Nicardipine

Intravenous nicardipine, a dihydropyridine calcium-channel blocker, is the most widely studied calcium-channel blocker for the treatment of APH. 44,61-68 Like other dihydropyridines, nicardipine is relatively selective for vascular smooth muscle and has little effect on cardiac conduction or inotropic activity in vivo. 69,70 Therefore, the predominant hemodynamic effect is vasodilatation of arterial resistance vessels, leading to a reduction in vascular resistance and MAP. There are small increases in cardiac output and heart rate and a variable effect on preload. 62,71 In addition, nicardipine has beneficial effects on myocardial metabolism, as evidenced by an increase in coronary blood flow and time to the development of angina or electrocardiographic evidence of ischemia during exercise. 71,72

In small open-label trials of APH in cardiac and noncardiac surgical patients, i.v. nicardipine effectively decreased MAP and SBP. 61,66-68 Nicardipine has been as effective as sodium nitroprusside 44,46 and nitroglycerin 45 and superior to placebo in the treatment of APH; 62 the overall response rate was 86–94%. 44,62 Compared with sodium nitroprusside, i.v. nicardipine produced more consistent control of MAP in cardiac and noncardiac surgical patients, requiring fewer dosage adjustments and less time to a therapeutic response. 44,64 The shorter time to a therapeutic response was probably due to protocol design rather than to true differences in pharmacodynamics.

The dosage regimen used for i.v. nicardipine in the larger, controlled trials was an initial infusion of 10 mg/hr increased by 2.5 mg/hr every 5 minutes to a maximum of 15 mg/hr or until the targeted MAP was achieved. The infusion was then decreased to a maintenance rate of 3 mg/hr and adjusted by 1–2.5 mg/hr every 15 minutes to maintain the targeted BP. 44,62,67 The mean time to a therapeutic response was 10–15 minutes, and the clinical effect was offset 15–20 minutes after discontinuation of the infusion. 62,68 The recommendation for a loading infusion followed by a maintenance infusion at a considerably lower rate may create an opportunity for medication errors. Therefore, the clinical staff administering i.v. nicardipine should be properly instructed about the use of this drug, and orders should clearly indicate the need to reduce the infusion rate once BP goals are achieved.

Adverse effects have been reported in 7–17% of patients participating in controlled clinical trials of i.v. nicardipine for the treatment of APH. 44,62 These were generally mild and transient, were less common than with sodium nitroprusside, and usually did not require discontinuation of the drug. The most common adverse effects were hypotension, sinus tachycardia, nausea, and vomiting.

Other calcium-channel blockers

Other calcium-channel blockers that have been evaluated for use in the treatment of APH include i.v. isradipine, 73,74 sublingual nifedipine, 75 intranasal nifedipine, 76-78 and i.v. diltiazem. 76 Although they are apparently effective options for lowering MAP, isradipine is not available intravenously and nifedipine is not available for intranasal administration. Sublingual nifedipine was as effective as captopril for lowering MAP after abdominal aortic surgery. 75 However, nifedipine is not appreciably absorbed from the sublingual space, 75 and opening the capsule and swallowing the contents may result in precipitous reductions in BP, poor standardization of the dosage, and an inability to adequately adjust the dosage to control the BP response. 80 Although oral and sublingual nifedipine have been popular for the management of APH, the drug has been inadequately studied for this indication, and it has been recommended that its use for the treatment of emergency elevations in BP be abandoned because of the risk of serious complications from excessive reductions in BP. 80

One study compared diltiazem with sodium nitroprusside and intra-
Hydralazine

Hydralazine has a direct effect on arteriolar smooth muscle, causing a reduction in arterial vascular resistance with no effect on venous smooth muscle or epicardial coronary arteries. The hemodynamic effects after rapid administration are a reduction in MAP, SBP, and DBP and an increase in heart rate, cardiac output, and myocardial contractility. An increase in sympathetic activity is observed that is predominantly a baroreceptor-mediated reflex, but hydralazine may also cause the release of norepinephrine from sympathetic nerve terminals, as well as directly increase cardiac contractility. Because of an increase in heart rate and contractility, no increase in epicardial blood flow, and the potential for coronary steal syndrome, hydralazine has negative effects on myocardial metabolism and may precipitate acute cardiac ischemia and infarction.

Although i.v. hydralazine has been widely used for many years in the treatment of APH,1,3,14,36,41 there are no formal evaluations of its use for this indication. Intravenous hydralazine is not considered a first-line agent for the treatment of APH, and its overall efficacy and safety have not been adequately defined for this indication. The initial dose should be 5–10 mg i.v. over two minutes, with additional doses used as needed. Single i.v. doses should not exceed 20 mg, and administration is usually repeated every six hours because of the long duration of action. Intravenous hydralazine is contraindicated in patients with known coronary artery disease or evidence of cardiac ischemia and should be used with caution in patients greater than 40 years of age.45 Intravenous hydralazine is not recommended for use in the treatment of APH because of its potential for adverse effects, the long duration of action, and the lack of adequate supportive data.

Fenoldopam

Fenoldopam is a selective dopamine type 1-receptor agonist with FDA-approved labeling for use in the short-term treatment of severe hypertension. The stimulation of vascular dopamine type 1 receptors results in the relaxation of vascular smooth muscle via a cyclic adenosine monophosphate-dependent pathway, with resulting vasodilation. These receptors are distributed throughout most arterial beds but have the highest densities on renal and splanchnic arteries. Stimulation of these receptors on renal tubular cells results in natriuresis and an increased urinary flow rate. The natriuretic effect may be augmented by an increase in renal blood flow and glomerular filtration rate.81

The predominant hemodynamic effect of fenoldopam is a reduction in systemic vascular resistance, with decreases in MAP, SBP, and DBP. Heart rate, cardiac output, and left ventricular stroke volumes are increased, and there is no significant effect on preload.50,82 Unlike sodium nitroprusside, fenoldopam does not significantly increase pulmonary shunt fraction.50

In the treatment of APH, fenoldopam has been shown to be superior to placebo after noncardiac surgery and equivalent to sodium nitroprusside and i.v. nifedipine after coronary artery bypass grafting.50,82 The mean time to achievement of therapeutic goals was 28 minutes in a placebo-controlled trial,83 and 70% of cardiac surgery patients achieved goal BP levels 30 minutes after the start of fenoldopam treatment.82 The time to a therapeutic response may have been affected by the protocol design and the rate of adjustment of the infusion. Because of fenoldopam’s short half-life (5–10 minutes), the drug’s effect dissipates relatively quickly after cessation of an infusion; about 50% of the effect is lost by 15 minutes.84

The effects of fenoldopam on renal blood flow and glomerular filtration suggest a theoretical advantage for fenoldopam in the treatment of severe hypertension, especially for patients with compromised renal function.50,82 However, to date there are no clinical data to support the supposition that fenoldopam improves renal function compared with other agents.84 The most common adverse effects of fenoldopam are hypertension, tachycardia, headache, flushing, dizziness, and bradycardia. Fenoldopam increases intraocular pressure and therefore should be avoided in patients with glaucoma or high intraocular pressure. Fenoldopam has been reported to cause electrocardiographic changes, specifically in T-wave morphology, although these changes do not appear to represent myocardial ischemia.84 The major disadvantage of fenoldopam is the high acquisition cost.

Angiotensin-converting-enzyme inhibitors

Angiotensin-converting enzyme (ACE) inhibitors inhibit the enzyme responsible for the conversion of angiotensin I to angiotensin II and the metabolism of bradykinin to its inactive form. The resultant pharmacodynamic effects include vasodilation,
a decreased sympathetic response, renal efferent arteriolar vasodilation, and decreased sodium retention. Bradykinin may also contribute to vasodilation. Hemodynamic effects include reductions in MAP, SBP, DBP, and preload and a variable effect on cardiac output. Reflex tachycardia is not observed, and arterial oxygenation is not affected.

ACE inhibitors have been studied following abdominal aortic surgery, intracranial surgery, and coronary artery bypass grafting. Sublingual captopril was as effective as sublingual nifedipine in reducing MAP and preload, without causing significant changes in heart rate, cardiac output, or blood gases, in patients with hypertension the day after abdominal aortic surgery. This study was small and did not include patients with APH but rather patients who remained hypertensive the day after surgery.

Intravenous enalaprilat was evaluated in a randomized trial in patients with APH following intracranial neurosurgery. Compared with the control group, the enalaprilat group had lower BP; the average time to onset of this effect was approximately 15 minutes after administration. The duration of response exceeded four hours. The effect was primarily due to a reduction in vascular resistance, with no significant change in cardiac output. There was a slight reduction in myocardial perfusion pressure, which may be of some concern for patients with evidence of myocardial ischemia.

The limited data available on the use of ACE inhibitors for APH suggest that these agents can effectively lower BP and are well tolerated. The initial dosage of i.v. enalaprilat should be 0.015 mg/kg, or 0.625–1.25 mg, administered over 5 minutes. The dose can be repeated after 20–30 minutes if the patient’s response is inadequate. Captopril may be administered orally or sublingually at a dose of 12.5–25 mg. The long duration of action of ACE inhibitors and the typically short duration of APH suggest that repeated treatment after an initial response would not be required for most patients.

The potential adverse effects of ACE inhibitor therapy include hypotension (which may be prolonged), decreases in renal function, hyperkalemia, and rare cases of angioedema. Patients with intravascular volume depletion are at greatest risk for hypotension and acute renal insufficiency, so careful attention should be paid to volume status. Patients with known bilateral renal artery stenosis should not be treated with ACE inhibitors for APH. The long duration of action of ACE inhibitors, while potentially advantageous with respect to the need for repeated doses, is also a disadvantage for those who have significant hypotension.

Clonidine

Clonidine is a centrally acting α₂-adrenergic-receptor agonist that reduces sympathetic-nervous-system activity and produces subsequent decreases in BP and heart rate. In addition to sympatholytic effects that may attenuate the catecholamine response to surgery, clonidine also has sedative and analgesic effects and has been used as an adjunct to anesthesia. All of these effects may be beneficial in the management of APH.

Although clonidine has been effective in the treatment of hypertensive crises, there are no published studies on the use of clonidine for APH. A randomized, double-blind study evaluated the effects of perioperative clonidine therapy on APH occurrence, hemodynamic response, plasma catecholamine concentration, plasma interleukin-6 concentration, and urinary cortisol and nitrogen excretion for 72 hours after major abdominal surgery. Patients received either oral clonidine and a transdermal patch the evening before surgery (with an oral dose available to the operating room on an on-call basis) or matching placebo treatments. The patients receiving clonidine had a significantly lower MAP at 24 and 48 hours, a lower frequency of APH, and a markedly lower plasma catecholamine concentration than the placebo group. Heart rate, plasma interleukin-6 level, and urinary excretion of cortisol and nitrogen did not differ significantly. It appears that clonidine may be a useful treatment option for APH, but further study is needed to evaluate the effects on postoperative hypertension.

The recommended dosage of clonidine for the treatment of a hypertensive crisis is 0.1–0.2 mg orally, repeated every hour as needed until a maximum total dose of 0.6 mg is reached. Whether this dosage regimen is appropriate for the management of APH is unknown. While the transdermal route is very appealing, clonidine’s onset of action with the transdermal system is delayed by 48–72 hours, rendering this approach useless for managing APH. The most common adverse effects of short-term clonidine use are sedation and dry mouth.

Discussion

Acute hypertension is common after major surgery and may be associated with an increased risk of serious cardiac, neurologic, and operative-site complications. Making absolute recommendations about treatment is difficult because of inconsistent definitions of APH, a lack of consensus concerning treatment thresholds and therapeutic targets, and a lack of data to show that aggressive treatment of APH with i.v. vasodilators translates into improved clinical outcomes. The treatment of persistent hypertension, defined as an increase in SBP, DBP, or MAP by >20% over baseline, in the early hours after surgery is currently recommended on the basis of the intuitive assumption that the risk of complications will be reduced and outcomes improved.
CLINICAL REVIEW

Acute postoperative hypertension

Treatable or reversible causes of hypertension, including pain, anxiety, and hypothermia, should be ruled out before initiating antihypertensive therapy. The preferred agent should have a rapid onset of action and a short to intermediate duration of action and should have demonstrated efficacy and safety in the treatment of APH. The current literature indicates that the agents of choice in most clinical situations are sodium nitroprusside, nitroglycerin, labetalol, and nicardipine. The choice of agent in specific cases should be determined by the clinical situation, the patient’s characteristics, the setting of care, and the experience of the clinicians. The treatment goal should be based on the patient’s preoperative BP; a conservative target would be approximately 10% above that baseline.81 Careful monitoring of patient responses as appropriate for the chosen therapy and timely adjustment of treatment are the keys to safe and effective treatment of APH.

Conclusion

APH is a potentially serious condition. When treatment is necessary, therapy should be individualized for the patient. No one agent is preferred, but effective options include sodium nitroprusside, nitroglycerin, labetalol, and nicardipine.

References

Acute postoperative hypertension


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