**Terlipressin Versus Norepinephrine to Correct Refractory Arterial Hypotension after General Anesthesia in Patients Chronically Treated with Renin-Angiotensin System Inhibitors**

Gilles Bocara, M.D., Ph.D.,* Alexandre Ouattara, M.D., M.Sc.,* Gilles Godet, M.D.,* Eric Dufresne, M.D.,* Michèle Bertrand, M.D.,* Bruno Riou, M.D., Ph.D.,† Pierre Coriat, M.D.,‡

**Background:** Terlipressin, a precursor that is metabolized to lysine-vasopressin, has been proposed as a drug for treatment of intraoperative arterial hypotension refractory to ephedrine in patients who have received long-term treatment with renin-angiotensin system inhibitors. The authors compared the effectiveness of terlipressin and norepinephrine to correct hypotension in these patients.

**Methods:** Among 42 patients scheduled for elective carotid endarterectomy, 20 had arterial hypotension following general anesthesia that was refractory to ephedrine. These patients were the basis of the study. After randomization, they received either 1 mg intravenous terlipressin (n = 10) or norepinephrine infusion (n = 10). Beat-by-beat recordings of systolic arterial blood pressure and heart rate were stored on a computer. The intraoperative maximum and minimum values of blood pressure and heart rate, and the time spent with systolic arterial blood pressure below 90 mmHg and above 160 mmHg, were used as indices of hemodynamic stability. Data are expressed as median (95% confidence interval).

**Results:** Terlipressin and norepinephrine corrected arterial hypotension in all cases. However, time spent with systolic arterial blood pressure below 90 mmHg was less in the terlipressin group (0 s [0–120 s] vs. 510 s [120–1011 s]; P < 0.001). Nonresponse to treatment (defined as three boluses of terlipressin or three changes in norepinephrine infusion) occurred in zero and eight cases (P < 0.05), respectively.

**Conclusions:** In patients who received long-term treatment with renin-angiotensin system inhibitors, intraoperative refractory arterial hypotension was corrected with both terlipressin and norepinephrine. However, terlipressin was more rapidly effective for maintaining normal systolic arterial blood pressure during general anesthesia.

**ARTERIAL hypotension following general anesthesia induction** that is refractory to ephedrine has been reported in patients undergoing long-term therapy with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin-II receptor antagonists (AIIRAs).1,2 Use of terlipressin (a drug precursor metabolized to lysine-vasopressin by plasmatic esterases) has been proposed for the treatment of refractory intraoperative hypotension in patients undergoing long-term treatment with renin-angiotensin system inhibitors.1–3 Terlipressin, which has been used for hemorrhage from rupture of esophageal varices, acts via the vasopressin system, which may be considered as the third physiologic system for the modulation of arterial blood pressure.4

The vasopressin system consists essentially of arginine-vasopressin, a postpituitary nine amino-acid peptide, which stimulates vasopressin receptors, especially vascular V1a receptors, inducing marked arterial constriction. Use of vasopressin has been previously suggested for the treatment of circulatory arrest and hemorrhagic and septic shock.5–7 Significant vasoconstriction has been noted in healthy and endotoxemic sheep (a 40% and 120% increase, respectively, in systemic vascular resistance) when terlipressin was infused 30 min before norepinephrine.8

Recently, when terlipressin was given with ephedrine, it was shown to be effective in reversing intraoperative systemic hypotension refractory to ephedrine alone.9 However, the administration of terlipressin on its own to treat intraoperative arterial hypotension has not been compared with use of vasopressors, such as sympathetic adrenoreceptor agonists. Therefore, we conducted a prospective randomized study to compare terlipressin to the standard vasopressor agent (norepinephrine) for treatment of refractory artery hypotension following general anesthesia in patients undergoing carotid surgery and chronically treated with ACEIs or AIIRAs.

**Methods**

**Study Population**

This prospective study was approved by the ethical committee for human research of our hospital, and written informed consent was obtained in all patients. Patients scheduled for elective carotid endarterectomy under general anesthesia and undergoing long-term treatment with ACEIs or AIIRAs for arterial hypertension were selected for this prospective study. Exclusion criteria included emergency surgery, administration of ACEIs for chronic cardiac failure, untreated or controlled coronary artery disease, chronic renal disease (estimated creatinine clearance less than 70 ml/min with
use of the Cockcroft and Gault formula,\textsuperscript{10} and contraindications to terlipressin, e.g., asthma, chronic pulmonary disease, and pregnancy. Refractory artery hypotension following general anesthesia was defined as a systolic arterial blood pressure (SBP) of less than 90 mmHg or a 30% decrease from the baseline value, despite administration of three intravenous 6-mg boluses of ephedrine. Only patients who had refractory artery hypotension were included for analysis in the study and received either terlipressin or norepinephrine. All these patients were randomly assigned to one of the two study groups (terlipressin or norepinephrine) by opening an envelope just before treatment.

**Anesthetic Management**

Before surgery, a detailed history was obtained and physical examination was performed by a staff anesthesiologist. Three sets of SBP and heart rate (HR) measurements were obtained during the 24 h preceding surgery and were averaged to establish baseline values. Serum cardiac troponin Ic measurement and 12-lead electrocardiography were performed before surgery.

One hour before surgery, all patients were premedicated with 5 mg oral midazolam and their usual cardiovascular medication, except ACEIs or AIIRAs, which were withdrawn 24 h before. Monitoring included five-lead electrocardiography with electrocardiographic wave segment trends on leads V_{1}, V_{5}, and II, invasive arterial blood pressure measurement, and determinations of pulse oxygen saturation, end-tidal carbon dioxide, and inspiratory and end-tidal anesthetic concentrations. The depth of hypnosis was monitored by bispectral index (BIS) analysis (BIS® monitor, Aspect Medical Systems, Newton, MA) (BIS index, 0–100) of the electroencephalographic wave. After placement of an intravenous catheter and 10-ml/kg crystalloid infusion (Ringer's lactate solution), the patients received a loading dose of 0.5 μg/kg sufentanil within 30 s, with additional boluses if required.

Target-controlled infusion of propofol (Diprifusor, Master TCI infusion system; Fresenius-Vial, Brezins, France) was administered, with a plasma concentration target of 2 μg/ml within 3 min. It was progressively increased until loss of consciousness and a BIS below 60 had been obtained. After 0.5-mg/kg infusion of atracurium and tracheal intubation, ventilation (10 ml/kg in 12 min) with an air/oxygen mixture of 50/50% was controlled to maintain an end-tidal carbon dioxide level of between 30 and 35 mmHg. Propofol was administered for maintenance of anesthesia, and the dose was adjusted to obtain a BIS of between 40 and 60.

The endotracheal tube was removed in the surgical room for all patients, and then they were installed postoperatively in the recovery room for at least 2 h. Postoperative care, including hemodynamic monitoring and treatments and standardized nursing care, was under the supervision of the attending anesthesiologist in the recovery room. Postoperative analgesia consisted of 2-g intravenous propacetamol infusion and intravenous morphine titration to obtain a visual analog pain scale (0–100) value less than 30 before discharge from the recovery room.

Twelve-lead electrocardiography was performed at the end of surgery, and findings were compared with those obtained preoperatively. Electrocardiography was repeated daily on the first 3 postoperative days. Serum cardiac troponin Ic levels were measured on induction, at 1 h after surgery, and on the first 3 postoperative days. These measurements were repeated if any abnormal value was detected.

**Experimental Protocol**

If arterial hypotension refractory to ephedrine occurred during anesthesia, the patient received terlipressin or norepinephrine. Both drugs were prepared before induction of anesthesia, and the study drug was revealed only after opening of the envelope when refractory hypotension occurred. Terlipressin (Glypressin; Ferring, Malmö, Sweden) was infused in 1-mg intravenous boluses up to 3 mg if needed. Norepinephrine (Noradrenaline; Agueuttant, Lyon, France) solution (50 μg/ml) was infused intravenously at an initial rate of 10 ml/h, and the dosage was changed incrementally by 2 ml/h if needed. Patients were considered to be nonresponsive to treatment if three or more terlipressin boluses and three or more norepinephrine infusion rate changes were required. If terlipressin failed to diminish arterial hypotension, a 0.5-mg intravenous bolus of epinephrine was used. If there was no response to norepinephrine treatment, a similar 0.5-mg intravenous bolus of epinephrine was given.

The SBP and HR signals obtained from the monitor (TRAM; Marquette Hellige Electronics, Roissy, France) were acquired at a 200/s sample rate and stored on a personal computer hard drive with use of an analog-to-digital converter data acquisition system (MP30; BIOPAC Systems, Goleta, CA). After checking for removal of artifacts and arterial catheter flushing, each complete arterial pressure tracing was scanned for a beat-by-beat analysis. SBP and HR values were stored on Excel 5.0 files (Microsoft, Redmond, WA) for each patient. All files were scanned again to determine whether the hemodynamic abnormalities were artifacts or real events. Then duration of arterial hypotension and the time spent with SBP between 90 and 160 mmHg was calculated for the period from induction of anesthesia to 5 min after extubation. In addition, the highest and lowest SBP values and the highest and lowest HR values during this period were recorded. The total volume of fluid infusion and the total doses of anesthetic agents, terlipressin doses, and norepinephrine infusion rate changes were recorded in both groups.
Besides hypotension, a hemodynamic event was defined as (1) hypertension lasting more than 1 min (i.e., an SBP value greater than 160 mmHg or greater than 30% of baseline value); (2) tachycardia lasting more than 1 min (i.e., an HR value greater than 90 beats/min or greater than 30% of baseline value); or (3) bradycardia lasting more than 1 min (i.e., an HR value lower than 45 beats/min or less than 30% of baseline value). The total durations and the number of patients experiencing these events were calculated.

Adverse events were defined by the occurrence of transient ischemic attack, nonreversible neurologic deficits, myocardial infarction, acute renal failure, or death. Transient ischemic attack was defined as a focal ischemic neurologic deficit of abrupt onset, lasting at least 30 s and resolving completely within 24 h. Nonreversible neurologic deficit was defined as a focal neurologic deficit persisting longer than 24 h. Myocardial infarction was defined as a cardiac troponin level higher than 1.5 ng/ml (Stratus TnIc assay; Dade Berhing, Massy, France), with or without associated electrocardiographic changes. Acute renal failure was defined as a creatinine clearance decrease to below 70 ml/min and/or a 20% serum creatinine concentration increase.

Statistical Analysis
The main endpoint was the incidence of nonresponse to treatment as defined above, i.e., if three or more boluses of terlipressin and three or more norepinephrine infusion rate changes were required. In a preliminary study, we observed that nonresponse occurred in 80% of cases with norepinephrine. Thus, we calculated that 18 patients would be necessary for the assessment of a 50% reduction in patients for whom the vasopressor treatment failed, with an α risk of 0.05 and a β risk of 0.20. Patients were allocated to treatment groups with a computer-generated random list equilibrated for every 10 patients. Comparison of two means was performed with the Student t test, comparison of two medians with the Mann–Whitney U test, and comparison of two percentages with the Fisher exact method. Data are expressed as mean ± SD, median (95% confidence interval), or number (percentages). All P values are two-tailed, and a P value of less than 0.05 was considered significant.

Results
Forty-two patients being treated on a long-term basis with renin-angiotensin system inhibitors for hypertension gave their informed consent and were enrolled in the study. Among them, 20 patients (47%) had arterial hypotension refractory to ephedrine following general anesthesia and randomly received either terlipressin (n = 10) or norepinephrine (n = 10). The patients’ characteristics and intraoperative data are shown in tables 1 and 2. The mean values of SBP and HR before general anesthesia induction were not significantly different between the groups (table 3). No significant differences were found in the lowest SBP values (table 3).

The mean duration of hypotension or hypertension was higher in the norepinephrine group (table 3). The rates of hypertension, hypotension, or tachycardia and the number of patients experiencing these hemodynamic events were higher in the norepinephrine group (table 3). No significant differences in volume loading were found between groups. Nonresponse to treatment of hypotension occurred less frequently in the terlipressin group (0% vs. 80%; P < 0.05) (fig. 1). Only two patients in the terlipressin group required two boluses of terlipressin. In both groups, terlipressin or norepinephrine was effective to counteract intraoperative arterial hypotension, and no patients required further treatment with epinephrine (fig. 2).

During the recovery period, the mean SBP values and the number of patients experiencing arterial hypertension were not significantly different between groups (table 4). No patient experienced bradycardia or hypotension. No significant changes in troponin Ic levels were found in any patients. No deaths occurred in the study population. One postoperative myocardial infarc-
tion was observed in the norepinephrine group on the first postoperative day, with electrocardiographic wave segment depression noted with electrocardiography and a troponin Ic level of 2.7 ng/ml. One postoperative transient ischemic attack occurred in the terlipressin group. No acute renal dysfunction was observed postoperatively.

Discussion

Our study demonstrates that terlipressin is better than norepinephrine in the treatment of arterial hypotension refractory to ephedrine following general anesthesia in patients undergoing long-term treatment with renin-angiotensin system inhibitors. Terlipressin was more effective and had more prolonged action than norepinephrine in controlling arterial blood pressure without any significant adverse effects. In addition, terlipressin was not associated with an undesirable arterial blood pressure increase and HR response.

Terlipressin is classically indicated for the treatment of gastrointestinal bleeding in patients with ruptured esophageal varices. Terlipressin or triglycyl-vasopres-
sin, a synthetic vasopressin system analog, is slowly metabolized to lysine-vasopressin by plasma esterases. In addition, terlipressin has interesting systemic vasoconstrictive properties because it activates the V1 vascular-specific receptors of vasopressin. Two to 3 minutes after administration, this drug exerts a long-lasting effect (30–60 min) on increasing arterial blood pressure (6–18%), in association with a slight decrease in HR (10–16%), in healthy volunteers and cirrhotic patients in whom terlipressin is used to treat hemorrhage from esophageal varices. Lysine-vasopressin activates specific vascular vasopressin receptor V1, inducing systemic arterial vasoconstriction. However, whether the same effect can be observed on coronary arteries is still a subject of controversy. Vasopressin can induce moderate coronary vasodilatation or vasoconstriction, depending on endothelial nitric oxide.

Arginine-vasopressin has already been proposed for treatment of intraoperative vasodilatation occurring after cardiopulmonary bypass in patients treated with amiodarone and ACEIs. Equally, terlipressin has been suggested as the ideal agent for patients undergoing long-term treatment by ACEIs when refractory hypotension to ephedrine occurs during anesthesia induction, since it acts on the third luminal vasopressor system, although the sympathetic system and the renin-angiotensin system are respectively blunted by general anesthesia and ACEIs or AIIRAs.

The successful terlipressin treatment of anesthesia-related hypotension refractory to ephedrine might suggest a post-fluid-treated vasodilatation state following late-phase hypovolemic shock. Mean arterial pressure and systemic vascular resistance evaluated from left ventricular wall stress on transesophageal echocardiography increased by 24% and 47%, respectively, with no major influence on myocardial performance. Eyraud et al. did not observe myocardial ischemia or any adverse cardiac outcome in patients receiving terlipressin. However, in the absence of chronic treatment with renin-angiotensin system inhibitors, the use of terlipressin to correct intraoperative arterial hypertension should be considered with caution, since myocardial ischemia has already been reported and its pathophysiologic mechanism is not yet established.

An intravenous 7.5-μg/kg infusion of terlipressin in healthy humans, the mean plasma concentration was 12 ± 6 nmol/l at 5 min and rapidly decreased, with a half-time elimination of 24 ± 2 min. Following intravenous terlipressin administration, lysin-vasopressin was measured only after 30–40 min and reached its maximal blood concentration (0.07 ± 0.01 nmol/l) within 120 min. Thus, terlipressin could immediately increase arterial blood pressure by either direct artery vasoconstriction or an increase in receptor affinity to adrenergic agents.

Previously, Eyraud et al. and Meerschaeert et al. have shown the effectiveness of terlipressin in treating arterial hypotension when it was infused simultaneously with ephedrine and therefore proved its adjuvant action with an sympathomimetic agent. It is recognized that ACEI induces a decrease in vascular adrenergic receptor sensitivity, limiting the clinical effect of adrenergic drugs such as ephedrine. Indeed, Licker et al. found an increase in the dose of adrenergic drug required to obtain the same vasopressor effect in patients with chronic blunting of the renin-angiotensin system.

A synergistic effect of vasopressin combined with ephedrine on the increase in intracellular calcium concentration in arterial smooth muscle cells has been previously reported. Vasopressin increases the response of α-1 adrenergic receptor to specific agonist, and α-adrenergic agonists enhance the vasopressin-induced vasoconstrictive effect by increasing the sensitivity of the vascular smooth muscle cells to calcium. These mechanisms might explain the beneficial effects of the combination of terlipressin, a vasopressin prodrug, and ephedrine to counteract arterial hypotension in patients whose renin-angiotensin system is chronically blunted. Nevertheless, the intrinsic effect on arterial blood pressure of terlipressin administered alone has not been previously studied. In our study, correction of arterial hypertension with terlipressin suggests a direct and rapid vasoconstrictive effect of terlipressin in anesthesia patients in whom the renin-angiotensin system is chronically blunted.

Norepinephrine, a potent and direct α-1 adrenergic agonist, is considered to be more effective in treating arterial hypertension than ephedrine, although less easy to administer. When ephedrine fails to treat intraoperative arterial hypertension, norepinephrine is still considered to be the ideal vasopressor agent. However, its short duration of action and potent vasoconstrictive effect requires a continuous infusion with incremental adjustment to correct arterial hypertension without inducing major hypertension.

In our study, the global analysis of SBP variations showed that time spent below 90 mmHg was shorter in the terlipressin group and the incidence of prolonged arterial hypertension was lower, suggesting better intraoperative hemodynamic stability than that obtained with norepinephrine. Terlipressin enabled us to obtain a stable arterial blood pressure during vascular surgery, which is mandatory to limit the risk of stroke and/or myocardial ischemia. Moreover, only two patients required two doses of terlipressin to reach acceptable intraoperative hemodynamic stability. This indicates that a single terlipressin intravenous infusion following general anesthesia was more potent in limiting the decrease in SBP and maintaining hemodynamic stability without several manual and unforeseeable changes in continuous adrenergic infusion.

Our results suggest that these beneficial hemodynamic effects of terlipressin can be obtained without any in-
creased risk of intraoperative hypotension or postoperative hypertension or tachycardia. These results are of particular interest with regard to patients undergoing carotid endarterectomy, which carries the risk of significant complications related to intraoperative and postoperative hemodynamic disturbances. We did not find any significant differences in SBP or HR changes between the two groups during the recovery period. The similar hemodynamic response to recovery in both groups shows that intraoperative stability observed with terlipressin is not associated with an increased circulatory response to recovery, which might have resulted from its pharmacokinetic properties.

Some remarks must be included to assess the clinical relevance of our study. First, terlipressin was administered following the failure of ephedrine to restore arterial blood pressure, and therefore the residual action of the sympathomimetic effect of ephedrine cannot be excluded. For ethical reasons, we infused terlipressin only after ephedrine administration. Ephedrine is considered to be the first-line drug for treatment, and it succeeds in 53% of patients with nonrefractory hypotension. By contrast, norepinephrine was used as a continuous infusion to avoid the unforeseeable changes in arterial blood pressure. However, the concentration of norepinephrine (50 μg/ml) and the high rate of infusion (less than or equal to 10 ml/h) led to a successful increase in arterial blood pressure in 5 min, and no intravenous bolus of norepinephrine or epinephrine was required.

Second, the sample size of our population was not sufficient to conclude definitively that the incidence of adverse effects did not differ between the two study groups. Further clinical studies in larger populations are needed. Last, propofol used in general anesthesia is recognized as having a dose-dependent vasorelaxant effect without myocardial inotropic action. However, propofol administered by target-controlled infusion under BIS monitoring was chosen to avoid inappropriate deep anesthesia and its undesirable cardiovascular consequences. It has been suggested that BIS monitoring to adjust the depth of general anesthesia with strictly controlled targets of 40–60 offers a reduction in intraoperative low arterial blood pressure during cardiac surgery. The use of fluid loading before induction and titration of propofol dosing has been previously proposed to obtain hemodynamic stability, mainly in cardiac and vascular surgeries.

Conclusion

Terlipressin was more effective than norepinephrine for treatment of arterial hypotension following general anesthesia in patients with a blunted renin-angiotensin system. This short-acting vasopressor agent appears to be a useful alternative to norepinephrine in patients undergoing carotid surgery who have received long-term treatment with renin-angiotensin system inhibitors. Further studies in a larger population are required to establish tolerance of terlipressin in this clinical condition.

The authors thank Dr. David Baker, D.M., F.R.C.A. (Department of Anesthesiology, CHU Necker-Enfants Malades), for reviewing the manuscript.

References