Treatment of Intraoperative Refractory Hypotension with Terlipressin in Patients Chronically Treated with an Antagonist of the Renin-Angiotensin System

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The goal of the present study was to determine whether terlipressin, an agonist of the vasopressin system, could counteract perioperative hypotension refractory to common vasopressor therapy and to analyze its circulatory effects. We enrolled 51 consecutive vascular surgical patients chronically treated with angiotensin-converting enzyme inhibitors or antagonists of the receptor of angiotensin II, who received a standardized opioid-propofol anesthetic. Of these 51 patients, 32 had at least one episode of hypotension, which responded to epinephrine or phenylephrine. In 10 other patients, systolic arterial pressure (SAP) did not remain above 100 mm Hg for 1 min, despite three bolus doses of ephedrine or phenylephrine. In these patients, we injected a bolus of 1 mg of terlipressin, repeated twice if necessary. Hemodynamic and echocardiographic variables were recorded every 30 s over 6 min. In eight patients, arterial pressure was restored with one injection of terlipressin; in two other patients, three injections were necessary. One minute after the last injection of terlipressin, the SAP increased from 88 ± 3 to 100 ± 4 mm Hg and reached 117 ± 5 mm Hg ($P = 0.001$) 3 min after the injection and remained stable around this value. This increase in SAP was associated with significant changes in left ventricular end-diastolic area (17.9 ± 2 vs 20.2 ± 2.2 cm^2; $P = 0.003$), end-systolic area (8.1 ± 1.3 vs 9.6 ± 1.5 cm^2; $P = 0.004$), end-systolic wall stress (45 ± 8 vs 66 ± 12; $P = 0.001$), and heart rate (60 ± 4 vs 55 ± 3 bpm; $P = 0.001$). Fractional area change and velocity of fiber shortening did not change significantly. No additional injection of vasopressor was required during the perioperative period. No change in ST segment was observed after the injection. **Implications:** Terlipressin is effective to rapidly correct refractory hypotension in patients chronically treated with antagonists of the renin-angiotensin system without impairing left ventricular function.

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Angiotensin-converting enzyme inhibitors (ACEI) have been established as an important treatment in arterial hypertension (1). Several reports have warned of profound hypotensive episodes in patients receiving ACEIs as long-term therapy, particularly during the induction of anesthesia and during surgical procedures involving major body fluid shifts (3,4). Reduction of perioperative morbidity in high-risk patients requires early and effective treatment of hypotension (5). In patients chronically treated with ACEIs, the efficacy of α_1-adrenergic agonists is reduced (6,7). Infusion of angiotensin II (AII) has been proposed to restore arterial pressure (AP) (8–10), but AII is no longer commercially available. A new class of antihypertensive drugs, the AII receptor antagonists (AIIR1A), has recently emerged. Because they competitively block AII receptors, they should suppress AII effects better than ACEI. Several studies (11–14) have demonstrated the role of vasopressin in maintaining AP, especially when the sympathetic and renin angiotensin systems are blunted. In the present study, we tested whether terlipressin, a vasopressinergic agonist, with effectively restored AP in patients chronically treated with ACEIs or AIIR1A and presenting with severe hypotension during anesthesia.

Methods

After institutional approval and informed patient consent had been obtained, we enrolled patients chronically treated with ACEI or AIIR1A who were undergoing vascular surgery. The usual cardiac medications were administered until the morning of surgery. ACEI

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Table 1. Clinical Characteristics and Therapy of the Patients

Characteristic	Refractory hypotension (n = 10)	No refractory hypotension (n = 41)
Age (yr)	72 ± 4	67 ± 1
Gender ratio (M/F)	9/1	34/7
Weight (kg)	75 ± 3	71 ± 2
Associated chronic treatment with calcium blockers or β-blockers	7 (70%)	29 (71%)
Carotid/aortic/peripheral vascular surgery	4/3/3	24/11/6
Indication for treatment with ACEI or AIIR1A		
Hypertension	7 (70%)	31 (75%)
Cardiac dysfunction	3 (30%)	10 (25%)
Clinical history of ischemic heart disease (mild angina, previous coronary bypass)	4 (40%)	14 (34%)
Preoperative		
SAP (mm Hg)	147 ± 6	151 ± 3
MAP (mm Hg)	102 ± 4	104 ± 2
DAP (mm Hg)	79 ± 4	82 ± 2

Values are n (%) or mean ± SEM.
SAP = systolic arterial pressure, MAP = mean arterial pressure, DAP = diastolic arterial pressure, ACEI = angiotensin-converting enzyme inhibitors, AIIR1A = angiotensin II receptor antagonists.

were stopped at least 12 h (captopril) or 24 h (others) before surgery. Patients chronically treated with direct AIIR1A received their usual dose on the morning of surgery. All patients were premedicated with oral midazolam (5 mg). A five-lead electrocardiogram (ECG) with computerized analysis of ST segment was used throughout the surgical procedure. A radial artery catheter was inserted before the induction of anesthesia for monitoring of arterial blood pressure.

All patients received 10 mL/kg lactated Ringer's solution before induction. Anesthesia was induced with propofol (1.5 mg/kg) and sufentanil (0.5 μg/kg) with patients breathing 100% oxygen. Atracurium (0.5 mg/kg) was then injected, and the trachea was intubated. Anesthesia was maintained with controlled ventilation (N_2O/O_2 60%/40%) and isoflurane at end-tidal expired concentration of 0.2%–0.4%. All study measurements were performed before incision.

After the induction of general anesthesia, a transesophageal echocardiographic (TEE) probe was positioned to obtain left ventricular (LV) cross-sectional images at the midpapillary muscle level (15). End-systolic and end-diastolic diameters and areas (ESD, EDD, ESA, EDA) were measured before and every 30 s after the injection of terlipressin and then over 6 min. Systolic, mean, and diastolic arterial pressures (SAP, MAP, DAP) and ECG were displayed together. Fractional area change (FAC), mean velocity of circumferential fiber shortening ($mVcf_c$), and end-systolic wall stress (ESWS) were then calculated to assess LV function and afterload as previously described (10).

Arterial hypotension was defined as a SAP of <85 mm Hg or a decrease in SAP >30% below baseline value. Baseline SAP was the mean of three measurements performed on the day preceding surgery in patients at rest for 10 min. If hypotension occurred, a bolus of 6 mg of ephedrine (heart rate [HR] <60 bpm) or 100 μg of phenylephrine (HR >60 bpm) was administered IV. This bolus was repeated twice if SAP did not remain >100 mm Hg during 1 min. If this goal was not reached, hypotension was considered as refractory, and we injected a bolus of 1 mg of terlipressin, repeated once or twice if SAP did not remain >100 mm Hg for 1 min within 3 min after the injection of terlipressin. Terlipressin (Glypressine; Ferring AB, Malmö, Sweden), triglycyl-lysine vasopressin, is a synthetic vasopressin analog with intrinsic vasoconstrictor activity. We chose the dose of 1 mg in agreement with our preliminary results, which showed that a smaller dose was not effective to increase SAP in this situation.

Results are expressed as the mean ± SEM. Comparison of means was performed using the paired Student's t-test. A P value <0.05 was considered significant. Hemodynamic and TEE values were compared before the injection of terlipressin and 3 min after the last injection.

Results

Of the 51 consecutive vascular surgical patients enrolled, 10 presented refractory hypotension after induction (Table 1). The clinical characteristics, including gender, type of surgery, age, and weight, were not different between the two groups, with or without refractory hypotension. Among the 10 patients who presented with refractory hypotension, 3 were chronically treated with AIIR1A and 7 were treated with ACEIs. In 41 other patients, 7 were chronically treated with AIIR1A and 34 with ACEIs. In these 41 patients, 32 presented with at least one episode of hypotension, which responded to ephedrine or phenylephrine.

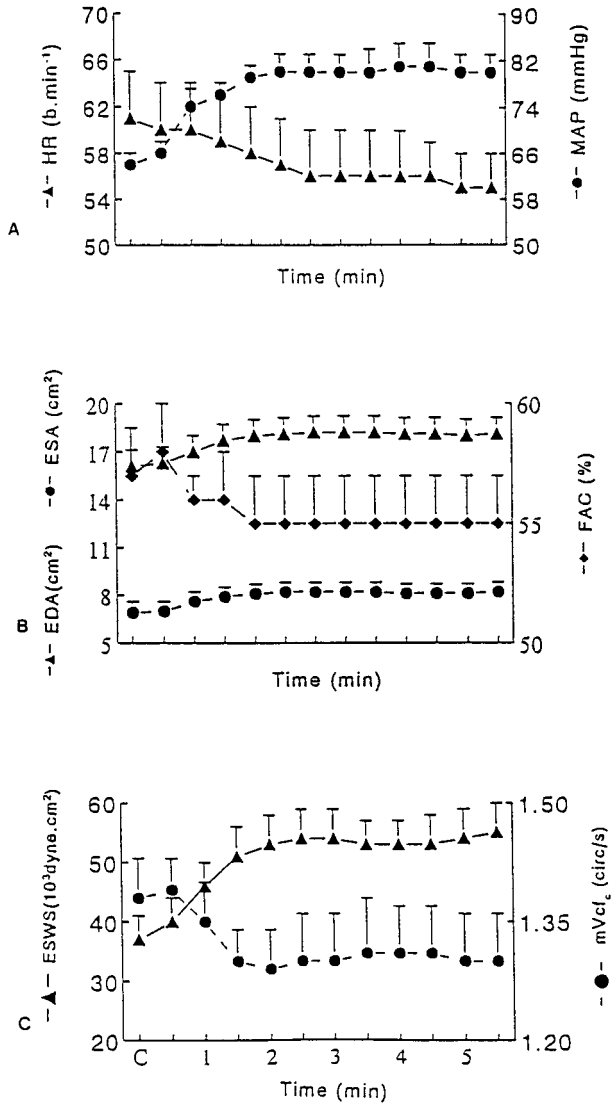

Figure 1. A, Evolution of mean arterial pressure (MAP) and heart rate (HR) after the last injection of terlipressin. B, Evolution of left ventricular end-diastolic area (LVEDA), left ventricular end-systolic area (LVESA), and fractional area change (FAC) after the last injection of terlipressin. C, Evolution of end-systolic wall stress (ESWS) and mean velocity of fiber shortening ($mVcf_c$) after the last injection of terlipressin. Values are expressed as mean ± SEM.

In patients with refractory hypotension, SAP decreased from 147 ± 6 to 82 ± 3 mm Hg during anesthetic induction. Refractory hypotension persisted despite the injection of ephedrine (n = 7) or phenylephrine (n = 3). Eight patients received one dose of terlipressin and two patients received three doses.

All patients showed significant increases in AP after the administration of terlipressin (Fig. 1). The onset of increase in SAP occurred at 60 s (Fig. 1). This was associated with a significant decrease in HR and a significant increase in EDA, ESA, and ESWS. No significant changes in FAC or $mVcf_c$ were noted (Table 2). No additional injection of vasopressor was needed during the perioperative period. No change in ST segment was observed.

Table 2. Comparison of Values Before and 3 Minutes After the Last Injection of Terlipressin

Variable	Control	Terlipressin	P
HR (bpm)	60 ± 4	55 ± 3	0.001
MAP (mm Hg)	65 ± 2	80 ± 3	0.001
EDA (cm^2)	17.9 ± 2	20.2 ± 2.2	0.003
ESA (cm^2)	8.1 ± 1.3	9.6 ± 1.5	0.004
FAC	0.56 ± 0.02	0.53 ± 0.02	
$mVcf_c$ (Circ/s)	1.30 ± 0.08	1.23 ± 0.08	
ESWS (10^3 dynes/cm^2)	45 ± 8	66 ± 12	0.001

Values are expressed as mean ± SEM.
MAP = mean arterial pressure, HR = heart rate, EDA = end-diastolic area, ESA = end-systolic area, FAC = fractional area change, $mVcf_c$ = mean velocity of circumferential fiber shortening, ESWS = end-systolic wall stress.

Discussion

Terlipressin was effective in rapidly restoring AP in patients chronically treated with ACEI or AIIR1A who presented with refractory hypotension after the induction of anesthesia. Changes in AP occurred at 60 s, and the peak occurred within 3 min after the injection. This rapid increase in AP was not associated with a decrease in LV function. This study also confirmed that significant hypotension may occur in patients chronically treated with ACEI or AIIR1A. Even if ACEI are discontinued the day before surgery, there is still the risk of hypotension at induction (4). This study showed that this risk also exists with AIIR1A.

The absent or limited effect of ephedrine or phenylephrine in patients chronically treated with ACEI confirms the attenuation of adrenergic response in these patients (7). Arterial blood pressure is maintained through the interplay of sympathetic, renin-angiotensin, and vasopressin systems. Blockade of one or two of these systems can be compensated by the others (11,13), but this compensatory effect may become compromised during anesthesia (16). In this situation, the role of vasopressin is increased (11). The exaggerated hypotensive response to induction is consistent with previous studies, which have shown that AII contributes to hemodynamic regulation during general and epidural anesthesia (13,17). It might also be the consequence of the specific effects of ACEI or AIIR1A on the loading conditions of the heart and/or the autonomic nervous system. The decrease in AP is accentuated by the presence of hypovolemia or impaired LV diastolic function, which are frequently seen in hypertensive and elderly surgical patients, in whom the vascular tonus is increased in the awake condition and decreased during anesthesia. Because sympathetic and renin-angiotensin systems were blunted in our patients by anesthesia and ACEI or

AIIR1A, their response to catecholamines was reduced, whereas the vasopressin system remained intact. Vasopressin has been recommended in the treatment ventricular fibrillation refractory to cardioversion (14), and has been shown to better increase coronary perfusion pressure and myocardial blood flow than epinephrine (18). Because vasopressin was not commercially available, we used terlipressin, a prodrug rapidly metabolized into lysine vasopressin, which binds to specific receptors on the vascular smooth muscle. Terlipressin is used to treat acute episodes of variceal bleeding in cirrhotic patients (19), but its use in refractory hypotension has never been reported. The time course (20) of the hemodynamic effects of terlipressin is consistent with previous reports concerning the injection of vasopressin in humans, as well as the absence of serious adverse effects, such as hypertension or myocardial ischemia (21).

Our results suggest that terlipressin restores AP mainly by increasing the vascular resistance, as shown by the increase in ESWS and ESA. The increase in EDA could be due to improvement in venous return (22), also explaining the lack of significant decrease in FAC in response to an increase in ESWS. The mean velocity of fiber shortening [a very sensitive variable to changes in ESWS but not to changes in EDA (18)], did not significantly decrease. This effect could be due to a slight improvement in LV function. Indeed, vasopressin enhances myocardial oxygen delivery and may increase cardiac contractility (18). This effect could be mediated by myocardial vasopressin.[1] Moreover, the moderate increase in AP explained the absence of a significant decrease in FAC or $mVcf_c$. In contrast, a bolus of 2.5 μg of AII caused a greater and more rapid increase in AP with a concomitant impairment in LV function (10). The increase in EDA could also be related to the increase in ESA and decrease in HR. It has been shown that vasopressin has no effect on capacitance vessels (24) but redistributes the cardiac output from long-time constant compartments, such as the splanchnic circulation. In contrast to AII, terlipressin preserved LV function and decreased HR. These effects might be beneficial in patients at risk of coronary disease because they could improve coronary perfusion and myocardial blood flow, in contrast to epinephrine (18) or AII (25).

The following points must be considered in the assessment of the relevance of our study: according to our protocol, it was not possible to compare terlipressin with AII because the latter drug is no longer commercially available. Finally we did not perform a dose-response study because a similar degree of blockade of the renin-angiotensin system would have been required in all patients to avoid methodological bias, and such conditions are very difficult to obtain *in vivo* (4).

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