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HYPERTENSIVE EMERGENCIES (BM BAUMANN, SECTION EDITOR)

Perioperative Hypertensive Emergencies

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Abstract The concept of "perioperative hypertensive emergency" must be defined differently from that of ambulatory hypertensive emergency in view of its unique clinical considerations in an atypical setting. It should be noted that moderately high normal blood pressure (BP) values in the perioperative setting often trigger situations requiring immediate treatment in what would otherwise be a "BP-acceptable" nonsurgical condition. Commonly recognized circumstances that may result in a perioperative hypertensive emergency include exacerbation of severe mitral insufficiency, hypertension resulting in acute decompensated heart failure, hypertension caused by acute catecholamine excess, rebound hypertension after withdrawal of antihypertensive medications, hypertension resulting in bleeding from vascular surgery suture lines, intracerebral hemorrhage, aortic dissection, hypertension associated with preeclampsia, and hypertension associated with autonomic dysreflexia. In addition, perioperative BP lability has been reported to increase the risk for stroke, acute kidney injury, and 30-day mortality in patients undergoing cardiac surgery.

Keywords Perioperative · Hypertension · Hypertensive emergency · Blood pressure · Control · Variability · Outcomes

Introduction

Hypertension affects nearly 1 billion individuals globally and is likely responsible for more than 15 % of cardiovascular deaths worldwide. According to several estimates, 70 % of persons in the United States will be diagnosed with hypertensive disease by the age of 60 – which, coincidentally, represents the group that constitutes the fastest-growing segment of the population requiring surgery [1–5].

Considering this prevalence, the management of patients with chronic hypertension undergoing surgery is of major clinical importance. By the year 2050, it is estimated that the annual number of surgeries performed worldwide will reach 500 million, with approximately 2 % of these in patients at high risk for developing cardiovascular complications. In the United States alone, more than 30 million surgical procedures are performed annually [6], and 2.5–10 % of these procedures are associated with perioperative cardiovascular morbidity and mortality [7, 8].

Although preexisting hypertension is present in over two-thirds of all patients over 60 years of age [8], a target threshold for perioperative blood pressure (BP) has not been clearly delineated, and optimal BP management strategy in high-risk patients undergoing surgery is even less well understood. Preexisting hypertension introduces further challenges, as it has been shown that the autoregulatory capacity of the brain [9–11] and kidney is impaired in patients with chronic hypertension, potentially influencing end-organ tolerance of high or low BP. As a result, the therapeutic window of acceptable BP during surgery is narrowed and shifted to the right for this patient population.

The Seventh Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure [12••] defined hypertensive crisis as characterized by a systolic BP of >180 mm Hg or a diastolic BP of >110 mm Hg. The term encompasses both hypertensive emergencies and urgencies. Hypertensive emergencies (i.e., severe elevations in BP complicated by evidence of impending or progressive target-organ dysfunction) require immediate BP reduction to prevent or limit further end-organ damage. Hypertensive urgencies are those situations associated with severe elevations in BP without progressive target organ dysfunction.

This article is part of the Topical Collection on *Hypertensive Emergencies*

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Hypertensive crises in the perioperative setting, which comprise the majority of cases, usually occur in hypertensive patients who are untreated or inadequately treated. This definition in the perioperative setting and consideration for clinical course, however, should not be confined to the magnitude of the rise in BP value. Rather, it should be noted that moderately high BP values in the perioperative setting can lead to emergency situations in a previously normotensive patient. Importantly, the definitions of "perioperative hypertension" and "perioperative hypertensive emergency" are unique to their settings and should be distinct from ambulatory hypertensive emergencies.

Elevated BP values in the perioperative setting often lead to situations that require acute management in what would otherwise be perceived as an acceptable non-surgical situation. Critical situations that may result in a perioperative hypertensive emergency include exacerbation of severe mitral insufficiency, hypertension resulting in acute decompensated heart failure, hypertension caused by acute catecholamine excess (e.g., pheochromocytoma), rebound hypertension after withdrawal of antihypertensive medications, hypertension resulting in bleeding from vascular surgery suture lines, intracerebral hemorrhage, hypertension resulting in aortic dissection, and hypertension associated with head trauma, preeclampsia, or autonomic dysreflexia. Intraoperative BP instability can both cause and be precipitated by events commonly seen in the perioperative setting, such as decreased fibrinolytic activity, hypercoagulability, increased/decreased vasomotor reactivity, vulnerable plaque rupture, catecholamine surges, tachycardia, and a heightened inflammatory state [13–19]. Acute intraoperative BP changes and associated physiologic stress with surgical procedures may contribute to adverse perioperative cardiovascular events, including cardiac death, nonfatal myocardial infarction, and nonfatal cardiac arrest [20–25]. Acute hypertensive emergencies defined as bleeding, myocardial infarctions, and/or cerebral ischemia, for example, occur in 5–35 % of perioperative patients and are associated with a fourfold greater risk of mortality.

Defining perioperative goals for BP control should consider patient factors such as the presence of preexisting hypertensive disease, the specific acute-care situation being managed, and the vulnerable end-organ. Specific BP goals should be defined for each patient in each instance, taking into account the situation (surgery, history, etc.), type of hypertension (DBP, SBP, MAP, pulse pressure), and condition (treatment effectiveness). [12••, 15, 26–31] Although management protocols, descriptive classifications, and monitoring guidelines have been well characterized for ambulatory patients with chronic hypertension, the clinical importance of managing acute perioperative hypertension to specific therapeutic targets is less well understood, and has remained largely untested prospectively despite intraoperative hemodynamic abnormalities reported to be associated with increased morbidity and mortality.

This review summarizes the impact of perioperative hypertension on outcomes in the setting of cardiac, non-cardiac, and non-vascular and neurologic surgery, recognizing that in any setting, high BP can cause bleeding from vascular surgery suture lines.

BP Control and Outcomes During Cardiovascular Surgery

Hypertensive urgencies occur in approximately 50 % of patients during and immediately after cardiac surgery, and management of BP during cardiovascular surgery is reported in up to 90 % of all cases [32]. This perhaps reflects the fact that poorly controlled BP during surgery is not tolerated, in part due to well-recognized safety concerns related to ischemia modulation, the need for aortovascular stress-strain modulation (e.g., clamping, unclamping), maintaining adequate perfusion conditions during cardiopulmonary bypass, and balancing these pressure-perfusion requirements with surgical bleeding concerns throughout surgery. It is well understood that perioperative hypertension increases myocardial oxygen consumption and left ventricular end-diastolic pressure and that it contributes to subendocardial low perfusion and myocardial ischemia. Perioperative hypertension also increases the risk of stroke, neuron-cognitive dysfunction, and renal dysfunction, and contributes to surgical bleeding from anastomotic sites. It is now also understood that poorly controlled BP during surgery can trigger hyperinflammatory and procoagulant conditions, including platelet activation, which may compromise microvascular blood flow [20–23]. In a case-control study of patients who died of a cardiac cause within 30 days of elective surgery, a preoperative history of hypertension was four times more likely than in an equal number of age-matched controls [33]. In addition, patients undergoing CABG surgery have significantly higher risk of complications when preoperative systolic hypertension or pulse pressure hypertension is present [34, 35].

Preoperative systolic hypertension and widened pulse pressure are known predictors of ischemic postoperative events [35, 36••, 37]. Perioperative BP lability in patients undergoing cardiac surgery increases the risk for stroke, neurocognitive dysfunction, renal injury, and 30-day mortality [36••, 37, 38••, 39–41]. In a prospective study of 16,184 consecutive adult patients undergoing cardiac surgery, the overall incidence of stroke was 4.6 % (CABG 3.8 %; beating-heart CABG 1.9 %; aortic valve 4.8 %; mitral valve 8.8 %; double/triple valve 9.7 %; CABG and valve 7.4 %) [42]. Stroke after cardiac surgery was found to be proportional to presenting pulse pressure. Among patients undergoing cardiac surgery, the

mean pulse pressure was greater in patients who suffered a stroke (81 vs. 65 mm Hg), with each additional 10 mm Hg contributing additive risk (odds ratio [OR] 1.35; 95 % confidence interval [CI], 1.13–1.62; p=0.001). In addition, poor perioperative hemodynamic control during cardiac surgery is also associated with increased risk of postoperative acute kidney injury [43, 44••, 45–54].

Intraoperative BP variability (independent from presenting BP before surgery) in patients undergoing cardiac surgery has been demonstrated to influence 30-day postoperative mortality. Among several indices of BP variability, the mean duration of systolic BP excursion either above or below a clinical target range was shown to be predictive of 30-day mortality in patients undergoing cardiac surgery [55••]. The ECLIPSE (Evaluation of CLevidipine In the Perioperative Treatment of Hypertension Assessing Safety Events) program compared clevidipine to nitroglycerin (NTG), sodium nitroprusside (SNP), and nicardipine (NIC) for the treatment of perioperative hypertension in patients undergoing cardiac surgery. ECLIPSE data were used to investigate the treatment-independent association between systolic BP control, a secondary endpoint of the ECLIPSE program, and 30-day mortality. Perioperative BP lability in cardiac surgical patients was associated with 30-day mortality proportional to the extent of SBP excursions outside 75–135 mmHg intraoperatively and 85–145 mmHg pre- and postoperatively. This predictive risk factor was more substantial among high-risk than low-risk patients. Aronson et al. reported an odds ratio of 1.16 (95 % CI, 1.04–1.30) for 30-day mortality risk per incremental systolic BP excursion of 60 mm Hg×min/h. Based upon the survival curves, the estimated survival probabilities were proportional to systolic BP duration×magnitude of excursion outside predefined thresholds during cardiac surgery (area under the curve – AUC). Higher AUC quartiles (Fig. 1) were associated with higher probabilities of mortality. Specifically, patients in the fourth AUC quartile (AUC≥38.41 mm Hg×min/h) experienced a significantly higher risk of 30-day mortality compared with patients in the pooled group of first to third AUC quartiles (log-rank p=0.0167). Moreover, patients in the third quartile (38.41 mm Hg×min/h>AUC≥ 9.44 mm Hg×min/h) experienced a significantly higher risk of 30-day mortality compared with patients in the pooled group of first and second AUC quartiles (log-rank p=0.0339).

Acute Mitral Insufficiency

Uncontrolled perioperative systemic hypertension can exacerbate mitral insufficiency. Acute hypertension can significantly exacerbate ischemic mitral regurgitation due to left ventricular systolic dysfunction and subendocardial myocardial ischemia [56].

Hypertension Resulting in Acute Decompensated Heart Failure

Acute systolic hypertension can lead to decompensated left ventricular function [57] due to an afterload mismatch of the left ventricle with diminished preload reserve. It addition, patients with acute hypertension during surgery – particularly the elderly – can experience acute pulmonary edema with normal left ventricular systolic or diastolic dysfunction [58, 59].

BP Control and Outcomes in Non-Cardiac Surgery

Aortic Dissection

Aortic dissection [60, 61] with hypertension is associated with a one-year mortality rate of 70–90 % and a five-year mortality rate of nearly 100 %. In aortic dissection, target organ damage occurs in the form of retrograde dissection into the heart, involvement of aortic branches, and endothelial injury. Mortality is four times higher in patients with critical end-organ damage. With adequate BP control, the one- and five-year mortality rates fall to 25 % and 50 %, respectively. Poorly controlled hypertension may cause aortic disruption, with potentially fatal bleeding, as well as progression of the intimal flap in the case of aortic dissection. Few randomized controlled trials are available to provide guidance on the treatment of hypertension in aortic dissection. A vasodilator alone promotes reflex tachycardia, increased speed of aortic ejection, and propagation of the dissection. As dissection is dependent not only upon elevated BP but also the speed of ventricular ejection, the best treatment option for these patients is the combination of a beta- blocker and a vasodilator. Antihypertensive therapy in acute aortic dissection should reduce aortic stress (dp/dt) in order to slow the propagation of the dissection and prevent aortic rupture, as well as to prevent myocardial ischemia, decrease left ventricular afterload, decrease myocardial oxygen consumption, and prevent rupture and bleeding from suture lines.

Stroke

Stroke in the perioperative period is primarily associated with major cardiovascular procedures, although it has been reported after general surgery as well [62]. A recent study of acute ischemic stroke in the non-cardiovascular population reported a 0.7 % incidence of stroke after hemicolectomy, 0.2 % after hip replacement, and 0.6 % after lobectomy or segmental lung resection. In patients 65 years and older, the incidence rose to 1.0 %, 0.3 %, and 0.8 %, respectively. Importantly, perioperative stroke was associated with increased mortality.

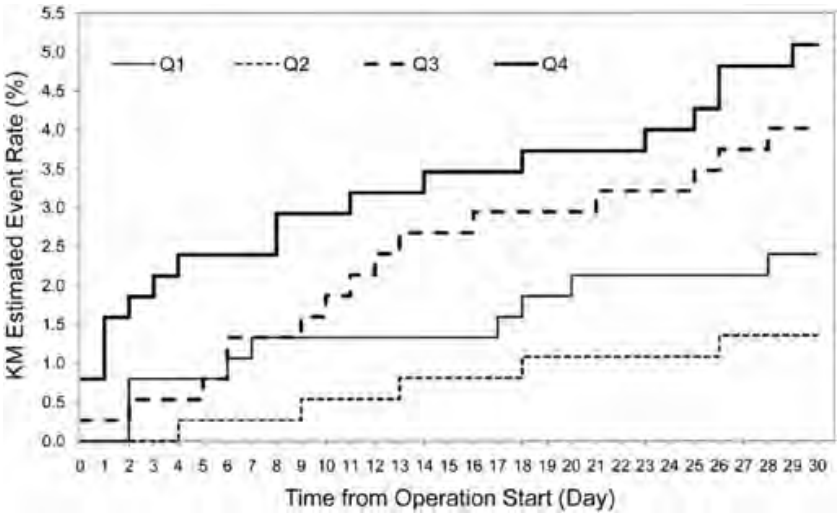

Fig. 1 Area under the curve quartile demonstration of 30-day Kaplan-Meier survival curves for BP control. BP control was associated with 30-day mortality in cardiac surgical patients, proportionate to the extent of SBP excursions outside 75–135 mmHg intraoperatively and 85–145 mmHg pre- and postoperatively. (Used with permission from Aronson, Dyke, Levy et al. Does perioperative systolic blood pressure variability predict mortality after cardiac surgery? An exploratory analysis of the ECLIPSE trials. Anesth Analg. 2011;113(1):19–30)

The need for tight BP control appears to be particularly critical, as both hypertension and hypotension are associated with increased risk of stroke. Data from the recent POISE (PeriOperative ISchemic Evaluation Study) trial [63] suggest that perioperative hypotension may be a mechanism for stroke in patients undergoing non-cardiac surgery.

Bijker et al. [64] investigated the incidence of stroke in 48,241 patients who underwent non-cardiac and non-neurosurgical procedures (2002–2009). They found a total of 42 cases of ischemic stroke (0.09 %) within 10 days after surgery, which were matched to 252 control patients. The authors concluded that the duration that intraoperative MAP was decreased >30 % from baseline was associated with the occurrence of postoperative stroke. In another study, Davis et al. [65] reviewed the charts of 129 patients and found that systolic BP >140 mmHg following non-cardiac surgery was an independent predictor for good neurologic outcome.

Preoperative hypertension was determined to be associated with perioperative stroke in an analysis of data on over 523,000 non-cardiac, non-neurologic surgery patients in the NSQIP database. An incidence of stroke of 0.1 % was noted, and was found to be influenced by the surgical procedure as well as preoperative hypertension. Perioperative stroke is associated with a four- to eightfold increase in perioperative 30-day mortality [66].

Intracerebral Bleeding

Perioperative BP lability is common in patients undergoing neurologic surgery, and increases the risk for stroke, neurocognitive dysfunction, and intracerebral bleeding with hematoma expansion [67]. In a case-control comparative analysis of 69 patients who developed intracerebral hemorrhage (ICH) postoperatively and 138 control subjects, 62 % of patients with ICH had perioperative hypertension versus 34 % of controls ($p<0.001$). Unlike ICH secondary to rupture of an arteriovenous malformation or to an intracerebral aneurysm, there is no clear evidence that increased BP causes more bleeding in patients with spontaneous ICH, and a sharp decline in BP may compromise brain perfusion [68, 69]. There are no specific recommendations on the most beneficial BP for a patient with ICH, although reducing SBP to <160/90 mm Hg during the first six hours of onset of ICH is associated with better functional outcome, and increased bleeding has been found to be more common in patients with isolated systolic BP [70].

Subarachnoid Hemorrhage

To date, no well-controlled studies have determined whether BP control in acute subarachnoid hemorrhage (SAH) affects re-bleeding, which is likely related to variations or changes in BP rather than absolute BP. In a retrospective review of 179 patients admitted within 24 hours of SAH, 17 % experienced re-hemorrhage that was associated with a systolic BP >150 mm Hg [71]. Another study found that re-bleeding was more common in patients with a systolic BP >160 mm Hg [72].

BP Control and Outcomes in Non-Cardiac and Non-Vascular Surgery

Rebound Hypertension After Withdrawal of Antihypertensive Medications

Clonidine withdrawal syndrome, which is characterized by excessive sympathetic activity with rebound hypertension,

often resembles the hypertensive crisis of pheochromocytoma. Symptoms of clonidine withdrawal syndrome are typically encountered 18–24 hours after sudden discontinuation of clonidine in patients taking more than 1.0 mg/day [73–76]. The concomitant use of a nonselective beta-blocker may exacerbate clonidine withdrawal syndrome. Dexmedetomidine is a rapidly acting parenteral form of this drug for use in patients who are unable to take oral medication in the perioperative period.

Hypertension Caused by Acute Catecholamine Excess (e.g., Pheochromocytoma)

Hypertensive crisis related to overdose of recreational drugs (e.g., cocaine, amphetamines, lysergic acid diethylamide [LSD] or ecstasy) is attributable to consumption of monoamine oxidase. Acute coronary syndrome arising from cocaine use is characterized by adrenergic receptor stimulation, and thus the treatment of choice is alpha-adrenergic blockers. Beta-blockers should be avoided, as they may give rise to an alpha-adrenergic storm and enhance the toxicity of cocaine.

Hypertension related to acute withdrawal syndrome is often caused by cessation of treatment with beta-adrenergic agonists. Pheochromocytoma is a manifestation of acute catecholamine excess, which is associated with as high as 80 % mortality when unsuspected, and is best treated with the alpha-1 blocker phentolamine, to which a calcium channel blocker may be added (nicardipine or clevidipine). Beta-adrenergic antagonists should be avoided in order to prevent beta-receptor antagonism, which would result in unopposed alpha-adrenergic activity, with a secondary effect of increasing BP level [77].

Hypertensive Crisis in Pregnancy: Preeclampsia and Eclampsia

Hypertension is one of the processes that can complicate a pregnancy, and can lead to preeclampsia. This syndrome, characterized by BP >140/90 mm Hg and proteinuria >300 mg/24 hours, usually occurs after 20 weeks gestation. Depending upon the series of patients, preeclampsia may affect up to 12 % of pregnancies, and is estimated to be involved in 18 % of maternal deaths. Initial treatment includes volume expansion, magnesium sulfate for seizure prophylaxis, and BP control. The objective, in addition to treating severe hypertension, is to avoid compromising cerebral and placental blood flow, as BP in this situation is most labile. The drugs of choice are labetalol and clevidipine, as both are safe and effective, easily titrated, and have a short half-life.

A rare and potentially life-threatening complication of preeclampsia is spontaneous rupture of a subcapsular liver hematoma. This occurs in approximately 1/45,000 live births, and the liver hematoma is often not suspected until it ruptures. In these cases, perioperative management is focused on managing acute hypotension due to blood loss [78, 79].

Severed Spinal Cord with Autonomic Dysreflexia

Autonomic dysreflexia is a medical emergency commonly occurring in patients with spinal cord injury at the T6 level and above. Hypertension is the most common presentation of autonomic dysreflexia, usually precipitated by bladder or rectal distension. This condition, if not treated early, will lead to uncontrolled hypertension and death due to brain hemorrhage. While usually occurring in patients with spinal cord injury, it may also result from non-traumatic causes such as spinal cord tumor or neurosurgery above the T6 level, and is associated with medical conditions such as multiple sclerosis and catecholamine-secreting tumors as well. It is not fully known how common autonomic dysreflexia is in patients with spinal cord injury [80]. The accepted mechanistic theory relates to an exaggerated reaction of sympathetic preganglionic neurons to afferent stimuli. The common stimulus for autonomic dysreflexia is bladder and rectal distension, but it can also be precipitated by urinary tract infection, deep venous thrombosis, skin irritants, hot or cold stimuli, dysmenorrhea, hemorrhoids, fractures, acute abdomen syndromes, and surgical interventions [81–83].

Summary/Conclusions

Hypertensive crises in the perioperative setting usually occur in hypertensive patients who are untreated or inadequately treated. It should be noted that moderately high BP values in the perioperative setting can lead to emergency situations in a previously normotensive person. Acute intraoperative changes in BP, common in the setting of pre-existing hypertension, may be a consequence of excessive release of catecholamines, rapid intravascular volume shifts, peripheral vasoconstriction, reduced baroreceptor sensitivity, renin-angiotensin activation, altered cardiac reflexes, inadequate anesthesia, reperfusion injury, or aortic occlusive clamps, as well as neural, humoral, and cellular responses. Increased BP during surgery may set up a unique pathophysiologic basis for perioperative vascular injury, which can trigger hyperinflammatory and procoagulation conditions as well as platelet and endothelial dysfunction that contribute to adverse events. Although perioperative hypertensive emergencies are uncommon in the traditional definition of hypertensive crisis terminology that characterizes an emergency as impending end-organ damage requiring treatment, acute perioperative hypertension requiring immediate management is indeed very common. As such, the criteria for defining perioperative hypertension, as well as

recommendations for treatment, should be distinct from ambulatory criteria in hypertensive emergency and hypertensive urgency settings.

Compliance with Ethics Guidelines

Conflict of Interest Solomon Aronson has received consultancy fees from The Medicines Company.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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