Management of Hypotension Associated With Angiotensin-Axis Blockade and General Anesthesia Administration

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HYPOTENSION, SOMETIMES REFRACTORY, is a well-recognized phenomenon associated with the administration of general anesthesia in patients who have angiotensin-axis blockade (AAB) because of the administration of either angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin-receptor blockers (ARBs). Hypotension in such patients usually occurs within 30 minutes of the induction of anesthesia and is more frequent in patients also receiving diuretics. There is an ongoing debate as to whether ACEIs and ARBs should be discontinued before surgery. Although omitting these agents before general anesthesia may avoid hypotension, some argue that their discontinuation is not required because the associated hypotension is easily treatable and subsequent hypertension may occur perioperatively requiring antihypertensive therapy. Furthermore, the discontinuation of ACEIs and ARBs might remove the potential beneficial effect of AAB on myocardial protection and continuation is not required because the associated hypotension is easily treatable. Hypotension associated with AAB therapy was not associated with postoperative myocardial infarction or renal failure compared with patients not receiving this therapy.

Recognizing the concern regarding hypotension associated with ACEI therapy during surgery, the American College of Physicians initially recommended stopping these agents on the day of surgery. This opinion has now been modified to “continue ACEI with caution” for patients with cardiac failure and “uncertain, although they are usually continued” for ARB and ACEIs as antihypertensive therapy. This statement is provided with the caveat that hypotension with the induction of anesthesia may occur with increased vasoconstrictor requirements if such agents are continued. It should be noted that when holding such therapy on the day of surgery, enhanced hypotension still occurs. Hence, the practicing anesthesiologist will be faced with the problem of hypotension irrespective of whether or not the agent is discontinued. This is likely because AAB may last for some time after stopping therapy (Table 1) because of persistent tissue-based activity.

There are multiple reports of different approaches to treating severe hypotension refractory to fluid administration associated with AAB agents. There are no summary guidelines for the management of this relatively common occurrence. The aim of this review was to summarize the current literature and to provide management guidelines for the practicing anesthesiologist to consider when dealing with hypotension after the induction of general anesthesia in patients on ACEIs or ARBs. In order to do this, the pharmacology of AAB, the autonomic and neurohumoral changes associated with the induction of general anesthesia, and the disruption by AAB of the compensatory systems that defend against hypotension are discussed first.

Pharmacology of AAB

The pharmacology of ACEIs and angiotensin-receptor blockade is complex because the effects occur at both the tissue level and systemically. A summary of this physiology is shown in Figure 1. More detailed reviews of the physiology of the renin-angiotensin system (RAS) can be found elsewhere.

Renin (half-life [t½] = 13 min) is released from the juxtaglomerular apparatus of the kidney in response to sympathetic stimulation (Fig 1A). Renin acts upon angiotensinogen, synthesized in the liver, to form angiotensin (Ang) I, which, in turn, is converted by ACE to Ang II (t½ = 30 seconds, Fig 1B). Ang II has multiple inotropic and pressor effects, acting directly on vasculature through binding the Ang-I receptor (AT1) with resultant vasoconstriction (Fig 1C) and through binding the Ang-2 receptor (AT2) with resultant vasodilation and potential cardiac depression (Fig 1D). Ang II also acts indirectly by inhibiting cardiac vagal activity as well as by increasing cardiac contractility, efferent sympathetic nerve activity, and responsiveness to circulating catecholamines (Fig 1E).

In addition, Ang II stimulates the secretion of arginine vasopressin (AVP, t½ = 4-20 minutes) by the posterior pituitary (Fig 1F) as well as the secretion of aldosterone (t½ = 30 min) by the zona glomerulosa (Fig 1G) and the release...
of norepinephrine ($t_{1/2} \approx 2$ min) and epinephrine ($t_{1/2} \approx 2$ min) from the adrenal glands (Fig 1H).  

ACEIs, such as captopril (Table 1), decrease plasma angiotensin II and aldosterone levels. The blockade of this enzyme also results in a reduced breakdown of bradykinin (Fig 1), thus increasing its plasma and tissue levels and enhancing the vasodilatory and the vagomimetic effects of this peptide. Moreover, because bradykinin increases the rate of conversion of norepinephrine ($t_{1/2} = 2$ min) and epinephrine ($t_{1/2} = 2$ min) from the adrenal glands (Fig 1H).

**Table 1. The Pharmacokinetic Profile of Angiotensin-Converting Enzyme Inhibitors and Angiotensin-Receptor Blockers**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Oral Dose (mg/d)</th>
<th>Bioavailability (%)</th>
<th>$t_{1/2}$ (h)</th>
<th>$t_{\text{max}}$ (h)</th>
<th>Max Effect† (h)</th>
<th>Duration of effect‡ (h)</th>
<th>Route of Elimination (%)</th>
<th>Kidney</th>
<th>Liver</th>
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<td>Alecepril</td>
<td>25-75</td>
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<td>75-91</td>
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<td>11</td>
<td>9.4</td>
<td>18-48</td>
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<td>24-48</td>
<td>30 70</td>
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**Angiotensin-converting enzyme inhibitors**

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<tr>
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<th>Bioavailability (%)</th>
<th>$t_{1/2}$ (h)</th>
<th>$t_{\text{max}}$ (h)</th>
<th>Max Effect† (h)</th>
<th>Duration of effect‡ (h)</th>
<th>Route of Elimination (%)</th>
<th>Kidney</th>
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<tr>
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<td>1 99</td>
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**Angiotensin-receptor blockers**

Abbreviation: $t_{\text{max}}$, time to maximum peak plasma concentration.

Adapted from Auron et al, Colson, Smith, Kirch et al, and Burnier and Maillard. The duration of effect in biologic systems from Williams. Time to maximum effect and the duration of the antihypertensive effect after single-dose administration from Israili.

Fig 1. A schematic description of the renin angiotensin system (RAS) and its interaction with the autonomic nervous system and other pathways regulating vascular tone. ACEI blockade causes an increase in bradykinin and a decrease in Ang II levels. ARB have effects only on the AT$_1$ receptor resulting in increased Ang II levels that are then available to bind with the AT$_2$ receptor with resultant cardiac and vascular depressor effects. JGA, juxtaglomerular apparatus.
of arachidonic acid to vasodilatory prostaglandins, increased levels of this peptide enhance the vasodilatory effect of ACE inhibition. In addition, ACE inhibition may affect baroreceptor function. In normotensive subjects, acute enalapril administration was associated with a resetting of the baroreflex function, resulting in a lack of reflex tachycardia observed during a nitroglycerin-induced decrease in blood pressure.\textsuperscript{38} Patients on ACEIs also may have impaired sympathetic vasconstrictor responses and may show enhanced parasympathomimetic effects\textsuperscript{36} because of decreased circulating Ang II levels.\textsuperscript{37} The impaired sympathetic vasconstrictor response has been shown as an impaired blood pressure responsiveness to norepinephrine infusion in such patients.\textsuperscript{38} The enhanced parasympathomimetic activity (or disinhibition)\textsuperscript{37} may be shown clinically as an absence of reflex tachycardia from decreases in blood pressure.\textsuperscript{39}

ARBs, such as valsartan (Table 1), block the AT\textsubscript{2} receptor but not the AT\textsubscript{2} receptors. Selective blockade of the AT\textsubscript{1} receptor in the juxtaglomerular apparatus results in increased Ang II release.\textsuperscript{27} Thus, unblocked AT\textsubscript{2} receptors are exposed to increased levels of Ang II in the presence of ARBs.\textsuperscript{24} It should be noted that the effect of AT\textsubscript{2} binding is controversial and not well defined as of yet. Some attribute cardiovascular depressor\textsuperscript{27} and vasodilator and bradynkinin synthesis/release effects.\textsuperscript{40} Others have postulated a vascular antiproliferative (protective) effect\textsuperscript{41} with regression of cardiac fibrosis and vascular remodeling as the result of AT\textsubscript{2} activation.\textsuperscript{42} Furthermore, similar to the effects of ACEI therapy, AT\textsubscript{1}-receptor blockade is associated with a decrease in aldosterone\textsuperscript{42} and AVP release.\textsuperscript{52} This effect on AVP release has been shown clinically in a study of patients on AAB presenting for mitral valve surgery. Plasma AVP levels were lower in patients receiving ARBs preoperatively when compared with patients not receiving ARBs (7.0 \pm 3.7 vs 19.6 \pm 11.5 pg/mL, mean \pm standard deviation, p < 0.05) before cardiopulmonary bypass (CPB). In addition, 15 minutes after the start of CPB, AVP concentrations were lower in patients on ACEIs (49.0 \pm 38.6 pg/mL) and ARBs (32.2 \pm 17.4 pg/mL) when compared with the control patients (109.7 \pm 45.7 pg/mL, p < 0.05).\textsuperscript{44}

In anesthetic practice, AT\textsubscript{1}-receptor blockade was associated with a greater incidence of hypotension and a need for ephedrine to restore mean arterial pressure after induction with a standardized anesthetic regimen than in patients receiving ACEI therapy preoperatively.\textsuperscript{7} A further factor that impacts the management of hypotension in patients with AAB is the demonstration that, at least for ACEIs, there is an attenuation of the effect of phenylephrine after the induction of anesthesia and of norepinephrine administration on vascular responsiveness shown during and after CPB.\textsuperscript{38}

In summary, patients with AAB presenting for surgery may be considered in a sympatholytic state with parasympathomimetic prominence. This is associated with a resetting of arterial baroreceptors to a lower set point with a decreased heart rate response to hypotension as well as a decreased responsiveness to exogenous catecholamines. Furthermore, patients on ACEI therapy may have lower circulating and tissue levels of Ang II, aldosterone, and AVP, whereas patients receiving ARB may have lower levels of aldosterone and AVP.

**The Autonomic and Neurohumoral Changes Associated with the Induction of General Anesthesia**

Although it is now well accepted that the hemodynamic alterations induced by general anesthetic agents are mediated in part by their effect on the sympathetic nervous system,\textsuperscript{46} there is still a relative paucity of data describing this because of the difficulty of quantifying efferent central nervous system activity.\textsuperscript{37} Nevertheless, with respect to the intravenous induction agents, Ebert et al\textsuperscript{48} showed that the induction of anesthesia with thiopental or propofol is associated with a decrease in tonic sympathetic activity and a reduction in the increased reflex sympathetic activity in response to hypotension compared with the awake state. In contrast, etomidate administration is associated with a preservation of both tonic and baroreflex sympathetic activity.\textsuperscript{49} Ketamine increases heart rate and mean arterial pressure\textsuperscript{50,51} while causing very little change in central autonomic outflow.\textsuperscript{52} Interestingly, although propofol and ketamine have different effects on cardiovascular function, both attenuated the baroreflex sensitivity of heart rate and renal sympathetic nerve activity in a dose-dependent manner, suggesting that baroreceptor sensitivity is a function of the depth of anesthesia rather than the effect of individual agents.\textsuperscript{51} The induction of anesthesia with midazolam or diazepam also is associated with a transient depression of baroreflex function and a sustained decrease in sympathetic tone.\textsuperscript{46}

Similar autonomic alterations have been shown with volatile anesthetic agents. For example, in human volunteers, Ebert et al\textsuperscript{53} showed that during steady-state periods of isoflurane and sevoflurane anesthesia (0.4-1.2 minimum alveolar concentration [MAC]) basal levels of sympathetic nerve activity and catecholamine levels were unchanged from the conscious baseline. Similar findings occurred with desflurane, but at a higher MAC (0.5-1.5), desflurane administration was associated with significantly higher sympathetic nerve traffic and higher catecholamine concentrations than the other 2 agents.\textsuperscript{53} In situations in which the administered volatile anesthetic was increased rapidly from 1 MAC to 1.5 MAC multiples, desflurane was associated with significant sympathetic activity, which also occurred with isoflurane (to a lesser extent) but was absent with sevoflurane administration.\textsuperscript{53,54} All 3 agents had similar effects on baroreflex activities induced by experimental hypotension (sodium nitroprusside) or hypertension (phenylephrine). With increasing MAC, isoflurane, sevoflurane, and desflurane had similar effects on decreasing baroreflex sensitivity determined by relating mean blood pressure changes to the patient’s heart rate (RR interval).\textsuperscript{53}

The induction of general anesthesia may result in a reduction in circulating catecholamines as shown by Goldmann et al,\textsuperscript{55} who studied a group of patients not receiving \( \beta \)-adrenergic receptor blockers or ACEIs. Anesthesia was induced using thiopental and fentanyl and maintained with isoflurane after oral premedication with midazolam. Compared with the awake state (n = 27), norepinephrine plasma levels decreased significantly by 52% from 264 \pm 162 to 127 \pm 78 pg/mL, whereas mean epinephrine levels decreased by 62% from 32.9 \pm 7.4 to 10.1 \pm 10.7 pg/mL (mean \pm standard error, p < 0.05) (A Goldmann et al, personal communication, July 2011). Mean
Ang II levels increased significantly by 67% from 8.1 ± 5.2 to 13.6 ± 9.2 pg/mL (p < 0.05), whereas vasopressin levels were unchanged (ie, 1.0 ± 0.9 to 1.9 ± 1.6 pg/mL). Vasopressin levels did increase significantly after incision (85.3 ± 78.9 pg/mL). Furthermore, the induction of anesthesia with midazolam or diazepam was associated with decreases in plasma catecholamine levels,\textsuperscript{69} whereas induction with propofol resulted in significant decreases in epinephrine concentrations. Norepinephrine concentrations were unchanged from baseline.\textsuperscript{69} In contrast, ketamine induction in human volunteers resulted in an increase in mean circulating norepinephrine concentrations from 187 to 415 pg/mL, and in mean epinephrine levels from 97 to 271 pg/mL.\textsuperscript{50}

**DISRUPTION BY AAB OF THE COMPENSATORY SYSTEMS THAT DEFEND AGAINST HYPOTENSION**

Blood pressure is regulated by the complex interactions of myocardial contractility and preload\textsuperscript{57}; venous, arterial, and capillary capacitance\textsuperscript{58}; blood volume and viscosity\textsuperscript{59}; and interactions among the autonomic nervous system,\textsuperscript{58} the RAS, and the arginine vasopressin pressor systems.\textsuperscript{12,60,61}

The normal compensatory responses to hypotension during general anesthesia may be exacerbated by the effects of pharmacological AAB. It has been shown in humans that the blockade of 1 or 2 of the 3 main systems responsible for the maintenance of hemodynamic stability (ie, sympathetic nervous system, RAS, or arginine vasopressin system) by the ACEIs, enalapril, or a vasopressin-receptor antagonist (β-mercapto-β, β-cyclopentamethylene-propionyl-O-Met-Tyr-Arg-vasopressin) or with thoracic epidural anesthesia, respectively, resulted in the maintenance of blood pressure by compensation of the other system(s).\textsuperscript{60} Only when all 3 systems were blocked did hypotension occur. Similarly, in conscious dogs, during autonomic blockade, arterial blood pressure was maintained by both Ang II and vasopressin.\textsuperscript{62} The blockade of 1 or 2 of the 3 described systems is compensated for by the other(s),\textsuperscript{63} and mean arterial pressure usually is well maintained as long as a single pressor system remains intact.\textsuperscript{60,62,63} However, under surgical stress and during anesthesia, this compensatory balance may become compromised. This has been shown in rats administered an ACEI in which hemodynamic recovery after blood loss is compromised despite reflex increases in catecholamines to near-normal levels and elevated vasopressin levels.\textsuperscript{64} It is clear that the activation of the RAS measured as plasma renin activity is not different in the conscious or anesthetized state,\textsuperscript{65} yet during anesthesia tolerance to hemorrhage is impaired. This may be because under anesthesia (with enflurane, 3%) the RAS system predominates as a defense mechanism against blood loss, whereas in conscious dogs the sympathetic-adrenal system predominates, and the RAS system is insufficiently powerful to prevent overall hemodynamic deterioration with hemorrhage.\textsuperscript{66} From these points, it is clear that during general anesthesia, inhibition of the RAS may significantly impair compensation for hemorrhage. Furthermore, in sheep under general anesthesia, blockade of the RAS and AVP systems results in hypotension.\textsuperscript{67} These studies indicate that in the face of an added insult, such as hemorrhage or anesthesia, blockade of only 1 or 2 of the components of this neurohormonal pressor system may lead to severe hemodynamic compromise.\textsuperscript{68} Thus, patients receiving preoperative AAB therapy who have depressed levels of AVP and decreased responsiveness to catecholamines may experience hypotension because of the sympatholysis associated with the induction of general anesthesia.

**THERAPY FOR HYPOTENSION**

**Routine Therapy (Phenylephrine and Ephedrine)**

Although phenylephrine,\textsuperscript{11,69,70} ephedrine,\textsuperscript{7,19,20} or both\textsuperscript{2,8,71} may be considered first-line agents, they have been reported to have varying effectiveness for treating\textsuperscript{7,6,20} hypotension during the induction of anesthesia in patients with AAB. Patients receiving ARBs required a larger dose of ephedrine (21 ± 3 mg v 7 ± 4 mg, mean ± SD, p < 0.001) than those receiving ACEIs and were more likely to have refractory hypotension (4/12 v 1/27, p < 0.05).\textsuperscript{7} A number of studies also defined the advent of “refractory” hypotension in patients in whom repetitive doses of ephedrine\textsuperscript{7,19,71} or phenylephrine and ephedrine\textsuperscript{71} could not treat hypotension adequately, requiring other therapy to address this problem. Thus, additional therapy other than phenylephrine or ephedrine may be needed for treating hypotension in patients receiving ARBs or ACEIs.

**Neurohumoral Therapy (Arginine Vasopressin, Terlipressin, and Angiotensin II)**

There is a paucity of literature describing the use of neurohumoral therapy with arginine vasopressin, terlipressin, or Ang II for the treatment of refractory hypotension after the induction of general anesthesia (Table 2).

**Arginine Vasopressin (AVP)**

AVP is a naturally occurring nonapeptide synthesized in humans in the hypothalamus and released in response to changes in osmolality and blood pressure.\textsuperscript{72} AVP acts predominantly through V1-receptor stimulation, resulting in vasconstriction in the mesentery, skin, and skeletal muscle and through V2-receptor activation in the kidney (in response to changes in osmolality) acting as an antidiuretic. V3-receptor stimulation results in the neurohumoral release of cortisol, angiotensin, growth hormone, and atrial natriuretic peptide. Synthetic AVP has a half-life of 4 to 20 minutes and, thus, needs to be infused for a continued effect.\textsuperscript{7,9,72}

The use of AVP to treat hypotension after the induction of anesthesia in a patient receiving ARBs only has been described in a single case report.\textsuperscript{73} In this report, AVP was administered in repetitive bolus doses of 0.4 to 2.0 U, followed by a continuous infusion (0.04-0.06 U/min) to treat hypotension refractory to phenylephrine, ephedrine, and epinephrine.\textsuperscript{71} The infusion of AVP has been well studied in cardiac surgery patients on ACEIs but only in the peri- and post-CPB period and not immediately after induction. Morales et al\textsuperscript{74} and Papadopolous et al\textsuperscript{75} reported that in patients receiving preoperative ACEIs, AVP given at a dose of 0.03 U/min beginning before CPB was more effective than placebo for preventing hypotension. Similarly, Hasija et al\textsuperscript{76} showed in patients receiving preoperative ramipril that AVP, 0.03 U/min, started during patient rewarming on CPB resulted in less need for catecholamine administration when compared with placebo.
Tertlipressin has been suggested as an effective agent for treating hypotension after anesthetic induction in patients on AAB therapy (Table 2). Ang II and tertlipressin (triglycyl-lysine vasopressin), which is not available in the United States, is a prodrug that is converted to lysine vasopressin by cleavage of the N-triglycyl residue by endothelial peptidases. It is reported to have an effective half-life of 6 hours, whereas lysine vasopressin, which is not available in the United States, is a prodrug that is converted to lysine vasopressin by cleavage of the N-triglycyl residue by endothelial peptidases. It is reported to have an effective half-life of 6 hours, whereas lysine vasopressin has an elimination half-life of 50 minutes. Tertlipressin was shown to be effective for treating hypotension after the induction of anesthesia in patients on ARBs or ACEIs with hypertension refractory to phenylephrine or ephedrine. Tertlipressin, 1 mg, restored blood pressure within 60 seconds in 8 of 10 patients, whereas 2 patients needed up to 3 mg. The mean arterial pressure increased from a predadministration value of 65 to 80 mmHg (3 minutes after the last tertlipressin dose), whereas heart rate decreased from 60 to 55 beats/min with no impairment in left ventricular function. No further blood pressure support was required for the remainder of the anesthetic, and no changes in ST segments were observed in the treated patients. Tertlipressin, 1 mg, with ephedrine, 15 mg, were compared with ephedrine, 15 mg, and simultaneously administered with placebo in patients on ACEIs with hypertension (mean arterial pressure <65 mmHg or <30% from baseline) after the induction of anesthesia in a blinded, crossover study. If the mean arterial pressure did not exceed the stated criteria 1 minute after the administration of the test medications, a second bolus of both test medications was administered. If 1 minute later blood pressure still was not restored, patients were crossed over to receive the alternative combination. The authors concluded that the combination of tertlipressin with ephedrine was more effective in achieving and maintaining blood pressure than ephedrine administered with placebo. No patient who received tertlipressin had postoperative hypertension, significant changes in serum creatinine concentrations, or elevated troponin I levels. These latter observations are important because, although high-dose vasopressin, 40 U, has been shown to improve survival in cardiac arrest, the effects of AVP on the coronary vascular bed are controversial. Thus, coronary vasocinstriction has been shown during normoxia and coronary vasodilation during hypoxia, whereas direct myocardial dysfunction has been attributed to a direct effect of AVP on contractility. Furthermore, AVP and tertlipressin may impair splanchnic perfusion despite the fact that both vasopressor agents are associated with beneficial effects on renal function in hepatorenal syndrome. It is to be noted that AVP extravasation may result in skin necrosis.

Ang II

Ang II is a naturally occurring octapeptide that has been synthesized since 1957 but currently is not available in the United States. It is quickly converted to the less active Ang III and so has a half-life of 30 to 60 seconds. The systemic physiologic effects of Ang II increase blood pressure through direct vasoconstriction; however, it is also responsible for the release of aldosterone and catecholamines, which is reviewed extensively elsewhere. Ang II has been administered in a bolus dose of 2.5 µg to increase blood pressure in patients undergoing vascular surgery receiving ACEIs experiencing hypotension after propofol and sufentanil administration (Table 2). The onset time to the restoration of blood pressure was 30 to 90 seconds, and the duration of effect was 15 minutes. The increase in blood pressure was associated with an unchanged heart rate, which has been attributed to the effect of Ang II on this cardiovagal system. Vasoconstriction has been shown during normoxia and coronary vasodilation during hypoxia, whereas direct myocardial dysfunction has been attributed to a direct effect of AVP on contractility. Furthermore, AVP and tertlipressin may impair splanchnic perfusion despite the fact that both vasopressor agents are associated with beneficial effects on renal function in hepatorenal syndrome. It is to be noted that AVP extravasation may result in skin necrosis.

<table>
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<tr>
<th>Agent</th>
<th>First Author and Reference</th>
<th>ARB</th>
<th>ACEI</th>
<th>Dose</th>
<th>Effect/Duration</th>
<th>Onset/Offset</th>
<th>Response Rate</th>
<th>Additional Dose Required to maintain BP</th>
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<td>Infusion rate 0.14 ± 0.03 µg/kg/ min</td>
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</tbody>
</table>

Abbreviations: ✓, indicates patient has been receiving this agent; BP, blood pressure; Δ, dose change.

*Only 1 patient achieved BP goal at the initial norepinephrine infusion rate; all required changes in infusion rate to avoid hypotension.
resetting the baroreceptor. This is a different response from that found with phenylephrine and vasopressin administration, which results in a decrease in heart rate. There also was an associated transient impairment in left ventricular function from Ang II administration, which returned to baseline after 5 minutes.

**Catecholamine Administration (Norepinephrine)**

Although epinephrine, dopamine, and metaraminol have been administered to patients experiencing hypotension after the induction of anesthesia when on AAB, norepinephrine is the only catecholamine that has been studied in this context.

**Norepinephrine**

Boccara et al randomized patients receiving AAB undergoing carotid endarterectomy to receive either norepinephrine, 8 to 12 μg/min (n = 10), or a 1-mg bolus of terlipressin repeated twice (n = 10) for hypotension from general anesthesia induction, with propofol administered to achieve a bispectral index level below 60 (Table 2). The authors concluded that “terlipressin was more effective and had more prolonged action than norepinephrine in controlling arterial blood pressure without any significant adverse effects.”

Morelli et al compared the effects of 1 mg of terlipressin with norepinephrine (0.1 μg/kg/min, increased to achieve prestudy blood pressure levels) in 2 study groups (each n = 16) undergoing carotid endarterectomy. They assessed cardiac performance, systemic hemodynamics, and gastric perfusion associated with the treatment of hypotension in such patients (Table 2). Patients were monitored using echocardiography and received volume loading before the induction of anesthesia. Measurements were taken at 30 minutes and 4 hours after the onset of hypotension at which times the mean arterial pressure for both groups was significantly improved but not different from baseline. However, the median cardiac index was significantly less in the terlipressin group when compared with the norepinephrine group at both the 30-minute (2.25 ± 0.3 vs 3.4 ± 0.7 L/min/m², median ± deviation from median, p < 0.05) and 4-hour (2.25 ± 0.2 vs 3.05 ± 0.2 L/min/m²) time points, respectively. There was an associated significantly lower median heart rate in the terlipressin group (54 ± 6 vs 82 ± 6 beats/min) and (67 ± 4 vs 89 ± 4 beats/min) at these time points, respectively, when compared with the norepinephrine group. The ejection fraction measured at baseline (38% ± 4% vs 40% ± 6%, median ± deviation from median) and at the 4-hour time point (37% ± 4% vs 40% ± 3%) were similar, respectively, suggesting that the cardiac index differences were related to the decrease in heart rates with terlipressin.

In addition, there were significantly higher median calculated pulmonary (495 ± 56 vs 334 ± 64 dynes·s·cm⁻³/m²) and systemic vascular resistance indices (3,171 ± 319 vs 2,148 ± 313 dynes·s·cm⁻⁵/m²) and a demonstrated decreased laser Doppler-measured gastric perfusion (−75% ± 17% vs 3% ± 1%, p < 0.05) in the terlipressin group. This was sustained for 4 hours; the mean serum lactate concentration also was significantly higher at this time point in the terlipressin group (2.6 ± 0.3 vs 0.8 ± 0.2 mmol/L, p < 0.05). These findings suggest that terlipressin, although effective for treating hypotension, decreases heart rate, resulting in a decreased cardiac output and gastric perfusion and increases lactate levels. In contrast, norepinephrine restores blood pressure while maintaining heart rate and cardiac output.

**Other Agents**

**Methylene Blue**

Methylene blue has a half-life of 40 minutes and acts through competition with nitric oxide in binding to the ferrous heme moiety of guanylate cyclase. This inhibits an increase in levels of the vasodilatory cGMP, counteracting the effects of vasodilators, such as nitric oxide, in vascular smooth muscle. Its use to treat hypotension chiefly has been suggested in settings in which “conventional” agents like phenylephrine, norepinephrine, and vasopressin have not been effective.

Methylene blue administration has not been described for the treatment of hypotension after general anesthetic induction in patients receiving AAB. However, methylene blue has been studied in patients receiving ACEI therapy during cardiac surgery with CPB bypass. In one such study, methylene blue (3 mg/kg) was compared with placebo for treating hypotension during CPB (n = 15) and compared with patients receiving placebo (n = 15). This study showed better maintenance of systemic vascular resistance and blood pressure, decreased phenylephrine requirements during bypass, and less norepinephrine requirements postbypass. Three further brief reports in cardiac surgery patients supported the use of methylene blue (2 mg/kg) in decreasing the need for high-dose norepinephrine to combat refractory hypotension in patients on ACEI therapy. Ozal et al studied the prophylactic use of methylene blue (2 mg/kg) before anesthesia induction in patients undergoing cardiac surgery including some patients receiving ACEIs. These investigators found that prophylactic methylene blue administration reduced the incidence and severity of vasopugic syndrome. The potential side effects of methylene blue include interference with SaO₂ monitoring; urine discoloration; and, possibly, angina, transient nodal inhibition, ventricular ectopy, and decreases in cardiac output, splanchnic and renal perfusion. However, the latter effects generally are not seen with doses under 2 mg/kg.
Anticholinergic Agents

Anticholinergic agents have not been studied to treat hypotension in patients receiving AAB, but have been administered as therapy.2 There is one case report describing the administration of atropine to combat extreme hypotension (and cardiac arrest) associated with the induction of anesthesia with sevoflurane, propofol, and dexmedetomidine administration for bronchoscopy in a 9-month-old patient on ACE inhibitors.104 Using an anticholinergic in situations in which an increase in vagal tone is anticipated and in which propofol is used for anesthesia is suggested (especially in pediatric patients) in the manufacturer’s guidelines because propofol has no vagolytic effects.105 Of interest, atropine administration has been shown to increase the pressor response from AVP while blunting AVP’s effect in decreasing cardiac output and causing bradycardia in conscious dogs.106

SUGGESTED MANAGEMENT GUIDELINES

Based on the considerations summarized, anesthesiologists are increasingly likely to need to manage hypotension associated with general anesthesia in patients who are receiving AAB, especially if patients are on angiotensin-receptor blockers,9 are hypovolemic1 (from diuretics or other causes), or in the face of blood loss64 or some other major stressor64 (eg, CPB).

This review has brought together the paucity of literature on the treatment of hypotension associated with general anesthesia induction (and maintenance) that is available to date. Hence, the recommendations for management can based only be on the limited evidence-based literature available (which has significant limitations in statistical power, Table 3), an understanding of the physiology and pharmacology of both AAB and general anesthetic induction, and the opinions expressed by other authors who have reviewed this literature.3,22

Anesthesiologists should recognize that because of treatment with AAB, patients are in a sympatholytic autonomic state37 with parasympathomimetic20 prominence (Fig 1). This is manifested as an absence of reflex tachycardia from decreases in blood pressure.19 Furthermore, these patients may show a reduced response to exogenously administered catecholamines and vasoconstrictors.38,45

Management of General Anesthetic Induction and Maintenance

General Anesthetic Induction

To monitor general anesthetic induction and maintenance, practitioners should have a lower threshold for placing an

Table 3. Proposed Therapy to Combat Hypotension Associated With the Induction of General Anesthesia in Patients With AAB

<table>
<thead>
<tr>
<th>Agent</th>
<th>Intravenous Dose</th>
<th>Effect/Duration</th>
<th>Comment</th>
<th>Classification of Recommendation</th>
<th>Level of Evidence</th>
<th>First Author and Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycopyrrolate</td>
<td>0.1-0.2 mg</td>
<td>t½, 48 min</td>
<td>Parasympatholytic effect overcomes parasympathomimetic prominence of AAB</td>
<td>Class II a</td>
<td>C</td>
<td>Comfere2</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>5-10 mg</td>
<td>10-15 min</td>
<td>Mixed acting α1 and β1 receptor stimulant, ↑ HR, ↑ CO, ↑ BP, tachyphylaxis</td>
<td>Class I</td>
<td>C</td>
<td>Brabant1, Bocarra19, Coriat20</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>250 μg</td>
<td>t½, 20 min</td>
<td>Potent α1 vasoconstrictor ↓ HR, ↓ CO, ↓ BP</td>
<td>Class I</td>
<td>C</td>
<td>Colson30, Ryckwaert70</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>4-8 μg/min</td>
<td>t½, 2 min</td>
<td>β1 stimulant replaces 50% of plasma concentration on induction ↑ CO, ↑ BP</td>
<td>Class II a</td>
<td>A</td>
<td>Bocarra19, Morrelli84</td>
</tr>
<tr>
<td>AVP (bolus)</td>
<td>0.4-2 U</td>
<td>t½, 2 min</td>
<td>Prompt response, may need infusion to maintain effect</td>
<td>Class II b</td>
<td>C</td>
<td>Wheeler73</td>
</tr>
<tr>
<td>AVP* (infusion)</td>
<td>0.03 U/min</td>
<td>t½, 4-20 min</td>
<td>May cause ↓ HR, ↓ CO, ↓ BP and ↓ splanchnic perfusion</td>
<td>Class II a</td>
<td>A</td>
<td>Morales74</td>
</tr>
<tr>
<td>Terlipressin</td>
<td>1 mg</td>
<td>t½, 6 h</td>
<td>May cause ↓ HR, ↓ CO, ↓ BP and ↓ splanchnic perfusion</td>
<td>Class II a</td>
<td>A</td>
<td>Hasija76, Meerschaert77, Bocarra19</td>
</tr>
<tr>
<td>Angiotensin II</td>
<td>2.5 μg</td>
<td>5 min</td>
<td>↑ BP no change in HR</td>
<td>Class II b</td>
<td>C</td>
<td>Eyraud25</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>10-20 μg</td>
<td>t½, 2 min</td>
<td>α1, β1, and β2 stimulant replaces 50% of plasma concentration on induction ↑ HR, ↑ CO, ↑ BP, ↓ splanchnic perfusion</td>
<td>Class II b</td>
<td>C</td>
<td>Wheeler73</td>
</tr>
<tr>
<td>Methylene blue*</td>
<td>1-2 mg/kg</td>
<td>t½, 40 min</td>
<td>↑ BP, possible ↓ CO, arrhythmias, ↓ splanchnic perfusion</td>
<td>Class II b</td>
<td>B</td>
<td>Maslow26, Ozal87</td>
</tr>
</tbody>
</table>

Abbreviations: HR, heart rate; BP, blood pressure; CO, cardiac output.

*Only studied in perioperative CPB period.

†Classification of recommendation classes. Class I, benefit >> risk; treatment should be performed; class II benefit >> risk. It is reasonable to perform treatment. Class II (b) benefit ≥ risk. Treatment may be considered. Class III no benefit or harm. Level of evidence:37 level A: data from multiple randomized clinical trials, level B: data from a single randomized clinical trial or nonrandomized study, and level C: only consensus opinion of experts, case studies, or standard of care.

‡Sakka et al.116
arterial catheter in those patients who might be at particular risk of hemodynamic instability. An intravenous preload of 10 mL/kg could be administered before induction in an attempt to minimize resultant hypotension. The induction of general anesthesia might be best served using a more cardiostable agent, such as etomidate or methohexitol rather than propofol. This is because propofol has a greater vasodilatory effect and resets the baroreceptor reflex downward with a resultant decreased compensatory reflex increase in heart rate. This is well illustrated in a study comparing the hemodynamic effect of etomidate and propofol for anesthetic induction in patients on enalapril therapy for at least 6 months. Etomidate resulted in significantly fewer episodes of hypotension and bradycardia than found with propofol induction. However, if propofol is to be used, an induction dose of 1.3 mg/kg is associated with the least need for pharmacologic intervention to treat bradycardia and hypotension in patients on ACEIs. Alternative induction agents (which have not been studied in this context) would be ketamine or midazolam. Ketamine would have a theoretic advantage because it increases heart rate and mean arterial pressure, while causing very little change in central autonomic outflow. In contrast, midazolam would not appear appropriate as an induction agent because it is associated with a transient depression of baroreflex function and a sustained decrease in sympathetic tone.

General Anesthesia Maintenance

The maintenance of general anesthesia with a volatile anesthetic could be guided by the fact that at levels below 0.5 MAC there are few differences between isoflurane, sevoflurane, and desflurane because they have similar effects on sympathetic nerve activity (and catecholamine levels), which have been found to be unchanged from conscious baseline in human volunteers. However, if there is need for a sudden increase in MAC above 1.0 or a need for higher than 0.5 MAC anesthetic administration, then desflurane theoretically would be better. This is because desflurane is associated with significantly higher sympathetic nerve traffic and higher catecholamine concentrations than the other 2 agents when administered at higher than 0.5 MAC concentrations.

Management of Hypotension

Glycopyrrolate

Should hypotension occur, practitioners could administer glycopyrrolate, 0.1-0.2 mg, to minimize parasympathomimetic effects on vasodilation and heart rate (Table 3 and Fig 2). Fluid therapy should be administered to achieve a euvolemic state.

Phenylephrine and Ephedrine

Phenylephrine (50-250 μg), ephedrine (5-10 mg), or both should be administered next (Table 3 and Fig 2). The choice of agent would depend on whether the anesthesiologist believes the patient to have a decreased cardiac output (in which case ephedrine would be a good choice) or a normal or increased cardiac output (in which case phenylephrine could be chosen). This is because phenylephrine would tend to decrease cardiac output, whereas ephedrine increases cardiac output.

Hypotension

Hypotension

Management of Hypotension

Glycopyrrolate bolus: 0.2 mg

Ephedrine bolus: 5-10 mg

Repeat prn

Phenylephrine bolus: 100-200 μg

Repeat prn

Refractory Hypotension

Norepinephrine bolus: 4 μg-8 μg + infusion 0.1 μg/kg/min

OR

AVP bolus: 0.4 U (2 min) + infusion 0.03 U/hr

Fig 2. The suggested treatment algorithm for hypotension after the induction of general anesthesia.

Norepinephrine

Norepinephrine would appear to be the ideal agent (Table 2) to combat hypotension after induction of anesthesia. This is because the administration of this physiologic agent (having both α1 and β1 effects) could help to replace the well shown significant decrease of this circulating catecholamine associated with the induction of general anesthesia, with the caveat that patients on AAB may have an attenuated response to exogenous catecholamine administration. Norepinephrine also has the advantage over AVP (as discussed earlier) that cardiac output seems to be better maintained and splanchnic perfusion less likely to be impaired. Norepinephrine could be started at 4 to 8 μg/min or 0.1 μg/kg/min (Table 3 and Fig 2.) However, there is a practical problem related to the administration of this agent; significantly more episodes of overshoot hypertension have been described with its use when compared with terlipressin administration.

AVP and Terlipressin

Both AVP and terlipressin administration have been studied (Table 2) and have the advantage that vasopressin action on vasoconstriction is not attenuated by AAB therapy (as is found with norepinephrine administration) and work independently of the RAS. Terlipressin could be administered as an initial dose of 1 mg (Table 3), If terlipressin is not available, the question arises as to whether AVP should be given as a bolus dose or put. In the event that the usual doses of these agents do not suffice in restoring the blood pressure, then the practitioner has a number of options.

Norepinephrine

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infused. There is only one case report advising the administration of 0.4 U of AVP as multiple bolus doses followed by an infusion (Table 2), while bolus-dose AVP administration is a relatively common but as yet unstudied practice. Thus, there is little guidance from the literature concerning the appropriate bolus dose for AVP administration. Instead, AVP infusions (0.03 IU/min) usually have been described in the context of cardiac surgery. The concern is that a too-high bolus dose of AVP could result in potential negative effects on heart rate, cardiac output, and splanchnic perfusion. In establishing an initial dose of AVP, the practitioner might be guided by a study in awake volunteers (n = 7) in whom AVP (0.2 pmol/kg/min) was infused for 15 minutes, resulting in an increase of plasma AVP concentration from 4.4 to 8.9 pg/mL. This translates to a dose of AVP of ~0.11 U (if it is assumed that the volunteers in the study were of average weight [ie, 70 kg], 1 U = 2.06 μg). It is to be noted that usually under anesthesia, plasma vasopressin levels remain unchanged after induction (1.0-1.9 pg/mL) although they do increase significantly after incision (85.3 pg/mL). Because AVP has a half-life of 4 to 20 minutes, a continuous infusion would be needed to provide a sustained effect.

Ang II

Ang II, 2.5 μg, would be a choice for those anesthesiologists who have access to this neurohormone (Table 3). Ang II has an effect within 60 to 90 seconds that lasts for 15 minutes at which time surgical incision with a concomitant rise in plasma AVP levels and endogenous catecholamine levels are likely to support the blood pressure.

Epinephrine

Epinephrine (10-20 μg) administration has been described but never studied. (Bocarra et al noted in their study on norepinephrine and terlipressin therapy mentioned earlier that epinephrine was never necessary when the latter 2 agents had been used to restore normotension.) The administration of epinephrine (having α₁, β₁ and β₂ effects) could help to replace the well-known significant decrease of this circulating catecholamine described as a consequence anesthetic induction. Because it has a half-life of 2 minutes, a continuous infusion may be necessary for a sustained response to its administration. Epinephrine added to norepinephrine infusion after cardiac surgery has been associated with decreased gastric mucosal perfusion.

Methylene Blue

In the event that none of these measures satisfactorily restores blood pressure, methylene blue (2 mg/kg) would be an unstudied option because doses in this range generally are not associated with adverse effects. Methylene blue has been used when conventional therapy with norepinephrine and vasopressin has failed to reverse severe vasopressor syndrome associated with ACEI therapy.

CONCLUSIONS

In conclusion, hypotension associated with general anesthetic induction and maintenance in patients with AAB is likely to remain a significant problem as more patients receive this potentially life-prolonging therapy. A review of the physiology and pharmacology of AAB during general anesthesia induction has been provided and a potential treatment strategy given.

A suggested approach to providing general anesthesia to such patients could best be summarized as follows: (1) provide adequate intravenous preload to ensure euvolemia before induction; (2) induce general anesthesia with etomidate; (3) maintain general anesthesia with desflurane; (4) treat initial hypotension depending on the heart rate and cardiac output with a combination of glycopyrrolate, phenylephrine, and ephedrine. (5) Should refractory hypotension occur therapy would best be initiated with norepinephrine, and an unstudied alternative, AVP could be considered. However, there are only limited data regarding the treatment of this condition, and more research into the safety and efficacy of potential therapies is necessary to ensure the appropriate risk/benefit for such recommendations.

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