REVIEW

“Perioperative hypertension: Diagnosis and Treatment”

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Abstract - With hypertension affecting more people every year, it is commonly encountered in the perioperative setting by anaesthesiologists, surgeons, intensivists, and internists. The presence of perioperative hypertension poses a risk for patients that can affect the morbidity and mortality of a surgical procedure. Despite well documented findings of complications that can arise from this condition, and the beneficial effects of therapeutic management, there are few diagnostic or treatment guidelines. Multiple agents can be used in the acute setting of perioperative hypertension, however some of the agents currently available are less than ideal. We have reviewed current and emerging pharmacological agents available.

Keywords - Hypertension, cardiac surgery, surgery, hypertensive crisis, hypertension management, preoperative, perioperative, postoperative

Introduction
It is estimated that there are currently 73 million people in the United States with hypertension [1]. Affecting more than 30% of the population over 20 years of age, it is one of the most common chronic medical pathologies [2]. Hypertension, seen as a significant public health problem, is not uniformly distributed as it occurs twice as often in African Americans compared with Caucasians [3] and affects men more than women [4]. From a global perspective, the World Health Organization has predicted that by 2025 one third of the world’s population will be hypertensive, and this will be responsible for over 7.1 million deaths per year [5].

Hypertension is a major risk factor for adverse cardiovascular outcomes, renal disease, and stroke [5]. Furthermore, it has been established that treating hypertension reduces the risk of these conditions developing [6]. Consequently, the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII) recommends risk factor modification and treatment with antihypertensive agents in patients with systolic blood pressure (SBP) greater than 140mmHg and/or diastolic blood pressure (DBP) greater than 90mmHg, regardless of age [7]. While these parameters represent a guide for chronic hypertension management, they are even more critical in patients undergoing operative interventions where the risks of adverse outcomes are increased.

Methods
We performed a PubMed search to identify suitable articles to review. A systematic review was performed with the following terms: hypertension epidemiology, management and complications, preoperative care, perioperative hypertension, postoperative hypertension, postoperative complications, and periprocedural hypertension. In addition, articles were sought in the specific areas of neurosurgical operations complications, cardiac and non-cardiac surgery mortality, and antihypertensive therapy/agents. From the results of our search we reviewed 45 papers.

Perioperative hypertension
Because hypertension is so common, it is frequently detected in patients about to undergo surgery [8]. The presence of preoperative hypertension portends more difficult haemodynamic control during anaesthesia, increased risk of intraoperative and postoperative cardiovascular events, and challenges with postprocedural blood pressure control [9]. Just the presence alone of hypertension is a risk factor for other cardiovascular diseases that may contribute to perioperative adverse events [9]. In fact, the National Veterans Administration Surgical Risk study of 83,000 patients found hypertension was the second most common risk factor associated with surgical morbidity [10].

Perioperative hypertension can occur during the induction of anaesthesia. Intraoperative hypertension is associated with acute pain-induced sympathetic stimulation that leads to vasoconstriction. In the post anaesthesia period, hypertension can be associated with pain-induced sympathetic stimulation, hypothermia, and/or hypoxia. Hypertension may also be the result of intravascular volume overload from excessive intraoperative intravenous fluid therapy, and persist 24 to 48 hours until the fluid has been mobilized from the extravascular space. Blood pressure can also rise due to discontinuation of blood pressure medications postoperatively [11]. Postoperative hypertension has a variable incidence ranging from 4% to 30%, following cardiac or non-cardiac surgery [12].
Preoperative hypertension
At least 25% of patients undergoing non-cardiac surgery will have hypertension before undergoing their procedure. This has important outcome implications as high blood pressure is associated with complications such as myocardial ischaemia. Preoperative hypertension is frequently a hypertensive urgency - not an emergency - as it doesn’t involve end organ damage and there is usually enough time to reduce the blood pressure [13]. It has been suggested that a DBP of 110 mmHg or above is considered a preoperative marker of perioperative cardiac complications in patients with chronic hypertension [8,11]. In a study by Forrest et al., preoperative hypertension was associated with perioperative bradycardia, tachycardia, and hypertension [14], and Browner et al found a 3.8 times increase on postoperative death when compared to normotensive patients [15].

When hypertension is detected, a work up for secondary causes of hypertension should be done. Even though pheochromocytoma is rare, if present, it can produce serious complications during a procedure. Long-term excess catecholamine stimulation can produce vasoconstriction and hypovolaemia that can potentially complicate management [9].

Clonidine withdrawal syndrome can simulate the hypertensive crisis of pheochromocytoma. This can be misdiagnosed as symptoms usually present 18 to 24 hours after sudden discontinuation of clonidine. When detected, clonidine withdrawal symptoms can be corrected simply by administering intramuscular clonidine or treating with labetalol and methyldopa [11].

Intraoperative hypertension
Intraoperative acute blood pressure elevations of over 20% during surgery are considered a hypertensive emergency, and chronic hypertensive patients are more likely to have labile haemodynamics during a procedure. Even small blood pressure elevations during surgery can result in increased risk of post-operative mortality and renal failure, especially during cardiovascular procedures. Hypertensive events occur more commonly in patients undergoing surgery of the carotids, followed by abdominal aorta, peripheral vascular procedures, intraperitoneal, and intrathoracic surgery [8]. Patients undergoing cardiac surgery represent a unique pathophysiologic cohort in perioperative hypertensive management. Hypertension in this group is characterized by peripheral vasoconstriction and reduced baroreceptor sensitivity. [16] Because of pre-existing underlying pathology, elevated blood pressure and heart rate can place a patient with preexisting left ventricle dysfunction or coronary artery disease at risk for developing myocardial ischemia or heart failure [17].

Acute postoperative hypertension (APH)
Postoperative hypertension is more common in preoperative hypertensive patients, and in those undergoing vascular procedures[18]. It has been defined as an SBP of above 190 mmHg and/or DBP of 100 mmHg on two consecutive readings after surgical intervention [11]. Postoperative hypertension episodes occur in the first 20 minutes of the postoperative period, although its resolution can require up to 3 hours [19-22]. If left untreated, postoperative hypertension increases the risk of myocardial ischaemia, myocardial infarction, cerebrovascular accidents, and bleeding [11].

APH is characterized by peripheral vasoconstriction, catecholamine release and reduced baroreceptor sensitivity [23]. Some of the complications associated with APH are, myocardial ischaemia, myocardial infarction, cardiac arrhythmia, congestive heart failure, pulmonary oedema, cerebral ischaemia, hemorrhagic stroke and encephalopathy; it also increases the risk of bleeding from the surgical site [5].

Myocardial ischaemia most commonly occurs in the postoperative setting and may present hours to days after the surgical procedure. Several factors may increase the risk of myocardial ischaemia, and include oxygenation problems, altered thrombotic potential, tachycardia, and postoperative hypertension that increases myocardial oxygen demand. Postoperative hypertension can also cause pulmonary oedema in patients with preexisting left ventricular systolic cardiac dysfunction [9].

Rose et al. found that patients that presented with intraoperative hypertension, excessive pain, and inadequate ventilation had a higher risk of developing APH, and also noted that these patients had more critical care admissions and a higher risk of mortality [24]. Additionally, a unique cause of hypertension may occur after surgical repair of coarctation of the aorta in two ways: an early component during the first 36 hours of systolic hypertension, and a late component of systolic and/or diastolic hypertension that persists beyond postoperative day two. If it persists beyond day two, there is an increased risk of developing postcoarctectomy syndrome, characterized by abdominal pain and associated mesenteric arteritis [25, 26].

Management
Before starting antihypertensive pharmacological treatment, other reversible causes of postoperative hypertension should be addressed. These include pain, hypoxia, hypercarbia, agitation, bladder distension and hypervolaemia [18]. Appropriate analgesia and sedation should be considered a prerequisite to the initiation of antihypertensive therapy [27]. If a patient is hypertensive and unable to take oral agents, parenteral therapy should be used [18], this makes drugs such as clonidine less attractive, as they are available only in oral or transdermal presentation and this makes titration a challenge. Volume status should be assessed as intravascular volume depletion can increase sympathetic activity and vasoconstriction, thus contributing to hypertension [5].

When hypertension is present, the distinction between an emergency and an urgency is useful. Hypertensive emergencies are defined by the coexistence of end organ damage, and a parenteral antihypertensive agent is usually necessary. In the acute setting, the goal of blood pressure management should be a 25% decrease in systolic BP. It is believed the immediate therapeutic goal should be to reduce DBP by 10% to 15% or to 110 mmHg in 30 to 60 minutes [11]. Some of the therapeutic
options for parenteral blood pressure management are described below (See Table 1):

**Clevidipine**
Clevidipine is a third generation dihydropyridine calcium channel blocker. Metabolized by red blood cell (RBC) esterases, it has a half-life of 1-2 minutes which is not altered by renal or hepatic failure. An arterially selective vasodilator, clevidipine reduces afterload without affecting cardiac filling pressures and is not reported to cause reflex tachycardia. A direct coronary vasodilator, clevidipine increases coronary blood flow while increasing stroke volume and cardiac output. Clevidipine protects against ischaemia/reperfusion injury, and maintains splanchnic blood flow and renal function [5].

A clevidipine infusion is started at a rate of 0.4µg/kg/min, titrating by doubling increments every 90 seconds up to 3.2µg/kg/min. Because it is manufactured in a lipid emulsion, it is recommended that the infusion set up be changed every four hours to prevent the possibility of bacterial contamination. Furthermore, the maximal 24 hour dosage should not exceed 2.5g/kg [28], and clevidipine should not be given to patients with soy or egg allergies.

A comparative effectiveness trial of clevidipine versus nitroglycerin, nicardipine, and nitroprusside has been performed [28]. The Evaluation of Clevidipine In the Perioperative Treatment of Hypertension Assessing Safety Events (Eclipse) trial prospectively evaluated outcomes in 1512 cardiac surgical patients that required treatment for APH. In this analysis, the clevidipine cohort was found to have a significantly lower mortality rate as compared to the nitroprusside group. Clevidipine was also found to achieve goal SBP more effectively than nitroglycerin or nitroprusside.

### Table 1. Therapeutic options in the management of perioperative hypertension

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE</th>
<th>TIME OF ACTION</th>
<th>CONTRAINDICATIONS/ADVERSE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clevidipine</td>
<td>Infusion rate started at a rate of 0.4 µg/kg/min, titrating by doubling increments every 90 seconds up to 3.2 µg/kg/min</td>
<td>Half-life of one minute, duration of action 5-15 mins</td>
<td>Cannot be given in patient with egg or soy allergy. Infusion set up should be changed every 4 hours</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>5mg/hr, increasing 2.5mg/hr every 5 minutes up to a maximum of 15mg/hr</td>
<td>Onset of action is 5 to 15 minutes, duration of action is 4 to 6 hours</td>
<td>Increased half-life may result in prolonged action by 24 hours of use</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Starting dose is 5 µg/kg/min, it can be titrated at 5 µg/kg/min every 3-5 mins, after dose exceeds 20 µg/kg/min, it can be incremented at 20 µg/kg/min</td>
<td>Onset of action is 2 to 5 minutes, duration of action is 3 to 5 minutes</td>
<td>Hypotension and reflex tachycardia. Methemoglobinemia with prolonged infusion</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>0.25 to 0.5mg/kg/min titrated every 1-2 minutes</td>
<td>Onset of action is seconds, the duration of action is 1-2 minutes, and plasma half-life is 3 to 4 minutes</td>
<td>Decreases renal blood flow and function. Decreases cerebral blood flow but increases intracranial pressure. Coronary steal Prolonged infusion may result in cyanide toxicity</td>
</tr>
<tr>
<td>Hydralazine</td>
<td><strong>IV bolus:</strong> 10-20 mg repeated every 1-4 hours as needed. <strong>IV Infusion:</strong> loading dose of 0.1 mg/kg, followed by a continuous infusion of 1.5-5 mcg/kg/min</td>
<td>Onset of action is 5 to 25 mins, drop in BP can last up to 12 hours. Circulating half-life is 3 hours</td>
<td>Reflex tachycardia in ischaemic heart disease may result in iatrogenic MI Avoid in patients with dissecting aneurysms. It can increase intracranial pressure</td>
</tr>
<tr>
<td>Fenoldopam</td>
<td>Starting dose is 0.1 µg/kg/min, titrated by increments of 0.05-0.1 µg/kg/min, up to a maximum of 1.6 µg/kg/min</td>
<td>Onset of action 5 mins, maximal response at 15 mins. Elimination half-life is 5 mins, duration of action is 30-60 mins.</td>
<td>Tachycardia Increase intracranial pressure</td>
</tr>
<tr>
<td>Labetalol</td>
<td>Loading dose 20mg followed by 20-80mg every 10mins. After initial dose, a 1-2mg/min infusion titrated until desired effect has been achieved</td>
<td>Onset of action 2-5 mins, it reaches a peak at 5-15 minutes and lasts up to 4 hours, its elimination half-life is 5.5 hours</td>
<td>Should not be used in patients with acute heart failure, bradycardia, heart block &gt;1° degree, bronchospasm</td>
</tr>
<tr>
<td>Esmolol</td>
<td>500-1000 µg/kg loading dose in 1 min, followed by infusion starting at 50 µg/kg/min and increasing up to 300 µg/kg/min PRN</td>
<td>Onset of 60 seconds and a short duration of action of 10 to 20 minutes</td>
<td>Anaemia can prolong its half-life. Should not use with acute heart failure, bradycardia, heart block &gt;1° degree, bronchospasm</td>
</tr>
<tr>
<td>Enalaprilat</td>
<td>1.25mg in over 5 min every 6 hours titrated by increments of 1.25mg at 12-24 hours to a maximum of 5mg every 6 hours</td>
<td>Onset of action 15 minutes, peak effect in an hour, duration of action is 6 hours</td>
<td>Variable response, slow onset of action, difficult to titrate to effect</td>
</tr>
</tbody>
</table>
**Nitroglycerin**

Nitroglycerin is a potent venodilator that does not cause arterial vasodilation until higher doses are reached. Its recommended starting dose is 5µg/kg/min, then titrated upward at 5µg/kg/min every three to five minutes. After the initial dose has exceeded 20µg/kg/min, dosage can be increased by 20µg/kg/min increments. Some clinical scenarios may require more rapid up titration, such as acute pulmonary oedema, although this should be done with caution and very close monitoring. Even though there are no dosing limits, the risk of iatrogenic hypotension increases at doses higher than 200 µg/kg/min. The onset of action of nitroglycerin is two to five minutes, and it has a duration of action of three to five minutes. Tachyphylaxis which begins as early as four hours after IV initiation, limits its utility as a long-term blood pressure management agent. Finally, excessively prolonged use has also been associated with methemoglobinemia [29].

The hypotensive effect of nitroglycerin is achieved by a reduction in preload and cardiac output. Therefore, it is not recommended for use in volume-depleted patients, or in those in whom cardiac output is preload dependent. Hypotension (i.e., overshoot of titration) and reflex tachycardia are common effects of nitroglycerin, and this could be exacerbated by volume depletion.

Nitroglycerin is recommended only as adjunct therapy for patients with acute coronary syndromes, or in the setting of acute pulmonary oedema. In other conditions it is not recommended as a single primary blood pressure control agent due to its unpredictability to reduce blood pressure and the early onset of tachyphylaxis.

**Nitroprusside**

Nitroprusside is an arterial and venous vasodilator and thus decreases both preload and afterload. It has onset of action measured in seconds, a duration of action of 1-2 minutes, and its plasma half-life is 3-4 minutes. It is given at an initial dose of 0.25 to 0.5 µg/kg/min and titrated every 1-2 minutes. Because of its significant hypotensive effects, nitroprusside use is commonly associated with precipitous blood pressure decreases (overshooting the desired blood pressure titration target). The clinician should be vigilant to address this iatrogenic complication promptly by termination of the infusion, and potentially administering a fluid bolus, should this occur.

The vasodilatory effect of nitroprusside can negatively impact end organ function. Because it decreases renal blood flow, this renal function can be impaired. Furthermore, while decreasing cerebral blood flow, its use results in increased intracranial pressure, therefore it should be avoided in patients undergoing craniotomies, or in those in whom increased intracranial pressure could be potentially harmful. Finally, the use of nitroprusside in patients with recent MI has been associated with increased mortality, hypothesized due to a reduction in regional blood flow (coronary steal). Ultimately, its use should also be avoided in these populations [5].

Nitroprusside contains a significant amount of cyanide that is released non-enzymatically in a dose-dependant fashion within the blood stream. It has been shown that the infusion of as little as 4µg/kg/min over 2-3 hours, can lead to toxic levels of cyanide. Nitroprusside can also cause toxicity with the release of nitric oxide generated by the formation of hydroxyl radical and peroxynitrite; this leads to lipid peroxidation [5].

Because of its potentially toxic effects, nitroprusside is only recommended for use when no other agent is available, and only if the patient has normal renal and hepatic function. Even in these settings, the use of nitroprusside should be limited to as short a time as possible, and the dose should not exceed 2µg/kg/min [5].

**Hydralazine**

A direct-acting arteriolar vasodilator, hydralazine demonstrates greater blood pressure lowering effect on diastolic, rather than systolic pressure. Hydralazine increases renal blood flow, which may provide some theoretical advantage for patients with impaired renal function. Regardless of whether administered intravenously or intramuscularly, its onset of action is 5 to 25 minutes, with a maximum effect generally within 10 to 80 minutes after administration. Hydralazine’s metabolism is dependent on hepatic acetylation and inactivation, which results in its prolonged effect. Although its circulating half-life is only three hours, it has a much longer effect on blood pressure. Once given, hydralazine can result in a drop in blood pressure that can last as long as 12 hours. Ultimately, hydralazine is not considered an ideal agent for hypertensive crises due to its difficult titration.

Hydralazine reduces peripheral vascular resistance, but can trigger reflex tachycardia. Because tachycardia in the setting of hypertension results in a subsequent increase in myocardial oxygen demand, hydralazine is not an ideal agent in patients with potential ischaemic heart disease. Furthermore, hydralazine should also be avoided in patients with dissecting aneurysms due to its potential for a reflex increase in cardiac output and myocardial contractility.

One population in whom hydralazine is preferred for use in blood pressure control is during pregnancy. While it has long been the drug of choice for preeclampsia, a population with little risk of harm due to reflex tachycardia and increased myocardial oxygen demand, a recent meta-analysis has suggested that its use is associated with an increase in materno-fetal complications [30].
Finally, hydralazine has also been reported to increase intracranial pressure [31]. Thus it should be avoided in patients in whom potentially increased intracranial pressures would be contraindicated.

**Fenoldopam**
Fenoldopam is a dopamine-1 receptor agonist that mediates vasodilation by its effect on peripheral dopamine-1 receptors. Quickly metabolized by conjugation in the liver, without the participation of cytochrome P-450 enzymes, fenoldopam mediates renal arterial vasodilation and activates dopamine receptors in the proximal and distal tubules. The net renal effects are to inhibit sodium reabsorption, thus promoting diuresis and natriuresis [5].

After administration of fenoldopam, the onset of effect is within 5 minutes, and maximal response is achieved by 15 minutes. The elimination half-life is 5 minutes and its duration of action is from 30 to 60 minutes. The starting dose is 0.1µg/kg/min, titrated by increments of 0.05-0.1µg/kg/min, up to a maximum of 1.6µg/kg/min. While fenoldopam reduces blood pressure, it often causes reflex tachycardia and can increase intraocular pressure. Therefore, fenoldopam should be avoided in patients at risk of myocardial ischaemia, intraocular or intracranial hypertension [11].

**Labetalol**
Labetalol is a combined selective α1- and non-selective β-adrenergic blocker, that is given as a bolus or a continuous infusion. Metabolized by the liver to form an inactive glucuronide conjugate, it has an onset of action within 2 to 5 minutes, reaches peak effects at 5 to 15 minutes, has an elimination half-life of 5.5 hours, and has a duration of action of up to four hours. These characteristics make it difficult to titrate labetalol as a continuous infusion. It is recommended that labetalol be administered by a 20 mg loading dose, followed by additional 20 to 80 mg boluses at 10 minutes intervals. After the initial loading dose, labetalol may also be given as an infusion of 1 mg to 2 mg per minute, titrated until the desired effect has been achieved.

Labetalol reduces systemic vascular resistance without affecting peripheral blood flow. Furthermore, cerebral, renal, and coronary blood flow are also maintained, as well as cardiac output, but heart rate may decrease due to its β-blocking effects. Labetalol has been found to be safe and effective for treating APH after vascular, cardiac, general, and intracranial surgical procedures, where a response rate of 85-100% has been reported [5]. Labetalol should not be used in patients with severe sinus bradycardia, asthma, and heart blocks greater than first degree [11].

**Esmolol**
Esmolol is an ultra-short acting cardioselective β-adrenergic blocking agent. It is metabolized via rapid hydrolysis of ester linkages by RBC esterases, and thus has the advantage of being unaffected by renal or hepatic dysfunction. Esmolol is recommended for use in hypertensive patients with increased cardiac output and heart rate [11]. Its hypotensive effect is achieved by decreasing heart rate and myocardial contractility, thereby reducing arterial pressure and it has no vasodilatory effect.

Esmolol is administered as a 500-1000µg/kg loading dose over one minute, followed by a continuous infusion starting at 50µg/kg/min and increasing up to 300µg/kg/min as necessary. It has an onset of 60 seconds and a short duration of action of only 10 to 20 minutes. Because of its RBC dependent metabolism, any condition associated with anaemia may result in a prolonged half-life and longer duration of hypotensive effects. The American College of Cardiology/ American Heart Association guidelines state esmolol is contraindicated in patients already on β-blockers, those with bradycardia, or in the setting of acute decompenated heart failure as it has the potential to excessively impair myocardial function.

**Enalaprilat**
An IV ACE inhibitor, enalaprilat is effective treating hypertension in patients with congestive heart failure and essential hypertension. It has also been found to prevent worsening renal function in patients with diabetic and non-diabetic nephropathy. For perioperative use, it has been specifically reported to be effective in patients undergoing craniotomies [32].

Enalaprilat is generally administered IV with a starting dose of 1.25 mg over five minutes and repeated every six hours as needed. It can be titrated in increments of 1.25 mg at 12 to 24 hour intervals, to a maximum of 5 mg every six hours.

The use of enalaprilat has several advantages. It can be administered as a bolus instead of a continuous infusion, it has no effect on intracranial pressure, and it doesn’t produce reflex tachycardia. Disadvantages to its use are that it has a delayed onset of action of 15 minutes, requires one hour to reach peak effect, and its six hour duration of action is excessively long in the potentially unstable patient. These disadvantages limit enalaprilat use in hypertensive emergencies as a slow onset and delayed time to peak effect make titration to a precise blood pressure challenging [11]. Despite these concerns, enalaprilat has been used to achieve postoperative blood pressure control when combined with a faster acting drug that is easier to titrate, such as labetalol or nicardipine [5].

**Conclusions**
Acute postoperative hypertension is common after cardiac and non-cardiac surgery and frequently requires pharmacological treatment. The goal of treatment should be to protect organ function, decrease complications, and improve the outcomes. As there are no guidelines for management and no definitive treatment exists, emphasis must be to individualize therapy based on the patient's risk factors and coexisting morbidities, the clinician’s experience, and the clinical setting.

With the implementation of antihypertensive therapy, patients should be closely monitored to reduce the risk of iatrogenic end organ hypoperfusion. The ideal pharmacological agent should have an immediate onset of action, a short to intermediate
duration of action, be easily and predictably titratable, have documented efficacy in treating perioperative hypertension, and should be proven safe. Nitroprusside should only be used when no other agents are available. Enalaprilat and nitroglycerin are recommended for combined therapy, but not as single agents. Labetalol, esmolol, hydralazine, and fenoldopam are recommended in very specific circumstances, and attention must be paid to their possible adverse effects. Nicardipine and clevidipine are currently the agents recommended for the majority of perioperative cases requiring hypertensive management as their efficacy has been well documented and they are proven to be safe.

References


