Anesthetic Management of the Hypertensive Patient: Part I

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Hypertension is an important health challenge that affects millions of people across the world and is a major risk factor for cardiovascular disease. It is critical that anesthesia providers have a working knowledge of the systemic implications of hypertension. This review article will discuss the medical definitions of hypertension, the physiology of maintaining blood pressure, outpatient treatment of hypertension, anesthetic implications, and the common medications used by anesthesia providers in the treatment of hypertension. Part I will provide an overview of hypertension and blood pressure regulation. In addition, drugs affecting predominantly renal control of hypertension, such as diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and renin-inhibiting agents, will be discussed. In part II, the remaining major antihypertensive medications will be reviewed as well as anesthetic implications of managing patients with hypertension.

Key Words: Hypertension; Antihypertensives; Anesthetic; Review.

Blood pressure typically fluctuates throughout the day, but hypertension, or high blood pressure, can cause undue stress on the patient's heart, vasculature, and other organs, leading to a variety of health problems. Those health problems include heart disease and stroke, which are the leading causes of death in the United States.[1] Almost half of Americans are identified as having high blood pressure according to the recent classification changes of high blood pressure in 2017 by the American Heart Association and the American College of Cardiology. Only an estimated 54% of those people have their condition under control.[2] Hundreds of thousands of deaths each year are primarily due to high blood pressure,[1] and this disease ends up costing patients in the United States $48.6 billion each year.[3]

Because of the growing public health concern that is associated with hypertension, it is important that dental providers are knowledgeable about the implications, management, and treatment options available for the hypertensive patient. This article will provide a contemporary review of the definition, physiology, pharmacologic management, and other concerns surrounding the anesthetic management of the hypertensive patient.

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CLASSIFICATION AND GUIDELINES

There are 2 types of hypertension: essential hypertension and secondary hypertension. Essential hypertension accounts for approximately 95% of the cases and represents a form of hypertension without a clear cause.[4] However, many health care providers recognize that a number of factors may contribute to increased blood pressure, including but not limited to obesity, insulin resistance, high alcohol intake, high salt intake, aging, sedentary lifestyle, stress, low potassium intake, and low calcium intake.[5] Secondary hypertension has a clear etiology with many causes that may include renal disease, hyperthyroidism, obstructive sleep apnea, hyperaldosteronism, and many others.[4]

There are 4 levels of blood pressure, as outlined by the American Heart Association/American College of Cardiology in the updated 2017 guidelines (see Table 1). The choice and the naming of the categories were based on a pragmatic interpretation of blood pressure–related cardiovascular disease risk and benefit of blood pressure reduction in clinical trials. Prior to diagnosing a person with hypertension, it is important to use an average based on greater than 2 readings obtained on more than 2 occasions to estimate the individual's blood pressure level.[5] The new guidelines also recommend allowing patients to rest at least 5 minutes prior to taking the blood pressure readings and taking the blood pressure measurement while the patient is seated, feet on the floor, and the arm at the level of the heart with an appropriately sized cuff that encircles at least 80% of the arm.[5,6]

Table 1. Classification of Hypertension*

Category	*Systolic, mm Hg*		*Diastolic, mm Hg*
Optimal blood pressure	<120	and	<80
Elevated	120–129	and	<80
Stage 1 hypertension	130–139	or	80–89
Stage 2 hypertension	≥140	or	≥90
Hypertensive urgency/crisis	>180	or	>120

* Updated in October 2017 according to the American College of Cardiology Foundation and the American Heart Association, Inc.

Currently, optimal blood pressure is a systolic pressure of less than 120 mm Hg and a diastolic pressure of less than 80 mm Hg. A patient is considered to have an elevated blood pressure if they have a systolic reading of 120 to 139 mm Hg and a diastolic reading of less than 80 mm Hg. The previous reading of 120/80 mm Hg is no longer considered ideal and is now categorized as stage 1 hypertension. Stage 1 hypertension begins when the systolic pressure is 130 to 139 mm Hg or the diastolic pressure is between 80 and 89 mm Hg. Stage 2 hypertension is now apparent when the systolic pressure is equal to or greater than 140 mm Hg or the diastolic is equal to or greater than 90 mm Hg. A hypertensive urgency or crisis involves a systolic pressure higher than 180 mm Hg or a diastolic reading higher than 120 mm Hg and the absence or presence of specific symptoms. The recommended blood pressure classification system is most valuable in untreated adults as an aid in decisions about prevention or treatment of high blood pressure. However, it is also useful in assessing the success of interventions to reduce blood pressure.[5]

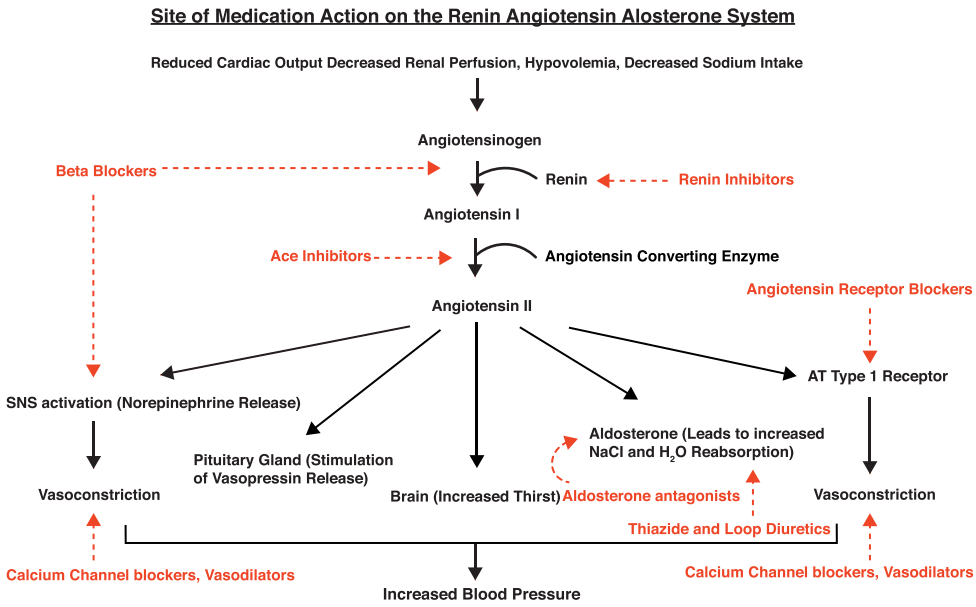
PHYSIOLOGY OF BLOOD PRESSURE REGULATION

The physiology of blood pressure regulation on a moment-to-moment basis, a daily basis, and a lifetime basis consists of a delicate balance of nervous system and hormonal control mechanisms to maintain arterial pressure at or near normal. Mean arterial pressure is the steady-state component of blood pressure and is crucial as the body regulates proper perfusion pressures to vital organs and also optimizes cardiovascular work. The basic scheme by which blood pressure is regulated is through a feedback control system consisting of pressure sensors and effector mechanisms.[7] The most important mechanisms for regulating blood pressure are a fast, neurally mediated baroreceptor mechanism and a slower, hormonally regulated renin-angiotensin-aldosterone mechanism.[8]

The sympathetic vasoconstrictor system is important in maintaining proper homeostatic blood pressure via the vasomotor center. The vasomotor center is located in the reticular substance of the medulla and in the lower third of the pons and is responsible for providing sympathetic and parasympathetic outflow to the effector organs. This center transmits sympathetic impulses through the spinal cord and peripheral sympathetic nerves to virtually all arteries, arterioles, and veins in the body as well as parasympathetic impulses through the vagus nerve to the heart.[9] The postganglionic nerve fibers of the sympathetic nervous system that terminate in the vasculature functionally produce a level of partial constriction and also have the ability both to dilate and to constrict adaptively around this level of resting tone.[7] Through this powerful influence of sympathetic outflow from the vasomotor center, the body can regulate vascular vasoconstriction and heart rate to maintain normal blood pressure values.

The most well-known autonomic nervous system mechanism for regulating arterial pressure is the baroreceptor reflex. This reflex is initiated by stretch receptors within the aortic arch and carotid bodies that transmit feedback signals to the central nervous system for minute-to-minute regulation of blood pressure. The baroreceptors in the carotid sinus near the bifurcation of the common carotid arteries are most sensitive to decreasing arterial pressures, whereas the baroreceptors in the aortic arch are most sensitive to increasing arterial pressures.[8] The baroreceptors respond rapidly to changes in arterial pressure; in fact, the rate of impulse firing increases within a fraction of a second during each systole and decreases again during diastole.[9]

The baroreceptor reflex signals the nucleus tracts solitarius in the medullary portion of the brain stem. These baroreceptor signals inhibit the vasoconstrictor center in the medulla and excite the vagal center, which stimulates parasympathetic activity via the glossopharyngeal nerve from the carotid sinus receptors and the vagus nerve from the receptors in the aortic arch. The resultant parasympathetic activity causes predominately (1) decreased heart rate and strength of cardiac contraction and less so (2) vasodilation of veins and arterioles.[10] This decreases the blood pressure due to a decline in cardiac output and peripheral vascular resistance. This baroreceptor reflex is also crucial in maintaining relatively constant blood pressures despite positional changes, such as when a person stands up after lying down or other activities that increase blood pressure, such as eating and exercise. A primary purpose of the arterial baroreceptor system is to reduce the minute-by-minute variation in arterial pressure to about one-third that which would occur if the baroreceptor system were not present.[9]



The renin angiotensin aldosterone system is a relatively slow, hormonal mechanism whereby there is a long-term blood pressure regulation.

The renin-angiotensin-aldosterone system (RAAS; see the Figure) is part of a powerful feedback system for long-term control of arterial pressure and volume homeostasis.[11] The RAAS is stimulated by reduced cardiac output, decreased renal perfusion, hypovolemia, and decreased sodium intake. The stimulation of the RAAS traditionally begins with angiotensinogen, which is generated by the liver and cleaved by renin, released from the juxtaglomerular cells in the kidneys, in response to hypotension or decreased renal perfusion pressure, to form angiotensin I. Angiotensin I is further cleaved by angiotensin-converting enzyme (ACE) produced primarily by the lungs to form the active hormone angiotensin II.[12] Angiotensin II is a hormone that acts on a variety of sites to increase blood pressure, primarily by binding to specialized receptors that induce vasoconstriction. Angiotensin II has other functions as it increases the neuroanatomic center for thirst, sodium appetite, and cardiovascular control, making extensive connections with the hypothalamus, limbic system, and brain stem.[13] Angiotensin II also stimulates the adrenal cortex to release aldosterone, which in turn promotes the retention of sodium and free water within the distal tubules of the kidneys and the excretion of potassium. Specifically, angiotensin II binds to angiotensin II (AT type 1) receptors on the blood vessels, resulting in vasoconstriction as well as constriction in specific organs, including the heart, adrenal cortex, and brain.[14]

In addition to the humoral control of angiotensin II in the RAAS, there are other hormones that are vasoactive and contribute to the regulation of blood pressure. Vasopressin, also known as antidiuretic hormone, is the key humoral component of the vasopressinergic system, which has a profound effect on blood pressure control. Vasopressin is synthesized in the paraventricular and supraoptic nuclei in the hypothalamus, and the most potent stimuli for vasopressin release are hypertonic conditions, severe hypotension, and hypovolemia.[15] The vasopressin receptors that are crucial in blood pressure control are V_1 receptors located on vascular smooth muscle and produce peripheral vasoconstriction, while V_2 receptors located in the collecting ducts in the kidneys promote water retention.[16]

Other regulators of blood pressure include another hormone, atrial natriuretic peptide, which is released when the atrial stretch receptors are stimulated. This results in increased natriuresis (increased sodium excretion) with resultant decrease in blood volume. In addition, chemoreceptors located in the carotid and aortic bodies are stimulated by low arterial oxygen concentrations and also play a role in blood pressure regulation. These chemoreceptors are stimulated when there is diminished blood flow that causes a decrease of oxygen and an increase in carbon dioxide and hydrogen ions (lowered serum pH). This chemoreceptor reflex is not a powerful arterial pressure controller until the pressure falls below 80 mm Hg.[9] Although the chemoreceptors indeed play a role in the regulation of blood pressure, they have a much more important role in respiratory control. Increased arterial partial pressure of carbon dioxide in cerebral ischemia also increases

blood pressure, which stimulates sympathetic outflow to the heart and blood vessels.

TREATMENT RECOMMENDATIONS

The first treatment recommendation for patients with hypertension primarily involves lifestyle modification. Weight loss is the most effective of all the nonpharmacologic measures to prevent and treat hypertension,[17] although increased physical activity and diet modification are usually recommended as well. The first-line pharmacologic treatment for uncomplicated stage 1 hypertension is usually a thiazide-type diuretic, an angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), or a calcium channel blocker. In stage 2 hypertension, the treatment typically expands to a 2-drug combination, which usually includes the aforementioned drugs and the introduction of β-adrenergic receptor blocking agents (β-blockers) or a second drug from the stage 1 category.[18]

The treatment of patients with hypertension is variable and contingent on other comorbidities, such as chronic kidney disease, diabetes mellitus, or heart failure. The treatment goals and medications are target oriented, and patients have a wide variety of target blood pressures and medication combinations for optimal treatment. The American Heart Association recommends that for most patients with hypertension, including patients with stable cardiovascular disease, chronic kidney disease, diabetes mellitus, and age-related issues, the target blood pressure treatment goal is <130/80 mm Hg.[5]

Common Antihypertensive Medications and Their Anesthetic Implications

A thorough understanding of the common antihypertensive medications is beneficial to all health care providers during the management of these patients. The major classes of antihypertensive agents include diuretics, ACEIs, ARBs, direct renin inhibitors, calcium channel blockers, α-adrenergic blockers, β-adrenergic blockers, α2-adrenergic agonists, and vasodilators. This also includes being familiar with the medications or factors that could worsen blood pressure control (Table 2).

Diuretics. Diuretics increase the rate of urine volume output and clinically act by decreasing renal tubular sodium reabsorption, causing natriuresis, which in turn leads to diuresis (increased water excretion).[9] Most diuretics decrease extracellular fluid volume by decreasing the sodium content in the body. Where sodium goes, water follows, and diuretics can be very effective in decreasing intravascular fluid volume to control blood pressure. There are many types of diuretics that mainly have a similar goal of inhibiting the tubular sodium reabsorption but have different mechanisms of action at different points in the nephron. Some common diuretics and their mechanisms and sites of action are outlined in Table 3.

Table 2. Factors That May Interfere With Blood Pressure Control

Commonly used medications[19]
• Nonsteroidal anti-inflammatory drugs (NSAIDs)
• Oral contraceptives
• Some antidepressants (eg, tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitors, bupropion, monoamine oxidase inhibitors)
• Sympathomimetics (eg, decongestants such as pseudoephedrine/ephedrine)
• Corticosteroids
Recreational or illicit drugs[19]
• Alcohol
• Cocaine
• Amphetamines
• Chewing tobacco
Significant predictors of nonadherence to antihypertensive medications[20,21]
• Age <50 y
• Male gender
• Hispanic or African American
• Low family income (<$55,000/y)
• No health insurance
• No medical visits within past year

Thiazide diuretics inhibit sodium transport in the distal convoluted tubule and also in part of the cortical ascending limb of the loop of Henle.[14] Loop diuretics act on the ascending limb of the loop of Henle at the sodium, potassium, and chloride symporters or membrane transporter proteins and inhibit sodium, potassium, and chloride uptake. Thiazide diuretics have a longer duration of action than loop diuretics and therefore are usually more effective for long-term hypertension management. It is important to recognize the effects that these diuretics have on calcium and potassium regulation. Thiazide diuretics activate epithelial sodium channels (which are inhibited by calcium) and thereby favor potassium secretion.[22] With regard to calcium levels, thiazide diuretics and loop diuretics have opposite effects on calcium balance; whereas thiazides promote calcium retention, loop diuretics enhance urinary calcium loss. This is possibly one reason why loop diuretics, which increase distal calcium delivery, result in lesser degrees of hypokalemia.[22,23]

Aldosterone antagonists, specifically spironolactone, act on the distal nephron to increase the amounts of

Table 3. Classes of Diuretics and Their Mechanisms and Sites of Action

Class of Diuretic	*Mechanism of Action*	*Site of Action*
Thiazide diuretics (hydrochlorothiazide)	Inhibit Na^+ and Cl^- transport	Early distal tubules
Loop diuretics (furosemide)	Inhibit Na^+, K^+, Cl^- uptake	Loop of Henle
Aldosterone antagonists (spironolactone)	Inhibit Na^+ reabsorption and K^+ secretion	Collecting tubules
Osmotic diuretics (mannitol)	Increase osmotic pressure and inhibit H_2O and solute reabsorption	Primarily proximal tubules
Carbonic anhydrase inhibitors (acetazolamide)	Inhibits carbonic anhydrase, which inhibits HCO_3^- and reduces Na^+ reabsorption	Collecting tubules
Sodium channel blockers (triamterene)	Directly inhibit Na^+ reabsorption and K^+ secretion	Collecting tubules

sodium and water to be excreted while potassium is retained.[14] Aldosterone antagonists provide competitive blockade of epithelial aldosterone receptors in the distal tubule and collecting duct.[24] Osmotic diuretics such as mannitol decrease water reabsorption by increasing the osmotic pressure of tubular fluid and are primarily used in the operating room and critical care settings.[9] Carbonic anhydrase inhibitors, as the name implies, inhibit the enzyme carbonic anhydrase, which decreases the reabsorption of bicarbonate and therefore reduces sodium reabsorption, resulting in diuresis. Acetozolamide, the classic carbonic anhydrase inhibitor used in altitude sickness, treatment of glaucoma, and control of edema in congestive heart failure, is seldom used for long-term treatment of hypertension. Sodium channel blockers, such as triamterene, which has decreased in use recently, act directly on the sodium channels of the collecting tubules and block sodium reabsorption to create their diuretic effects. This is similar to aldosterone antagonists, but instead of acting indirectly through aldosterone, these diuretics directly block the entry of sodium in the sodium channels located in the collecting tubules. The latter 2 agents are termed *potassium-sparing* diuretics and can be combined with thiazide diuretics to minimize hypokalemia.

Anesthetic Implications. Because thiazide and loop diuretics are not potassium sparing, an adverse effect is hypokalemia with metabolic acidosis. In contrast to this, the potassium-sparing agents may produce hyperkalemia. Because of this, it is important to monitor serum potassium levels after administration of these diuretics. In an outpatient setting, 1-time potassium lab values are practical. The measurement of a 24-hour urinary potassium excretion is appropriate for patients who are at high risk, for example, those patients with congestive heart failure.[25]

Diuretics can cause dehydration. The volume status of a patient can be difficult to assess in the outpatient and ambulatory setting without laboratory values, yet indirect measures of volume status may include an observation of mucous membranes, quality of peripheral pulses, increasing resting heart rate accompanied by decreased blood pressures from normal, orthostatic heart rate and blood pressure changes from positional changes, urine specific gravity, and decreased urinary flow rates and output.[26] The early reduction in blood pressure with thiazide use is due to a reduction in blood volume, and chronic thiazide treatment results in blood pressure control through reduced vascular resistance despite return of fluid to pretreatment levels.[14] Thiazide diuretics may aggravate glucose control, especially in combination with β-blockers.[24] Although modest increases in blood glucose are reported, this is an uncommon presentation in the outpatient setting unless the patient has a history of uncontrolled blood glucose levels. In addition, thiazide diuretics appear to prolong neuromuscular blockade with nondepolarizing neuromuscular blockers. Diuretics may be continued in the perioperative period but can be discontinued if there is reason to suspect volume depletion or hypokalemia.[27] In addition, diuretic-induced volume depletion on a biochemical level is due to the loss of sodium from the body. Diuretics, along with other hypertension medications, may induce a hyponatremic state, which leads to decreased extracellular fluid osmotic pressure. This results in a shift of fluid into the cells and therefore causes a hypovolemic state.[28] Many long-term hypertensive patients therefore have a masked state of hypovolemia. Prudent volume augmentation in ambulatory settings with a crystalloid solution prior to the induction of anesthesia may help with masked hypovolemia.

ACEIs. ACEIs block the conversion of angiotensin I to angiotensin II in the renin-angiotensin system. Blocking angiotensin II formation is a key antihypertensive strategy since angiotensin II promotes vasoconstriction as well as salt and water retention by stimulating aldosterone secretion by the adrenal gland and thus sodium reabsorption by the proximal tubule.[29] Furthermore, ACEIs promote the accumulation of bradykinin in or at the vessel wall.[30] Bradykinin is a powerful vasodilator that increases capillary permeability, possibly leading to angioedema (0.3%-0.6%), which can involve the glottic or laryngeal regions.[31] In

addition, there is a bradykinin-evoked sensitization of airway sensory nerves, coupled with an accumulation of kinins, substance P, and prostaglandins, which may contribute to the pathogenesis of the common and bothersome ACEI cough.[32,33] This ACEI cough can occur in up to 10% of patients and is the most common adverse effect of ACEIs. The treatment of choice is to discontinue the ACEI.[32]

There are 3 classes of ACEIs that differ in potency, bioavailability, half-life, and route of elimination. Class I ACEIs, such as captopril, have the shortest half-life (6–12 hours vs 24 hours) and contain a problematic sulfhydryl (not sulfonamide) group that can cause a skin rash, loss of taste, neutropenia, and proteinuria.[14] Class II ACEIs, such as enalapril, are prodrugs that are converted to active drugs by the liver. Enalaprilat is a parenteral form that can be administered to patients on ACEIs during the perioperative period. Lisinopril is the only class III ACEI and is not a prodrug, but it is water soluble and excreted unchanged by the kidneys without hepatic metabolism.[14]

Anesthetic Implications. Because of an increased risk of refractory hypotension, ACEIs are typically held on the day of surgery if general anesthesia or some type of deep sedation is planned, particularly during induction of general anesthesia. Coriat and colleagues[34] found that ACEIs were associated with hypotension in 100% of patients during induction versus approximately 20% in whom ACEIs were withheld on the morning of the surgical procedure. If the patient did take their usual dose of ACEI on the day of surgery, some sources suggest administering an intravenous bolus of 250 mL to 1 L of crystalloid solution prior to the induction of general anesthesia to decrease the severity of hypotension.[35] If traditional vasopressor options such as phenylephrine or ephedrine have been used without the desired clinical response for the treatment of hypotension, then further treatment options include vasopressin, epinephrine, and norepinephrine. ACEIs may generally be continued during the perioperative period if moderate sedation is planned.

As mentioned above, angioedema is a known adverse effect of ACEIs. It is important to make the distinction between the histamine-mediated edema that is often associated with urticaria or anaphylaxis and the bradykinin-mediated angioedema that is associated with ACEI use.[30] Although the incidence of ACEI angioedema is low, Banerji et al[36] reported that 30% of angioedema cases that presented to the emergency department were due to ACEIs. Discontinuation of the ACEI, maintaining airway patency, and supportive therapies are the mainstay of treatment.[35] Corticosteroids and antihistamines are typically given to rule out histamine-mediated angioedema and are usually ineffective in the bradykinin-mediated angioedema, as seen with ACEIs. Some newer agents, such as bradykinin receptor antagonists such as icatibant or kallikrein inhibitors (eg, ecallantide), may provide novel alternatives for the treatment of ACEI-induced angioedema.[37,38]

ARBs. ARBs, otherwise known as angiotensin II receptor antagonists, whose generic names all end in -*sartan*, block angiotensin II from binding to the angiotensin II (AT type 1) receptor on vascular smooth muscle cells. This blockade results in a decrease in peripheral vasoconstriction, thereby decreasing systemic vascular resistance and arterial blood pressure and increasing angiotensin II and normal bradykinin plasma levels.[39]

Anesthetic Implications. ARBs have no effect on bradykinin metabolism; therefore, their use is associated with significantly reduced incidence of cough and angioedema as compared with ACEIs. Because of this decreased incidence of angioedema, some patients are shifted toward ARB therapy from ACEI therapy. However, it is important to note that there is still a small angioedema risk involved. The current thinking among many anesthesiologists is that, similar to ACEIs, ARBs should be withheld on the day of surgery to avoid refractory hypotension during induction of general anesthesia. Heightened awareness of the possible refractory hypotension that can occur with ACEIs and ARBs and recognition of the need to treat with an adequate dose of vasopressin, epinephrine, or norepinephrine are required.[40] In addition to the refractory hypotension that can occur during induction, there have been incidents of rebound hypertension following the discontinuation of ARBs. The risks and benefits of continuing or withholding ARBs should be taken into consideration during any medication adjustment in the perioperative period.

Direct Renin Inhibitors. The direct renin inhibitor aliskiren binds to the S3bp binding site of renin and inhibits the RAAS by blocking the conversion of angiotensinogen to angiotensin I.[14] This is a relatively new drug that received approval from the US Food and Drug Administration in 2007. Because it does not significantly affect the cytochrome P450 system, it has been associated with few drug interactions.[41]

Anesthetic Implications. It is well known that ACEIs and ARBs are associated with refractory hypotension during induction of general anesthesia, and it can be assumed that direct renin inhibitors, which act earlier on the same pathway and produce similar if not more exaggerated downstream effects, would have similar anesthetic implications.[42] If the standard treatment for postinduction hypotension, such as a fluid bolus, ephedrine, or phenylephrine administrations, is ineffec-

tive, then an infusion of vasopressin (0.03–1 U/min) or methylene blue (2 mg/kg over 20 minutes) can be given with documented success.[43] Aliskiren has also been associated with an increased incidence of nonfatal stroke, renal complications, and hyperkalemia.[14]

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CONTINUING EDUCATION QUESTIONS

This continuing education (CE) program is designed for dentists who desire to advance their understanding of pain and anxiety control in clinical practice. After reading the designated article, the participant should be able to evaluate and utilize the information appropriately in providing patient care.

The American Dental Society of Anesthesiology (ADSA) is accredited by the American Dental Association and Academy of General Dentistry to sponsor CE for dentists and will award CE credit for each article completed. You must answer 3 of the 4 questions correctly to receive credit.

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CE questions must be completed within 3 months and prior to the next issue.

1. All of the following are levels of hypertension according to the new American Heart Association/ the American College of Cardiology hypertension guidelines published in October 2017, except:

   A. Elevated
   B. Prehypertension
   C. Stage 1
   D. Stage 2

2. Angiotensin-converting enzyme inhibitors (ACEIs) promote the accumulation of which substance that can lead to airway angioedema?

   A. Aldosterone
   B. Bradykinin
   C. Norepinephrine
   D. Renin

3. Which of the following blood pressure regulation mechanisms provides moment-to-moment control of blood pressure?

   A. Autonomic nervous system
   B. Baroreceptor reflex
   C. Renin-angiotensin-aldosterone system
   D. Vasopressinergic system

4. Which of the following medications is generally NOT a common first-line outpatient treatment for hypertension?

   A. ACEIs
   B. Angiotensin receptor antagonists
   C. β-blockers
   D. Diuretics