This review assessed the utility of vasopressin and vasopressin analogues for the treatment of refractory hypotension associated with angiotensin-converting enzyme (ACE) inhibitors in the perioperative setting. A systematic review of the literature was conducted using MEDLINE, Embase, and ProQuest.

Six randomized controlled trials met eligibility criteria. In the perioperative setting, continued use of ACE inhibitors within 24 hours before surgery remains controversial. Authors of the reviewed studies suggested that the morning dose of the ACE inhibitor be held, and those patients experienced decreased catecholamine use postoperatively and shorter duration of decreased mean arterial pressure. No incidence of refractory hypertension from withholding the morning dose of the ACE inhibitor was mentioned. All of the patients receiving vasopressin demonstrated improved hemodynamic stability with small, intermittent doses, without profound ischemic changes. For management (prevention and treatment) of ACE inhibitor–associated hypotension in the perioperative setting, all studies showed statistically significant success with vasopressin or vasopressin analogues for improvement of systemic blood pressures. Before vasopressin is widely accepted as a standard of care, further studies are needed to confirm these findings and assess the general utility of vasopressin in surgical populations for management of ACE inhibitor–associated refractory hypotension.

Keywords: Angiotensin-converting enzyme inhibitor, perioperative, refractory hypotension, vasopressin.

Low-Dose Vasopressin and Analogues to Treat Intraoperative Refractory Hypotension in Patients Prescribed Angiotensin-Converting Enzyme Inhibitors Undergoing General Anesthesia: A Systematic Review

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Inadequate systemic blood pressure can cause renal impairment, neurocognitive changes, and organ failure. Therefore, it is of the utmost importance to maintain adequate systemic blood pressures in the perioperative setting. A minimum mean arterial pressure of 50 to 60 mm Hg should be maintained to preserve organ perfusion, and even higher mean arterial pressures are required for patients who experience preexisting renal dysfunction, coronary artery disease, diabetes, and hypertension.1

Hypertension is a common condition in many patients who require surgery with general anesthesia. Patients treated for hypertension may be taking an angiotensin-converting enzyme (ACE) inhibitor for blood pressure control and may have taken the medication the night before or the morning of their procedure. Many of these patients prescribed an ACE inhibitor are possibly combining an ACE inhibitor with other antihypertensives as part of a multimodal regimen.2 A patient who receives an ACE inhibitor within 24 hours of general anesthesia may experience hypotension intraoperatively that is refractory to standard treatments such as a fluid bolus, ephedrine, or phenylephrine.2 Angiotensin-converting enzyme inhibitors induce a decrease in adrenergic receptor sensitivity, limiting the clinical effect of adrenergic drugs such as ephedrine. Chronic blunting of the renin-angiotensin-aldosterone system necessitates an increase in dose as well as the refractory effect.3 Further hypotension is associated with the interference of anesthesia on the sympathetic system, which creates angiotensin dependence of the arterial blood pressure. This state of autonomic dysfunction is also referred to as “vasoplegia,” in which the patient experiences low systemic vascular resistance and high cardiac output.4 Although ACE inhibitor–associated refractory hypotension in the perioperative setting is a recognized problem, guidelines regarding its management are lacking.2

Currently, there is a paucity of literature regarding withholding or continuing use of ACE inhibitors before surgery, and a consensus has not been reached regarding a standardized protocol.5 Suggestions have been made to
avoid intraoperative hypotension by stopping use of the medications before surgery, usually on the day of surgery or the day before the procedure. Further suggestions have been made to continue use of the ACE inhibitor on the day of surgery to avoid rebound hypertension. However, according to the large, prospective randomized controlled trial by Twersky et al., discontinuing use of ACE inhibitors and angiotensin renin blockers (ARBs) in patients on the day of surgery did not result in an increased incidence of pre- or postoperative hypertension compared with those patients who continued use of these medications on the morning of surgery. Therefore, it is safe to discontinue use of ACE inhibitors and ARBs on the day of surgery without increasing the potential for adverse hemodynamic changes. According to Smith and Jackson, ACE inhibitors and ARBs increase the likelihood of intraoperative hypotension and should be held on the day of surgery; however, if these instructions seem to confuse patients, they should be told to take all their medications rather than risk missing their β-blocker or calcium channel blocker. These reviewers were not referring to refractory hypotension, commenting that most hypotension can be reversed by standard treatment modalities.

Controversy also surrounds the use of ACE inhibitors on the day of surgery because of the probability of the medication causing upper airway complications. As shown in Figure 1, ACE inhibitors increase the total tissue bradykinin, which has the potential to increase cough, angioedema, and bronchospasm. Turan and colleagues concluded there were no significant associations between preoperative ACE inhibitor use and intraoperative or postoperative respiratory complications.

Angiotensin-converting enzyme inhibitors block the renin-angiotensin-aldosterone system by inhibiting the conversion of angiotensin I to angiotensin II. By blocking this stage of the body’s blood pressure regulation center, systemic blood pressure is decreased. Receiving an ACE inhibitor before surgery can result in marked hypotension because the half-life is more than 10 hours. Perioperative hypotension may also be associated with other medications administered in the operating room, such as propofol and inhaled anesthetic agents. These agents inhibit the sympathetic nervous system, resulting in a decrease in the overall cardiac output and systemic vascular resistance, further contributing to the vasodilatory shock. Patients presenting on the day of surgery are also volume depleted as a result of fluid restrictions before surgery, which may exacerbate their hypertensive state.

In recent years, vasopressin and vasopressin analogues have been documented as treatment options for patients experiencing vasoplegia in the perioperative setting. Vasopressin is a neurohypophysial hormone naturally occurring in humans. Its primary functions are to retain water and to constrict the blood vessels, leading to an increase in the overall fluid load in the intravascular compartment. The vasopressin system is the only endogenous vasopressor system that is not blocked during general anesthesia in patients receiving ACE inhibitors, which may be the reason vasopressin has been a potential successful treatment modality.

A systematic review regarding vasopressin and its analogues for the treatment of refractory hypotension in neonates has been completed; however, this was not specific to the adult surgical population, and the documented hypotension was not a specific response to the use of ACE inhibitors. Although studies have been documented to address the efficacy of vasopressin for treating ACE inhibitor–associated refractory hypotension in the perioperative setting, a systematic review of the literature in populations other than neonates has yet to be conducted. To address this gap in the literature, the purpose of this systematic review was to examine evidence regarding vasopressin and vasopressin analogues for the treatment of refractory hypotension associated with ACE inhibitors in the perioperative setting.

**Materials and Methods**

We conducted a systematic review of the literature, aiming to examine the best available current knowledge of vasopressin and vasopressin analogues for the treatment of refractory hypotension associated with ACE inhibitors in the perioperative setting. A protocol for this review was developed in collaboration with a health service librarian (online supplemental content). Search terms were developed using the synonyms listed in Table 1.
We structured our search using the PICOT method, which stands for patient population, intervention, comparison intervention, outcome, and type of study.\textsuperscript{11} The reviewers included studies with a patient population that received an ACE inhibitor within 24 hours of the induction of general anesthesia. In particular, we focused on studies of hypotension resistant to standard treatment modalities. The interventions of interest included the administration of vasopressin or vasopressin analogues (terlipressin) alone or in combination with another medication for the prevention or treatment of ACE inhibitor–associated refractory hypotension. The comparison interventions, or standard treatment medications, for hypotension in the operative setting included ephedrine and phenylephrine. The primary efficacy outcomes included in this review are the achievement of normotension and hemodynamic stability as described by the original studies’ authors. We included studies with randomized controlled trial (RCT) or controlled clinical trial designs as the type of study. We did not exclude any comorbid conditions or disease states in the review.

The search strategy was aimed to find both published and unpublished studies. We searched MEDLINE, Embase, and ProQuest theses and dissertations databases, limited to English-language articles and human studies. We did not limit the year of publication in MEDLINE and Embase, but used a 10-year limit in ProQuest to narrow results. The reference lists from the identified RCTs and controlled clinical trials were reviewed for additional studies. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)\textsuperscript{12} flow diagram (Figure 2) depicts the process for screening and selecting studies. Initially, 2 review authors (K.F.H and C.L.M.) independently read through each of the study’s titles and abstracts to determine if the study met inclusion and exclusion criteria. Any differences were resolved by discussion to consensus. If no consensus was reached, the study was included in the full text screening. We abstracted the sample size, purpose, and key findings from each study. The evidence was appraised using a domain-based approach,\textsuperscript{13} in which the study was assessed for risk of bias in random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcomes assessment, incomplete outcomes data (both short term and long term), and selective reporting.
Results

From a total of 47 potential studies, 6 RCTs met eligibility criteria, with a pooled sample size of 216 individual patients.9,13-17 Table 2 summarizes the study sample size, purpose, and key findings for each of the 6 included studies. All the studies included were RCTs. The studies included had the same general purpose, that is, to understand the efficacy of vasopressin or vasopressin analogues in maintaining blood pressure in patients who experienced ACE inhibitor–associated hypotension.9,13,16 The remaining studies examined the role of vasopressin or terlipressin in the treatment of refractory hypotension.14,15,17 Hasija et al.,14 Morales et al.,15 and Papadopoulos et al17 included only patients undergoing coronary artery bypass, whereas Meersschaert et al.,9 Boccara et al.,13 and Morelli et al16 included only patients undergoing vascular surgery.

Figure 3 depicts the quality of evidence using a domain-based approach to summarize the risk of bias in the individual studies.12 All the studies displayed a low risk of selection bias.9,12,14-17 Most of the studies also displayed a low risk of performance and detection bias. The risk of attrition bias was unclear, because most of the studies did not address outcomes data after the postoperative recovery period. There was a mix between unclear risk and higher risk of reporting bias among the studies.

Discussion

This review examined the best available current knowledge of vasopressin and vasopressin analogues for the treatment of refractory hypotension associated with ACE inhibitors in the perioperative setting. This study adds to the existing literature, in which only a review using neonates was previously found.10

Of the 6 studies included in our review, all were RCTs with reasonably little bias.9,13-17 Although all of the studies reported a sample between 27 and 50 subjects, the samples were adequate to achieve statistically significant differences in each study. In addition, some studies specifically reported an adequate number of subjects to achieve power analyses greater than 75% and 90%. Therefore, it is reasonable to consider the clinical utility of vasopressin and vasopressin analogues for the treatment of ACE inhibitor–associated hypotension in the perioperative setting. However, this evidence is limited to patients undergoing coronary artery bypass or vascular surgery, and research in other surgical populations is needed.

For the management (prevention and treatment) of ACE inhibitor–associated hypotension in the perioperative setting, each of the studies reviewed demonstrated success with vasopressin or terlipressin for improvement of systemic blood pressures. Boccara and colleagues13 state that 1 to 2 U of intravenous vasopressin is appropriate for the management of refractory hypotension intraoperatively once the standard doses of ephedrine and phenylephrine have been tried without success. The benefit of using vasopressin to treat hypotension far outweighs the deleterious effect of profound hypotension. Discontinuation of the ACE inhibitor on the day of surgery does not put the patient at risk of profound hypertension and should be considered the preferred method of blood pressure regulation for patients prescribed this medication presenting on the day of surgery.

In common clinical practice, clinicians may have also encouraged the use of an anticholinergic medication such as atropine or glycopyrrolate. However, these medications were not included in the studies reviewed here. This could possibly be due to the concurrent tachycardia that patients may exhibit in their vasoplegic state. Future studies should incorporate anticholinergic agents as an additional comparison outcome.

Although terlipressin was used frequently in the research and shown to be efficacious in maintaining systemic blood pressure, it is not currently available in the United States.2 Therefore, additional studies may be necessary to determine comparative doses of vasopressin agonists available in the United States. Morelli and colleagues16 did suggest the potential detrimental effects of terlipressin on the gastrointestinal mucosa, stating that a decrease in gastric mucosal perfusion was detected by laser Doppler flowmetry over 30 minutes, but this decrease was notable only with a continuous infusion of vasopressin. Future research would be useful to assess for the potential negative outcomes associated with vasopressin or terlipressin when used intermittently for the treatment or prevention of ACE inhibitor–associated refractory hypotension in the perioperative setting. However, it can be inferred from the included studies that patients who exhibit refractory hypotension and are taking an ACE inhibitor may exhibit more hemodynamic stability if administered a dose of vasopressin intraoperatively. Synergism between vasopressin and ephedrine is also a proposed method of increased arterial blood pressure.14

The studies reviewed did not address long-term outcomes data, introducing some potential long attrition bias. The studies reviewed included only patients undergoing coronary artery bypass14,15,17 or vascular surgery.9,13,16 Therefore, findings of the studies may not be representative of all surgical patients who experience ACE inhibitor–associated refractory hypotension. Limitations also include the generalizability of the studies included in the systematic review due to a small sample size limited to coronary artery bypass and vascular surgeries. However, this is currently the evidence available for review, and a larger meta-analysis or randomized control trial is warranted.
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<th>Author, year</th>
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| Boccara et al,13 2013 | 42             | To compare terlipressin to the standard vasopressor agent (norepinephrine) for treatment of refractory hypotension after general anesthesia in patients undergoing carotid surgery and treated long term with ACE inhibitors or angiotensin II blockers | • Terlipressin and norepinephrine corrected hypotension in all cases. Time spent with systolic blood pressure < 90 mm Hg was less in the terlipressin group.  
• Terlipressin was more effective than norepinephrine and had more prolonged action in controlling arterial blood pressure without any significant adverse effects.  
• Terlipressin was not associated with undesirable arterial blood pressure increase or heart rate response.  
• Proposed fluid loading before induction and titration of propofol to obtain hemodynamic stability. |
| Hasija et al,14 2010 | 47             | To compare the effects of continuation vs discontinuation of the ACE inhibitor ramipril and assess the efficacy of prophylactic vasopressin infusion on hemodynamic stability and vasoactive drug requirements in patients undergoing coronary bypass surgery | • Patients who discontinued use of their ramipril the morning of their surgery had higher mean arterial pressures and systemic vascular resistance compared with those who continued use of their ramipril the morning of surgery.  
• The low-dose vasopressin group required lower norepinephrine doses and had fewer hypotensive episodes and shorter intubation times.  
• No ischemic complications were noted, and urine output in patients who received vasopressin was similar to that in the control group. |
| Meersschaert, et al,9 2002 | 40             | To test the administration of terlipressin with ephedrine vs ephedrine alone to restore blood pressure in ACE inhibitor-treated patients undergoing anesthesia | • Hypotensive episodes requiring vasoconstrictive treatment are frequent after the induction of general anesthesia in patients treated long term with ACE inhibitors.  
• Hypotensive episodes may be unresponsive to ephedrine administration, and the combination of ephedrine and terlipressin is a more effective treatment of hypotension occurring in these patients.  
• With a partially blocked endogenous response to hypotension, the use of a vasopressin analogue is useful in maintaining intraoperative blood pressure. |
| Morales et al,15 2003 | 27             | In patients undergoing cardiopulmonary bypass, this study sought to examine whether initiation of vasopressin before bypass would diminish hypotension postoperatively by avoiding vasopressin deficiency | • Vasopressin reduced the number of hypotensive episodes and decreased the duration of catecholamine infusions, leading to earlier extubation.  
• Vasopressin increases cytosolic calcium levels through inositol trisphosphate second messenger system and antagonizes the vasodilatory mechanisms of shock. |
| Morelli et al,16 2005 | 32             | To compare effects of terlipressin and norepinephrine on systemic and regional hemodynamics when used to treat anesthesia-induced hypotension in patients treated long term with ACE inhibitors or angiotensin II receptor blockers | • Norepinephrine group experienced increased mean arterial pressures as well as an increase in gastric mucosal perfusion as noted by Doppler flowmetry.  
• Terlipressin was associated with an overall reduction in oxygen consumption as well as gastric mucosal perfusion, but an increase in mean arterial pressure.  
• Terlipressin did not increase the heart rate significantly; however, norepinephrine did increase the heart rate. |
| Papadopoulos et al,17 2010 | 50             | To examine the possible role of prophylactic infusion of low-dose vasopressin during and for 4 hours after cardiopulmonary bypass to reduce vasoplegic shock for patients currently receiving ACE inhibitors with a low ejection fraction | • Incidence of vasodilatory shock was significantly lower in the vasopressin group (4%) compared with the control group (20%).  
• Cannot conclude an appropriate dose of vasopressin because of lack of evidence.  
• Showed that pulmonary vascular resistance and mean pulmonary artery pressure were not affected by the vasopressin infusion.  
• Increased 24-hour diuresis in the patients in the vasopressin group.  
• Catecholamine infusion time was significantly lower in the vasopressin group. |

Table 2. Matrix of Studies, Sample Size, Purpose, and Key Findings
Abbreviation: ACE, angiotensin-converting enzyme.
Another possible limitation in the review is the patients’ compliance when asked to discontinue use of their medications on the day of their procedure and to continue use of other medications such as β-blockers. Confusion among patients regarding their preoperative instructions could limit the findings of the 6 studies mentioned. There is also potential for the patient’s record to be augmented, especially in the paper charts where providers may omit low blood pressures. Terlipressin also remains unavailable in the United States, which does not allow for practitioners to administer the vasopressin analogue. Further research is needed with the use of computer charting as well as addressing clear patient instructions in the preoperative interview regarding the continuation or discontinuation of their current medications.

**Conclusion**

Each of the included studies provides evidence to suggest success with small bolus doses of vasopressin or terlipressin for improvement of systemic blood pressure in the perioperative period for patients taking an ACE inhibitor 24 hours before surgery. Suggested dosing for vasopressin according to Boccara and colleagues\(^\text{13}\) was 1 or 2 U for intraoperative hypotension refractory to standard doses of phenylephrine or ephedrine. Before vasopressin is widely accepted as a standard of care, further studies would be beneficial to assess the general utility of vasopressin in surgical populations for treatment or prevention of ACE inhibitor–associated refractory hypotension. However, suggestions can be made for its use intraoperatively in a patient experiencing refractory hypotension currently receiving an ACE inhibitor.

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The authors have declared they have no financial relationships with any commercial interest related to the content of this activity. The authors did discuss off-label use within the article.

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