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Terlipressin versus *Norepinephrine to Counteract Anesthesia-induced Hypotension in Patients Treated with Renin-Angiotensin System Inhibitors: Effects on Systemic and Regional Hemodynamics*

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Background: **Terlipressin has been suggested as the ideal drug to treat anesthesia-induced hypotension in patients under long-term renin-angiotensin system inhibitor treatment for arterial hypertension. The authors compared the effects of terlipressin and norepinephrine on systemic hemodynamic parameters and gastric mucosal perfusion using a laser Doppler flowmetry technique in patients treated with renin-angiotensin system inhibitors who experienced hypotension at induction of anesthesia.**

Methods: **Thirty-two patients scheduled for carotid endarterectomy under general anesthesia and treated with renin-angiotensin system inhibitors had hypotension after induction of general anesthesia. They were randomized to receive 1 mg of terlipressin (n = 16) or norepinephrine infusion (n = 16) to counteract anesthesia-induced hypotension. A laser Doppler probe was introduced into the gastric lumen. All measurements were performed just before surgery, during hypotension, at 30 min, and at 4 h.**

Results: **Terlipressin produced an increase in mean arterial pressure and a decrease in gastric mucosal perfusion detected by laser Doppler flowmetry ($P < 0.05$) over 30 min that were sustained for 4 h. During the infusion, norepinephrine produced an increase in mean arterial pressure and in gastric mucosal perfusion detected by laser Doppler flowmetry ($P < 0.05$). If compared to norepinephrine, terlipressin reduced oxygen delivery and oxygen consumption ($P < 0.05$) and increased arterial lactate concentrations ($P < 0.05$).**

Conclusion: **This study showed the efficacy of terlipressin in the treatment of hypotension episodes in anesthetized patients chronically treated with renin-angiotensin system inhibitors, angiotensin converting-enzyme inhibitors, and angiotensin II receptor antagonists. However, the negative effects on gastric mucosal perfusion and the risk of iatrogenic oxygen supply dependency of terlipressin need to be taken into account.**

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ANGIOTENSIN converting-enzyme inhibitors (ACEIs) and angiotensin II receptor antagonists (AIIRAs) are widely and indifferently used as first-line therapy in arterial hypertension in high-risk patients.[1,2] However, ACEIs and AIIRA therapy can strengthen the hypotensive effect of anesthetics, leading to severe hypotension.[3,4] Sympathetic adrenoceptor agonists are considered the standard treatment for anesthesia-induced hypotension.[5,6] Because the sympathetic system is impaired by general anesthesia and chronic ACEIs or AIIRAs therapy, terlipressin was suggested as the ideal drug to treat anesthesia-induced hypotension in patients with long-term ACEIs or AIIRAs treatment. Eyraud *et al.*[7] and Meersschaert *et al.*,[8] and recently Boccara *et al.*[9] have shown that terlipressin is effective in treating refractory hypotension in patients chronically treated by ACEIs or AIIRAs. Terlipressin acts *via* the vasopressin system, which may be considered an important physiologic system for the regulation of arterial blood pressure. This long-acting synthetic analog of vasopressin has a half-life of 6 h and a higher vascular selectivity for vascular receptors compared with vasopressin.[10] Significant vasoconstriction was clearly demonstrated in experimental setting.[11] In addition to its effects on microvascular blood flow, terlipressin also reduces cardiac output *via* reflex mechanisms mediated through glossopharyngeus baroreceptors reflex (aortic/carotid sinus baroreceptors).[12] The potent vasoconstrictor response on splanchnic macro and microcirculation, associated with the consequent decrease in cardiac output, may cause, or at least worsen, gut mucosal ischemia. Therefore, we conducted a prospective randomized study to compare the effects of terlipressin and norepinephrine on systemic and regional hemodynamics when used to treat anesthesia-induced hypotension in patients chronically treated with ACEIs or AIIRAs.

Materials and Methods

Patients

The study protocol was approved by the local institutional ethics committee of University "La Sapienza" of Rome, Italy. Patients gave informed written consent to participate in the study. Among 162 patients scheduled for elective carotid endarterectomy under general anesthesia, 50 consecutive patients chronically treated with

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Table 1. Characteristics of Patients Analyzed in the Study

Characteristics	Norepinephrine (n = 16)	Terlipressin (n = 16)
Age (yr)	67.8 ± 6	70 ± 7
Male/Female	13/3	14/2
Percutaneous coronary angioplasty	1	1
Coronary artery bypass graft	2	1
Chronic obstructive pulmonary disease	5	4
Diabetes mellitus	7	4
Perioperative treatment		
Calcium blockers	1	2
Beta blockers	1	1
Nitrates	3	2
Angiotensin-converting enzyme inhibitor		
Enalapril	9	10
Lisinopril	1	0
Captopril	2	1
Angiotensin II receptor antagonist		
Losartan	3	2
Candesartan	1	3

Data are mean ± SD or number of patients. There were no significant differences between groups.

renin-angiotensin system inhibitors (ACEIs or AIIRAs) for arterial hypertension and poor left ventricular function (left ventricular ejection fraction <45%) were enrolled in the study. Among the 50 patients enrolled, 32 experienced hypotension at the induction of anesthesia and hence were randomized and analyzed in the study. Anesthesia-induced hypotension was defined as mean arterial pressure (MAP) <60 mmHg or <30% of prestudy value. The prestudy value was the mean of four sets of measurements obtained 24 h before surgery. We analyzed only patients who experienced hypotension in presence of prefixed volume status, defined as pulmonary artery occlusion pressure (PAOP) between 12 and 18 mmHg in the presence of left ventricular end-diastolic volume index ≥70 ml/m^2. Patients were excluded if they had untreated and uncontrolled coronary artery disease, ACEI treatment for chronic symptomatic heart failure (New York Heart Association class III or IV), chronic renal disease (measured creatinine clearance less than 60 ml/min), or if the patient had a documented peripheral vascular disease. The clinical characteristics of the study groups are summarized in table 1.

Anesthetic Management

One hour before surgery all patients received their usual medications except ACEIs or AIIRAs, which were discontinued the day before surgery. A standardized induction technique was performed: 0.4 μg/kg of sufentanil were administered slowly (40 s) and then propofol was administrated using a target-controlled total intravenous anesthesia device (Diprifusor®, Fresenius Vial SA, Brezin, France) to reach a target drug concentration of 4 μg/ml at the effect site in 1.5 min. After loss of consciousness, atracurium 0.5 mg/kg was given to facilitate intubation. After tracheal intubation, all patients were mechanically ventilated to maintain an end-tidal carbon dioxide between 30 and 35 mmHg and an arterial oxygen tension (Pa_{O_2}) between 120 and 130 mmHg. Anesthesia was maintained with propofol in target concentration at the site effect (2.5–4 μg/ml) to maintain bispectral index between 40 and 60.[13,14] Sufentanil boluses (5 μg) were administered as required in the presence of intraoperative hypertension or tachycardia related to surgical stimulation. During the postoperative period of the study, patients received oxygen *via* Venturi mask to maintain Pa_{O_2} at greater than 100 mmHg.

Parameters Investigated

Systemic Hemodynamic and Oxygenation Parameters. Clinical monitoring of the patients included a pulmonary artery catheter (7.5-French; Arrow International Inc, Reading, PA) and a radial artery catheter. MAP, right atrial pressure, mean pulmonary arterial pressure, and PAOP (Solar M8000; Marquette Hellige Medical System, Milwaukee, WI) were measured at end-expiration. Heart rate (HR) was analyzed from a continuous recording of electrocardiogram with ST segments monitored. Cardiac output was measured by thermodilution (Solar M8000; Marquette Hellige Medical System) from the average of four injections of 10 ml of saline solution at room temperature. Arterial and mixed venous blood samples were taken for measuring arterial and mixed venous oxygen and carbon dioxide tensions (GEM Premier 3000; Istrumentation Laboratory, Lexington, MA). Systemic vascular resistance index, pulmonary vascular resistance index, arterial oxygen delivery index, and oxygen consumption index were calculated (Solar M8000; Marquette Hellige Medical System).

Echocardiography Measurements

To provide the correct volemic status of the patients, a complete echocardiography was performed (Philips, Sonos 7500, Andover, MA), paying particular attention to the calculation of volumes through the Simpson technique. The echocardiography was performed using a multiplanar 2–4 mHz probe for the bidimensional scan and a Matrix® probe for real-time three-dimensional scanning (Philips). The left ventricular end-diastolic volume index, the left ventricular end-systolic volume index, and the left ventricular ejection fraction were calculated. We opted for a transthoracic rather than transesophageal method to avoid the laser Doppler intragastric probe displacement.

Gastric Mucosal Parameters.

Gastric mucosal perfusion was evaluated by a laser Doppler technique flowmeter (Periflux System 5000, Perimed®, Stockholm, Sweden), using a gastric probe for

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the measurement of gastric mucosal perfusion (P 424, Perimed®). Because the probe is at the tip of a nasogastric tube, we fixed the probe to the mucosa generating a negative pressure through a 4-mm hole at 20 mm from the reading surface of the probe. When the laser Doppler signal was satisfactory, aspiration *via* the probe held the tip of the probe against the gastric wall at the site of measurement. The degree of aspiration (40 torr) was determined to produce adequate adhesion without affecting the laser Doppler signal.[15] The signal was considered as reliable when pulse waves and respiratory-synchronous fluctuation could be identified and were free of motion artifacts; then it was continuously monitored on a personal computer using Perisoft® software (Perimed®). The software enabled continuous monitoring and the acquisition and processing of the laser Doppler signal for the entire duration of the protocol, with a period of 240 s at each set of measurements to average the laser Doppler flowmetry values over this period. Because the data of gastric mucosal perfusion were measured in arbitrary units (perfusion units), the results were expressed as a percentage of change between the reference values, defined as the prestudy value, and each measurement. This was calculated according to the following formula: gastric mucosal perfusion = (measured value × prestudy value/prestudy value).

Experimental Protocol

Before the induction of general anesthesia, local anesthesia was induced for the insertion of the pulmonary artery catheter through the subclavian vein and for radial artery catheter placement. An initial prestudy set of echocardiography, hemodynamic, and gastric mucosal perfusion measurements was taken just before the induction of anesthesia. After a prestudy fluid challenge to obtain PAOP between 12 and 18 mmHg, a continuous intravenous infusion of hydroxyethyl starch 6% (VOLUVEN®; Fresenius-Kabi, Frankfurt, Germany), at a starting dose of 80 ml/h, was performed to maintain constant PAOP during the protocol. Both terlipressin and norepinephrine were prepared before the induction of anesthesia. Patients who experienced hypotension at induction of anesthesia were randomized to received a bolus dose of 1 mg of terlipressin (n = 16) or norepinephrine infusion at starting dose of 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and progressively titrated to increase MAP to the prestudy values (n = 16). The bolus dose of 1 mg of terlipressin was selected taking into account previous studies on terlipressin.

In case of failure of both treatment and if MAP was not restored (*i.e.*, MAP was <60 mmHg or <30% of prestudy value) within 10 min, patients received an intravenous bolus dose of 0.5 mg of epinephrine. Systemic hemodynamics and gastric mucosal perfusion measurements were performed before the induction of anesthesia (prestudy measurements set), at the episode of hypotension (hypotension measurements set), and taking into account of the pharmacokinetic profile and the possibility of delayed side effects of the terlipressin, at 30 min and at 4 h from the episode of hypotension. Data at hypotension and 30 min were obtained before surgery. Data at 4 h were obtained after surgery. MAP and HR were recorded every minute until hypotension was corrected. Echocardiography was performed just before the induction of anesthesia (prestudy measurements set) and then at 4 h. We did not perform an echocardiography measurement at the episode of hypotension and at 30 min because of the interference of intermittent positive pressure mechanical ventilation. The protocol required urine collection starting before the induction of anesthesia and lasting 4 h. At the end of protocol, urine and blood samples were sent to the central laboratory to measure creatinine clearance. In the same way, a urine collection of 5 h was performed to measure creatine clearance on the day before surgery. Arterial lactate concentrations and cardiac troponin concentrations were measured just before the induction of anesthesia and at the end of the protocol (4 h).

Statistical Analysis

A prospective power calculation indicated that 30 patients would be needed to achieve a 90% power to detect modification in gastric mucosal perfusion percentage at 30 min. The measured variables showed skewed distributions. Therefore, we used a nonparametric statistical analysis. We tested for differences in prestudy, baseline, 30 min, and 4 h characteristics between the experimental groups using a Mann–Whitney U test. We tested for changes from prestudy to baseline, 30 min, and 4 h in variables within each study group using the Wilcoxon and the Friedman tests. All *P* are two-tailed and a *P* value of less than 0.05 was considered as significant. All data are expressed as median ± absolute deviation from median. Analyses were performed with the statistical software SPSS (SPSS, Version 9, Chicago, IL).

Results

There were no complications associated with either the administration of terlipressin, norepinephrine or the use of the laser Doppler flowmeter. During recovery and postoperative period, no patient experienced bradycardia, tachycardia, hypertension or hypotension that required medication. Terlipressin and norepinephrine administrations did not alter the position of the ST segment on the electrocardiogram and did not result in arrhythmias. No new echocardiographic regional wall motion abnormalities were found at the end of the study period in the two study groups. No statistical differences were found at different data collection times for cardiac troponin concentration and for creatinine clearance in the two study groups. Hemodynamic, echocardiographic,

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Table 2. Hemodynamic Variables

	Terlipressin (n = 16)				Norepinephrine (n = 16)			
	Pre-study	Hypothens	30 min	4 h	Pre-study	Hypothens	30 min	4 h
MAP (mmHg)	95 ± 7.9	58 ± 4.4*	97 ± 7.6†	100 ± 6.5†	90.5 ± 7.4	59.5 ± 4*	90 ± 7.8†	96 ± 4.6†‡
HR (beats/min)	88 ± 5.3	67.5 ± 7.5*	54 ± 5.7*†§	67 ± 4.1*‡§	83.5 ± 6.6	65.5 ± 11.1*	82 ± 6.4*†	89 ± 3.8*†‡
RAP (mmHg)	13 ± 0.8	12 ± 0.7	12.5 ± 0.6	12.5 ± 0.6	13 ± 0.8	13 ± 0.9	13 ± 0.7	13 ± 0.4
PAOP (mmHg)	13 ± 0.4	13 ± 0.7	13 ± 0.8	13 ± 0.6	13 ± 0.06	13 ± 0.9	13 ± 0.3	13 ± 0.3
MPAP (mmHg)	25 ± 1.9	22 ± 1.8*	25 ± 1.7	25.5 ± 1.2	25 ± 2	20.5 ± 3.3*	24.5 ± 2.2†	25.5 ± 1.7†
CI (L/min/m^2)	3.1 ± 0.2	3.1 ± 0.2	2.25 ± 0.3*†§	2.25 ± 0.2*†§	2.9 ± 0.35	3.3 ± 0.6	3.4 ± 0.7	3.05 ± 0.2
SVRI (dyn/s/cm^5/m^2)	2240 ± 267	1225.5 ± 128*	3171 ± 319*†§	3303.5 ± 312.6*†§	2296 ± 271.6	1105.5 ± 226.8*	2148 ± 313*†	2281.5 ± 24*†
PVRI (dyn/s/cm^5/m^2)	319 ± 59	244 ± 44.2*	495 ± 56*†§	517 ± 43.7*†§	375.5 ± 62.4	200 ± 74.4*	334 ± 66.4†	369 ± 60.6†
Do_2I (mL/min/m^2)	679 ± 95.6	647 ± 80.4	463 ± 53*†§	462 ± 52.7*†§	601 ± 98.6	602.5 ± 143.4	685 ± 101	588 ± 97.3
Vo_2I (mL/min/m^2)	161 ± 26	150 ± 19.8	108 ± 12*†§	110.5 ± 12.6*†‡§	150 ± 2.3	148.5 ± 31.7	179.5 ± 27.7	142 ± 26.3

Values are expressed as median ± absolute deviation from median.

CI = cardiac index; Do_2I = oxygen delivery index; HR = heart rate; MAP = mean arterial pressure; MPAP = mean pulmonary arterial pressure; PAOP = pulmonary artery occlusion pressure; PVRI = pulmonary vascular resistance index; RAP = right atrial pressure; SVRI = systemic vascular resistance index; Vo_2I = oxygen consumption index.

* significantly different versus Pre-study $P < 0.05$; † significantly different versus Baseline $P < 0.05$; ‡ significantly different versus 30 min $P < 0.05$; § significantly different versus norepinephrine $P < 0.05$.

and gastric mucosal values are summarized in table 2, table 3, and table 4 and shown in figs. 1 and 2. All of the patients completed the study. Nonresponse to treatment of hypotension did not occur in the two study groups and none of the patients required epinephrine to counteract hypotension. In all patients, MAP was restored within 6 min. The norepinephrine infusion rate required to achieve prestudy MAP values was 0.14 ± 0.03 $\mu g \cdot kg^{-1} \cdot min^{-1}$. In patients treated with norepinephrine, the drug infusion was discontinued within 5 min. Once prestudy MAP values were achieved, no patients required continued norepinephrine infusion to maintain the prestudy MAP values in the subsequent 4 h of the protocol. Patient groups were well matched so that there were no significant differences between the terlipressin and norepinephrine groups at prestudy and baseline values. For each patient no statistical differences were found for left ventricular end-systolic index, left ventricular ejection fraction, PAOP, pH, Pao_2, $Paco_2$, and hemoglobin concentration at different data collection times during the protocol, suggesting that volume status and ventilatory support were maintained constant. As compared with baseline values (during induction-induced hypotension), after the bolus dose of terlipressin or norepinephrine infusion, MAP was significantly increased over 6 min ($P < 0.05$) and compared to prestudy value no significant changes were found at 30 min and 4 h, either in the terlipressin and in the norepinephrine group. In the terlipressin group, this was accompanied by an increase in systemic vascular resistance index ($P < 0.05$) and a reduction in cardiac index ($P < 0.05$) at 30 min and 4 h. As compared to prestudy values in the norepinephrine group, cardiac index showed no significant changes at 30 min and 4 h. Although mean pulmonary arterial pressure and PAOP showed no significant changes as compared to prestudy values, pulmonary vascular resistance index was significantly increased at 30 min and at 4 h in the terlipressin group ($P < 0.05$), whereas no changes were observed in the norepinephrine group. As compared with baseline values, despite an increase in MAP, laser Doppler gastric mucosal perfusion was significantly reduced in the terlipressin group over 30 min and remained decreased for at least 4 h ($P < 0.05$). Terlipressin administration affected oxygen transport; oxygen delivery index and oxygen consumption index were significantly reduced after 30 min and 4 h ($P < 0.05$). No changes in oxygen delivery index and oxygen consumption index were observed in the norepinephrine group. Arterial lactate concentrations showed a slight but significant increase at 4 h in the terlipressin group ($P < 0.05$), whereas no significant changes were observed in the norepinephrine group.

Table 3. Echocardiography Variables

	Terlipressin (n = 16)		Norepinephrine (n = 16)	
	Pre-study	4 h	Pre-study	4 h
LVEDVI (mL/m^2)	72.5 ± 11.4	73 ± 10.5	79 ± 8.4	76 ± 8.2
LVESVI (mL/m^2)	45.5 ± 7.2	45.5 ± 5.3	46 ± 7.3	47 ± 5.7
LVEF %	38 ± 3.9	37.5 ± 4.1	40 ± 4.6	40.5 ± 3.1

Values are expressed as median ± absolute deviation from median.

LVEDVI = left ventricular end diastolic volume index; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end systolic index.

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Table 4. Gastric Mucosal Perfusion and Biological Variables

	Terlipressin (n = 16)				Norepinephrine (n = 16)			
	Pre-study	Hypothens	30 min	4 h	Pre-study	Hypothens	30 min	4 h
GMP (%)	–	−7.5 ± 1.4	−75.5 ± 17.4†§	−29 ± 14.4†‡§	–	−8 ± 0.9	3 ± 0.8†	5 ± 0.6†‡
Troponin (ng/mL)	0.08 ± 0.01	–	–	0.07 ± 0.02*	0.09 ± 0.01	–	–	0.08 ± 0.01*
Arterial lactate (mmol/L)	0.8 ± 0.2	–	–	2.6 ± 0.3*§	0.85 ± 0.1	–	–	0.8 ± 0.2
Creatinine clearance (mL/min)	90 ± 7.8	–	–	92 ± 8.1	90 ± 8.4	–	–	93.5 ± 8.6

Values are expressed as median± absolute deviation from median.

GMP (%) = gastric mucosal perfusion expressed as a percentage of change between the prestudy value and each measurement, calculated according to the following formula: GMP (%) = (measured value − prestudy value/prestudy value).

* significantly different versus Pre-study $P < 0.05$; † significantly different versus Baseline $P < 0.05$; ‡ significantly different versus 30 min $P < 0.05$; § significantly different versus norepinephrine $P < 0.05$.

Discussion

In the current study, we demonstrated that patients chronically treated with renin-angiotensin system inhibitors (ACEIs or AIIRAs) and experiencing anesthesia-induced hypotension responded to norepinephrine administration by an increase both in MAP and gastric mucosal perfusion. On the contrary, patients responded to terlipressin with an increase in MAP and with a sustained decrease in gastric mucosal perfusion. Angiotensin converting-enzyme inhibitors (ACEIs) and angiotensin II receptor antagonists (AIIRAs) are widely and indifferently used as first-line therapy in arterial hypertension in high-risk patients without clear differences in primary endpoints.[1,2] AIIRAs act directly on AT_1 receptors and their action is similar to ACEIs except with regard to bradykinin production. This can represent an advantage of AIIRAs compared with ACEIs because of the decreased incidence of side effects. Hypotensive episodes are frequent after induction of general anesthesia in patient chronically treated with ACEIs or AIIRAs.[5,6] Under anesthesia, the sympathetic, renin-angiotensin, and vasopressin systems are involved in the control of MAP. The agonists of the sympathetic system are used as standard therapy to treat intraoperative hypotension. However, in patients under chronic treatment with ACEIs or AIIRAs, anesthetic-induced hypotensive episodes are mainly linked to a reduced adrenergic vasoconstrictive response[16] as a result of a decrease in vascular adrenergic receptor sensitivity, so these patients may be unresponsive to ephedrine administration. An α-1 adrenergic agonist like norepinephrine is considered as more effective than ephedrine in treating arterial hypotension. An alternative vasopressor like terlipressin may be effective in treating hypotension in such patients because it acts on the vasopressin-humoral vasopressor system, although the sympathetic system and renin-angiotensin are blunted by general anesthesia and ACEIs or AIIRAs. Eyraud *et al.*[7] have demonstrated that a bolus of terlipressin can restore MAP with no concomitant impairment in the left ventricular function. Meersschaert *et al.*[8] showed the efficacy of a combination of terlipressin and ephedrine to counteract anesthesia-induced hypotension in patients chronically treated with ACEIs. Recently, Boccara *et al.*[9] showed the efficacy of terlipressin as compared with norepinephrine in counteracting the anesthesia-induced hypotension in this kind of patients.

According to these previous studies, our results showed the efficacy of terlipressin in the treatment of anesthesia-induced hypotension in patients chronically treated with ACEIs or AIIRAs. Moreover, compared to

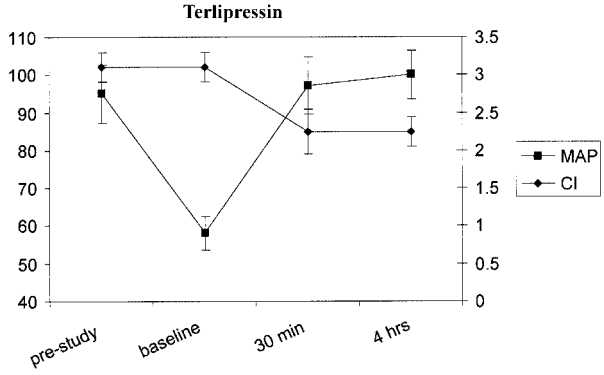

Fig. 1. Modification of cardiac index (CI, L/min/m^2) and mean arterial pressure (MAP, mmHg) after an intravenous bolus doses of terlipressin. Values are expressed as median ± absolute deviation from median.

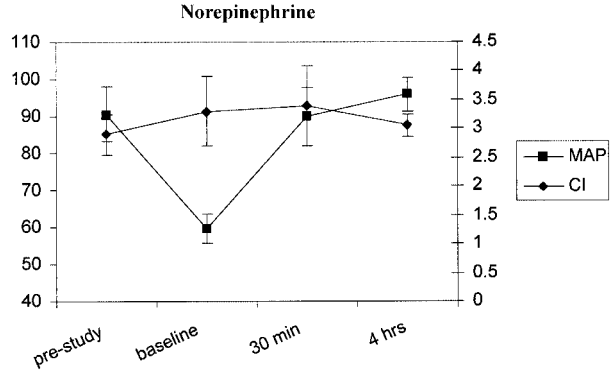

Fig. 2. Modification of cardiac index (CI, L/min/m^2) and mean arterial pressure (MAP, mmHg) after norepinephrine infusion. Values are expressed as median ± absolute deviation from median.

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the prestudy evaluations, at the end of the protocol we did not find any concomitant impairment in left ventricular loading and ejection fraction after terlipressin administration, as indicated by the echocardiography.

It is unclear whether terlipressin could be harmful to the splanchnic circulation. In our study, after a bolus dose of terlipressin, despite the restoration of MAP, we observed a significant decrease in cardiac index as a result of an increase in vascular resistance. The vasoconstriction after terlipressin administration[17–20] could cause, or at least worsen, hypoperfusion-related alterations in organ function. Accordingly, the main finding of the study was the significant decrease in gastric mucosal perfusion, mainly linked to the potent vasoconstriction with the resultant decrease in cardiac index observed after terlipressin as compared with norepinephrine. The reduction of cardiac index is correlated not only to the rapid increase of the vascular resistances (mathematically coupled) but also to the reduction of HR. The phenomenon of the decrease in HR is attributable to a strong reflex suppression of cardiac output that is seen even at physiologic plasma concentrations of arginine vasopressin.[12] On the other hand, this result could be partially explained by a negative redistribution effect of cardiac output on hepatosplanchnic macrocirculation and microcirculation, resulting in a decrease of blood flow toward the mucosa with a reduced margin of safety against hypoxia,[21] a microvascular condition that might be avoided in major vascular surgery (*i.e.*, risk of hemodynamic instability or splanchnic hypoperfusion). This aspect is particularly important because the gut mucosa in particular is a tissue vulnerable to hypoxia resulting from the low oxygen tension at the tip of the villus microcirculation,[22] and intestinal ischemia has been implicated in the activation of the inflammatory response and subsequent multiple organ failure.[23] Moreover, these regional and systemic hemodynamic alterations after terlipressin administration were accompanied by an imbalance between oxygen delivery and consumption. The terlipressin-associated reduction in oxygen consumption is another interesting finding of our study, and it is in accordance with the recent work of Westphal *et al.*[24] The decrease in cardiac index and, more importantly, the decrease in oxygen consumption in response to terlipressin might suggest that the patients were hypovolemic during the time of the study despite the PAOP value between 12 and 18 mmHg. In these patients the hypertensive disease leads to left ventricular hypertrophy with an altered left ventricular compliance, which, in case of hypovolemia, maintains an increased pulmonary artery occlusion pressure although the left ventricular preload is markedly reduced. Because adequate volume loading is the cornerstone of hemodynamic management of ACEI or AIIRA patients, we performed an echocardiographic measurement of the end-diastolic volume index to provide a prefixed volemic status at prestudy. Moreover, we adjusted the infusion rate to keep the pulmonary artery occlusion pressure at prestudy values (PAOP value between 12 and 18 mmHg) to guarantee sufficient fluid challenge during the protocol. However, as a result of the lack of echocardiograph measurement of the end-diastolic volume index during the period of hypotension and the short duration of the period itself, we can not exclude that the prefixed volemic status of the patients in the two study groups was an optimal volemic status that allowed for an acceptable circulatory status. In our study, terlipressin administration compromises oxygen delivery. The decrease in oxygen delivery resulted from a reduction in cardiac index because there were no changes in oxygen saturation after terlipressin administration. The terlipressin-associated reduction in oxygen delivery and more important in oxygen consumption suggests an oxygen supply dependency that is usually associated with some degree of tissue ischemia. In this light, we found a slight but significant increase in arterial lactate concentration in the terlipressin group. However, the increase in arterial lactate could probably result from decreased hepatic uptake of lactate as a result of decreased hepatic blood flow instead of hepatic or substantial tissue ischemia. Our protocol does not allow supporting or refuting any of these hypotheses; these aspects should be addressed in further studies. On the contrary, for the same MAP we did not find any imbalance between oxygen delivery and consumption or changes in arterial lactate concentrations in the norepinephrine group. Moreover, norepinephrine administration increased both MAP and gastric mucosal perfusion. These results are in accordance with a recent trial in which titrating norepinephrine to a MAP between 65 and 85 mmHg did not affect splanchnic blood flow in patients with septic shock while cardiac output increased by 15–20%. Thus, norepinephrine administered at doses sufficient to achieve an arterial blood pressure of 65 to 80 mmHg does not seem to impair total hepatosplanchnic blood flow.[25]

Myocardial damage is the actual complication to be feared in patients undergoing vascular surgery.

The circulatory response to these vasopressors may very differently influence myocardial oxygen balance. The correction of MAP in the terlipressin group with no increment in HR might be beneficial in vascular surgery patients with a high risk of coronary artery disease because it increases the coronary perfusion pressure without any heart rate-induced increase in myocardial oxygen consumption. This is an important advantage of terlipressin compared with norepinephrine. However, myocardial oxygen consumption is also related to the afterload and we must also consider that terlipressin can cause a remarkable increase in systemic vascular resistance index and that this increase remains steady over time. In fact, in our study for the same MAP, systemic vascular resistance index was significantly higher in the

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terlipressin group as compared with the norepinephrine group, and values remained high for the whole duration of the protocol. Although the decrease of oxygen consumption in the presence of a decreased HR could not imply inadequate oxygen delivery and ischemia, the contemporary imbalance between oxygen delivery and consumption after terlipressin can lead in extreme cases to myocardial infarction, as recently showed by Medel *et al.*[26] Another aspect that must be taken into account is the modification of pulmonary vascular resistance index in the two study groups. In the terlipressin group, for the same mean pulmonary arterial pressure, pulmonary vascular resistance index was significantly increased as compared with the prestudy value. In accordance with Westphal *et al.*,[24] we can reasonably assume that in the terlipressin group, the reduction in cardiac index was responsible for the increase in pulmonary vascular resistance index, although it is important to take into account the limitations of the mathematical coupling.[24,27,28] As compared with norepinephrine, this terlipressin potent pulmonary vasoconstrictive effect might worsen a present or suspected pulmonary hypertension that can unmask a right ventricular dysfunction.

This study has a number of limitations. Oxygen delivery and consumption were calculated according to the thermodilution technique. Because both parameters are mathematically coupled, the reduction in oxygen consumption observed in the terlipressin group could have been the result of the decrease in cardiac index. We did not perform calorimetry to measure oxygen consumption independent of oxygen delivery. Laser Doppler flowmetry was closely correlated with other flow-measuring techniques.[29–31] However, it does have several limitations. Laser Doppler measurements are recorded from a tissue area of only a few square millimeters (2–4 mm^2) and a shallow penetration depth (1 mm), providing a tissue volume of only 1 mm^3. Another limitation is the difficulty of maintaining optical coupling between the laser Doppler probe and the gastric mucosa. Nevertheless, the degree of aspiration and the dimension of the tip of the P424 probe made it possible to maintain it in a stable position in the gastric lumen for the entire duration of the protocol. More important, we measured flow modifications without comparing them to any reference value. Furthermore, the high intraindividual variability resulting from clinical conditions and the flow measurement expressed in perfusion arbitrary units make it difficult to single out a reference value that can be defined as a normal laser Doppler perfusion value. As observed by others,[32] the P424 probe as used in this study does detect perfusion of the gastric mucosa. On the other hand, there are conflicting findings demonstrating that the values obtained reflect the perfusion of the entire wall of the stomach.[33] Moreover, this methodology does not allow for detailed characterization of microvascular blood flow. For these reasons, laser Doppler flowmetry and other techniques including gastric mucosal pH or gastric mucosal-arterial carbon dioxide tension have not yet been validated as standard for measurement of gastric mucosal perfusion.

In conclusion, this study showed the efficacy of terlipressin in the treatment of hypotension episodes in anesthetized patients chronically treated with renin-angiotensin system inhibitors (ACEIs or AIIRAs). However, the negative effects on gastric mucosal perfusion and the risk of iatrogenic oxygen supply dependency of terlipressin need to be taken into account. Further studies in a larger population are required to establish the tolerance and safety of terlipressin, especially in major vascular surgery.

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