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Long-term Angiotensin-converting Enzyme Inhibitor Treatment Attenuates Adrenergic Responsiveness without Altering Hemodynamic Control in Patients Undergoing Cardiac Surgery

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Background: **The sympathoadrenal and the renin-angiotensin systems are involved in blood pressure regulation and are known to be markedly activated during cardiac surgery. Because unexpected hypotensive events have been reported repeatedly during anesthesia in patients chronically treated with angiotensin-converting enzyme (ACE) inhibitors, the authors questioned whether renin-angiotensin system blockade would alter the hemodynamic control through attenuation of the endocrine response to surgery and/or through attenuation of the pressor effects of exogenous catecholamines.**

Methods: **Patients with preserved left ventricular function undergoing mitral valve replacement or coronary revascularization were divided into two groups according to preoperative drug therapy: patients receiving ACE inhibitors for at least 3 months (ACEI group, n = 22) and those receiving other cardiovascular drug therapy (control group, n = 19). Anesthesia was induced using fentanyl and midazolam. Systemic hemodynamic variables were recorded before surgery, after anesthesia induction, during sternotomy, after aortic cross-clamping, after aortic unclamping, as well as after separation from cardiopulmonary bypass (CPB) and during skin closure. Blood was sampled repeatedly up to 24 h after surgery for hormone analysis. To test adrenergic responsiveness, incremental doses of norepinephrine were infused intravenously during hypothermic CPB and after separation from CPB. From the dose-response curves, pressor (defined as mean arterial pressure changes), and vasoconstrictor (defined as systemic vascular resistance changes) effects were analyzed, and the slopes and the dose of norepinephrine required to increase mean arterial pressure by 20% were calculated (PD_{20}).**

Results: **At no time did the systemic hemodynamics and the need for vasopressor support differ between the two treatment groups. However, for anesthesia induction, significantly less fentanyl and midazolam were given in the ACEI group. Although plasma renin activity was significantly greater in the ACEI group throughout the whole 24-h study period, plasma concentrations of angiotensin II did not differ between the two groups. Similar changes in catecholamines, angiotensin II, and plasma renin activity were found in the two groups in response to surgery and CPB. The pressor and constrictor effects of norepinephrine infusion were attenuated markedly in the ACEI group: the dose-response curves were shifted to the right and the slopes were decreased at the two study periods; PD_{20} was significantly greater during hypothermic CPB (0.08 μg/kg in the ACEI group *vs.* 0.03 μg/kg in the control group; $P < 0.05$) and after separation from CPB (0.52 μg/kg in the ACEI group *vs.* 0.13 μg/kg in the control group; $P < 0.05$). In both groups, PD_{20} was significantly less during hypothermic CPB than in the period immediately after CPB.**

Conclusions: **Long-term ACE inhibitor treatment in patients with preserved left ventricular function alters neither the endocrine response nor the hemodynamic stability during cardiac surgery. However, a significantly attenuated adrenergic responsiveness associated with incomplete blockade of the plasma renin-angiotensin system supports the hypothesis that inhibition of angiotensin II generation and of bradykinin degradation within the vascular wall mediates some of the vasodilatory effects of ACE inhibitors. (Key words: Hormones: renin-angiotensin system. Pharmacology: angiotensin-converting enzyme inhibitors. Surgery: cardiac; cardiopulmonary bypass. Sympathetic nervous system: catecholamines; epinephrine; norepinephrine.)**

DURING the last decade, angiotensin-converting enzyme (ACE) inhibitors have been established as first-line therapy in patients with arterial hypertension, congestive heart failure, and mitral valve regurgitation.[1,2] Improved quality of life, substantial reduction in mortality, and fewer serious cardiovascular events have been reported after prolonged treatment with

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these drugs. Experimental data suggest that the inhibition of angiotensin II formation in the blood and most importantly within the vascular wall and the myocardial tissue is the predominant mechanism mediating the antihypertensive effects and the regression of cardiac and vascular hypertrophy.[3]

The renin-angiotensin system (RAS) contributes in a complex way to cardiovascular homeostasis, because, in addition to its direct vasoconstrictor action, angiotensin II potentiates the pressor effect of norepinephrine, enhances sympathetic tone, and promotes vascular growth.[4] In acute experimental situations where the RAS is known to be strongly activated such as during hemorrhage, the suppression of angiotensin II generation has been demonstrated to precipitate the onset of circulatory shock and to prevent restoration of adequate blood pressure during resuscitation.[5]

Conflicting results have been reported concerning the use of ACE inhibitors during anesthesia. Although hemodynamic stability has been noted after acute and short-term treatment,[6–8] several clinical reports have warned of profound hypotensive episodes occurring in patients receiving long-term therapy, particularly during induction of anesthesia and during surgical procedures involving major body fluid shifts.[9–11] Occasionally, arterial hypotension was even refractory to conventional therapy; yet, the administration of angiotensin II always restored a normal perfusion pressure.[12]

During major surgical procedures where both the RAS and the pituitary-hypophyseal axis are stimulated, one may thus question whether chronic ACE inhibition alters perioperative blood pressure control as well as the hemodynamic response to adrenergic agents. This is a relevant clinical issue, because patients undergoing heart surgery not infrequently require temporary inotropic or vasopressive support for successful separation from extracorporeal circulation.

The purpose of the current study therefore was to document whether chronic ACE inhibition is associated with unstable hemodynamic control and interferes with the activation of the sympathoadrenal system as well as with the systemic vasoconstrictive response to adrenergic stimulation in two groups of patients undergoing cardiac surgery, one receiving preoperative ACE inhibitor treatment.

Materials and Methods

Patient Selection

After obtaining institutional Ethical Committee approval and informed consent, 41 patients scheduled for elective coronary artery bypass graft (CABG) surgery or mitral valve replacement (MVR) were studied during a 14-month period. All had moderate to well-preserved global left ventricular function (ejection fraction of at least 40%). Patients referred with mitral valve incompetence were selected for the study if no episode of congestive heart failure had occurred during the previous 3 months while receiving appropriate therapy and if left ventricular end-diastolic pressure was less than 18 mmHg. Patients with unstable angina, recent myocardial infarct (less than 30 days), diabetes mellitus, and those receiving amiodarone or α-adrenergic therapy were excluded from the study. According to medical history, patients were divided into two groups, those not receiving ACE inhibitors (control group, n = 19) and those treated with ACE inhibitors for at least 3 months (ACEI group, n = 22; captopril, n = 9 and enalapril, n = 13); this was based on previous clinical investigations demonstrating evidence for regression of myocardial hypertrophy and improvement in arterial vascular compliance as soon as 3 months after initiation of treatment.[13]

It was determined that patients in each group would either receive a norepinephrine dose-response challenge to assess adrenergic responsiveness (control-norepinephrine group, n = 10 and ACEI-norepinephrine group, n = 13) or receive saline to assess the "spontaneous" hemodynamic changes related to cardiopulmonary bypass (CPB) and the neuroendocrine responses to surgery (control group, n = 9 and ACEI group, n = 9). Hormonal analysis was not performed in patients receiving the norepinephrine dose-response challenge because plasma renin activity (PRA), plasma angiotensin II, and catecholamines concentrations would have been influenced, directly or through counterregulatory mechanisms by the prolonged norepinephrine infusion (10–25 min). Patients who were treated preoperatively with calcium channel blockers were excluded from the norepinephrine dose-response study because this treatment has been associated with reduced α_1-adrenergic responsiveness during anesthesia and surgery.[14]

Patient Management

The usual cardiac medications, including nitrates, β-blockers, calcium channel blockers and ACE inhibitors, were administered until the morning of surgery. After overnight fasting, each patient received 7.5 mg morphine intramuscularly and 5–10 mg diazepam orally as premedication 1 h before surgery. On arrival at the

induction room, the electrocardiogram (standard lead II and V_5) was monitored for heart rate, rhythm, and ST changes. Arterial radial and pulmonary catheters were inserted under local anesthesia for continuous monitoring of mean arterial pressure (MAP) and central venous pressure, as well as for intermittent determination of cardiac output by the thermodilution technique. General anesthesia was induced according to standard practice by an experienced anesthesiologist not involved in the study: for induction, 10–30 μg/kg fentanyl and 0.03–0.06 mg/kg midazolam were administered in incremental doses to produce unconsciousness while maintaining hemodynamic stability; pancuronium was given to facilitate ventilation and tracheal intubation; thereafter, anesthesia was maintained with a continuous infusion of midazolam (0.10 $mg \cdot kg^{-1} \cdot h \cdot ^{-1}$ during normothermic circulation and 0.05 $mg \cdot kg^{-1} \cdot h \cdot ^{-1}$ during hypothermic extracorporeal bypass) and additional intravenous boluses of fentanyl (up to a total dose of 60 μg/kg. Mechanical ventilation was adjusted to maintain normocapnia and normoxia with an inspired oxygen concentration of 50% (oxygen-air mixture) before CPB and 100% after separation from bypass.

After aortic and right atrium cannulation, CPB was instituted with a membrane oxygenator primed with 1.5 l crystalloids and body temperature was decreased to 26–28°C. After aortic clamping, a St. Thomas's cardioplegic solution (600–900 ml) was administered through the aortic root and repeated at 30-min intervals. A nonpulsatile pump flow rate (PFR) greater than $1.8\ l \cdot min^{-1} \cdot m^{-2}$ was maintained during moderate hypothermia and increased up to $2.4\ l \cdot min^{-1} \cdot m^{-2}$ during rewarming. After completion of the surgical procedure and systemic rewarming, patients were weaned from CPB when a rectal temperature of at least 35.5°C had been reached.

In the intensive care unit, repeated boluses (1 mg) of morphine and/or diazepam were administered to keep the patient pain-free and comfortable; weaning from the ventilator was started during emergence from anesthesia and when stable hemodynamics and normothermia had been maintained for at least 1 h.

Measurements and Calculations

Cardiac output was averaged from three consecutive determinations (within 10% of each other) and cardiac index (CI) was obtained as cardiac output divided by body surface area. In all patients, systemic hemodynamic variables (MAP, heart rate, CI, or PFR) were recorded at these time periods: before anesthesia (preanesthesia), after anesthesia induction and before tracheal intubation, 2 min after sternotomy, 5 min after aortic cross-clamping, 5 min before aortic unclamping, 10 min after separation from CPB, and during skin closure. Systemic vascular resistance index (SVRI) was calculated by the standard formula (MAP-central venous pressure/CI or PFR) · 80 ($dynes \cdot s \cdot cm^{-5} \cdot m^{-2}$).

Arterial blood was sampled at each hemodynamic measurement period (except after anesthesia induction) as well as 12 and 24 h after the end of surgery. Blood was collected in 5-ml polypropylene tubes containing ethylenediaminetetraacetic acid and after cold centrifugation, the decanted plasma was stored frozen until analysis. Plasma epinephrine and norepinephrine concentrations were determined in duplicate by high-pressure liquid chromatography coupled with electrochemical detection. The lower limit of sensitivity for the assay was 0.3 nM/L and 0.1 nM/L for norepinephrine and epinephrine, respectively; intraassay and interassay precision (or coefficient of variation) were 6.8% and 8.7% for norepinephrine, and 7.0% and 8.9% for epinephrine. Plasma renin activity was estimated by a modification of the method described by Haber using New England reagents.[15] Immunoreactive plasma angiotensin II was determined in duplicate using a standard radioimmunoassay technique after plasma extraction by means of Sep-pak cartridges (Waters, Milford, MA) with methanol/water; the lower detectable angiotensin II concentrations were 0.01 pg/ml, intra- and interassay precision were 8% and 12%, respectively. Hormone concentrations were corrected for the hemodiluting effect of CPB according to the change in hematocrit, that is, hormone concentration × Hct_p/Hct_s, where Hct_p and Hct_s are the hematocrit values prevailing before anesthesia and during CPB, respectively.

Norepinephrine dose-response curves were generated during two study periods: (1) 5 min after aortic cross-clamping during conditions of constant circulatory flow (PFR of 1.8 to $2.2\ l \cdot min^{-1} \cdot m^{-2}$) and temperature (hypothermic CPB), and (2) after separation from the bypass circuit and heparin neutralization, during stable hemodynamic conditions (normothermic post-CPB). Norepinephrine (1 mg/ml; 0.5 mg free-base of norepinephrine diluted to 50 ml with 0.9% saline) was infused continuously *via* the side port of the internal jugular vein catheter or directly into the CPB venous reservoir. The rate of norepinephrine administration was increased in a stepwise fashion (0.01, 0.02, 0.04,

0.08, 0.16 $\mu g \cdot kg^{-1} \cdot min^{-1}$) at 5-min intervals until MAP exceeded values 25% above baseline or reached 105 mmHg. Hemodynamic measurements (MAP, central venous pressure, cardiac output, or PFR) were recorded during the last minute of each infusion step, and the derived values were calculated (CI, SVRI). The vasopressor and vasoconstrictor responses were defined as the changes in MAP and SVRI induced by the norepinephrine infusion.

To assess the hemodynamic changes related to surgery and to the institution of hypothermic bypass alone, hemodynamic variables were measured in patients receiving a saline infusion rather than norepinephrine (*i.e.*, patients in whom blood was withdrawn for hormonal analysis only); variables were recorded over 20 min at the same times as described earlier, *i.e.*, after aortic cross-clamping (hypothermic CPB) and after discontinuation of CPB (normothermic post-CPB).

Time to extubation, total fluid requirements, and the need for vasopressor (phenylephrine) and inotropic support (dobutamine or dopamine at >5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, norepinephrine at >0.08 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was recorded intraoperatively and postoperatively.

Data Analysis

To assess the vasopressor or vasoconstrictive effects of norepinephrine and those related to the institution of hypothermic bypass, norepinephrine dosage and time were used as independent variables and changes in MAP and SVRI as the dependent variables. The dose of norepinephrine required to increase baseline MAP by 20% was calculated and defined as the pressor dose 20 (PD_{20}). To consider the simultaneous changes in MAP and flow, changes in SVR *versus* log dose norepinephrine or *versus* time were described. A log linear for best fit was constructed for individual dose-responses and the slopes were compared between treatment groups. Parametric data were expressed as mean ± SEM and analyzed using two-way analysis of variance with Dunnett's test for within-group changes with respect to baseline. Mann-Whitney *U* test and Wilcoxon paired tests were used for between- and within-group comparisons of non-Gaussian distributed data that were expressed as median (lower and upper quartile). A chi-square analysis with Yates's correction was used to compare percentages of patients in the two groups. Differences were considered to be significant when $P < 0.05$. For hormonal analysis, data were log transformed and the concentration equal to the sensitivity of the assay was assigned the value of the statistical limit of significance.

Results

General Patient Characteristics and Outcome

The two treatment groups were not significantly different with regards to clinical and surgical characteristics (table 1), except for preoperative treatment: in the control group, β-adrenergic and/or calcium channel blocking medications were prescribed in 16 patients (13 with CABG and 3 with MVR) whereas only 7 patients (5 with CABG and 2 with MVR) in the ACEI group received one of these drugs ($P < 0.05$); in the ACEI group, enalapril (10–20 mg/day) or captopril (30–100 mg/day) were administered for a median period of 14 months (range, 5–24 months) or 12 months (range, 4–16 months), respectively. There were no complications attributable to the study protocol, in particular, no patients developed ST changes during norepinephrine administration. Perioperative fluid requirements tended to be greater in the ACEI group, although differences were not sta-

Table 1. Preoperative and Intraoperative Patient Characteristics

	Control Group (n = 19)	ACEI Group (n = 22)
Preoperative characteristics		
Age (yr)	59 ± 10	58 ± 11
Weight (kg)	77 ± 11	75 ± 10
Height (cm)	163 ± 7	168 ± 6
Sex (M/F)	14/5	16/6
EF (%)	59 ± 15	52 ± 10
β blockers	12	5*
Calcium-channel blockers	8	2*
Nitrates	10	10
Intraoperative characteristics		
CABG/MVR	11/8	14/8
Aortic clamping time (min)	104 ± 22	95 ± 27
Hematocrit (%)		
During CPB	26 ± 3	26 ± 4
After CPB	29 ± 4	27 ± 3
Temperature (°C)		
During CPB	26.8 ± 0.6	27.2 ± 0.7
After CPB	35.7 ± 0.9	35.1 ± 1.0

Data are mean ± SD.

ACEI = angiotensin-converting enzyme inhibitor; CABG = coronary artery bypass graft; MVR = mitral valve replacement; EF = ejection fraction; CPB = cardiopulmonary bypass.

* $P < 0.05$ *versus* control group (chi-square).

tistically significant (3,422 ± 340 ml in control group *vs.* 4,238 ± 452 ml in ACEI group). In the intensive care unit, the use of pharmacologic circulatory support and mechanical ventilation did not differ between the two groups: 5 patients in the control group and 9 in the ACEI group required inotropic or vasopressive support for at least 2 h (not significantly different) and time to extubation was similar in the two groups (560 ± 105 in the control group *vs.* 605 ± 135 min in the ACEI group).

Hemodynamic Effects

Perioperative hemodynamic variables did not differ between the two types of surgery (CABG *vs.* MVR) as well as between the two types of ACEI inhibitors used (enalapril *vs.* captopril); therefore, these hemodynamic data were pooled in the control and ACEI groups.

For anesthesia induction, significantly less fentanyl (−44%) and midazolam (−9%) were required in the ACEI group compared with the control group (table 2). Phenylephrine was administered in two patients in the ACEI group and in one patient in the control group to correct arterial hypotension after anesthesia induction. There were no hemodynamic differences between the two groups at any time, with the exception of a significantly lower heart rate in the control group compared to the ACEI group during the preanesthesia period (60 ± 2 *vs.* 67 ± 2 beats/min, $P < 0.05$), a finding that was most probably related to the more frequent use of preoperative β-blockers in this group. From the start of CPB until aortic unclamping, MAP and CI or PFR and SVRI were all significantly reduced compared with the preanesthesia baseline values, in both groups. After complete rewarming and separation from CPB, CI rose up to preanesthesia levels, although MAP and SVRI remained significantly lower (table 3). After chest closure, three patients in each group required inotropic or vasopressor support and CI was significantly reduced compared to preanesthesia values in both groups, whereas SVRI returned to baseline values.

Hormonal Changes

In our laboratory setting, preoperative measurements of PRA and plasma epinephrine, norepinephrine, and angiotensin II concentrations obtained in the control group gave a range of values similar to those obtained in a group of outpatients of similar age referred to the cardiologist (fig. 1). There were no differences between the two groups in plasma angiotensin II and catecholamines concentrations at any sampling period. Long-term treatment with ACE inhibitors resulted in significantly higher preoperative PRA in the ACEI group (1.7 $ng \cdot ml^{-1} \cdot h^{-1}$, median value) compared to the control group (0.12 $ng \cdot ml \cdot^{-1} \cdot h^{-1}$, median value). Within each group, a significant increase in PRA as well as in plasma catecholamines concentrations occurred during and after CPB; greater PRA were consistently observed in the ACEI group, up to 24 h after surgery. In the two groups, angiotensin II plasma concentration decreased transiently after aortic cross-clamping due to pulmonary exclusion, thereafter angiotensin II increased significantly toward the end of surgery. At 12 and 24 h after surgery, plasma catecholamines and angiotensin II concentrations did not differ from preoperative values in the two groups.

Table 2. Mean Dose of Anesthetics Given during Anesthesia Induction and Surgery

	Control Group (n = 19)	ACEI Group (n = 22)
Anesthesia induction		
Midazolam (μg/kg)	54 ± 4	45 ± 2*
Fentanyl (μg/kg)	27 ± 2	15 ± 4†
Surgery		
Midazolam (μg/kg)	448 ± 15	456 ± 15
Fentanyl (μg/kg)	28 ± 4	30 ± 4

Data are mean ± SEM.

ACEI = angiotensin-converting enzyme inhibitor.

* $P < 0.05$ *versus* control group.

† $P < 0.01$ *versus* control group.

Norepinephrine Dose-response Studies

During the first 10 min of hypothermic CPB and under constant blood flow conditions, the spontaneous increase in MAP was attenuated in the ACEI group compared to the control group (11 ± 1 mmHg *vs.* 25 ± 2 mmHg, $P < 0.01$; fig. 2A); the slope of the regression line (SVRI/min) was less steep in the ACEI than in the control group, (31 ± 3 *vs.* 86 ± 11, $P < 0.05$; fig 3A). After weaning from CPB, MAP and CI remained stable during the 20-min observation period in patients receiving saline infusion; as a result, SVRI did not change (−2 ± 3% in the control group and +4 ± 2% in the ACEI group).

The hemodynamic response to norepinephrine administration was accentuated during the hypothermic compared to the normothermic CPB period because the PD_{20} value was significantly smaller and the slope

Table 3. Systemic Hemodynamic Variables

Variable	Group	Pre-CPB			Post-CPB	
		Preanesthsia	2 min after Sternotomy	After Aortic Clamping	Before Aortic Unclamping	After 5 min	At Skin Closure
MAP (mmHg)	Control	95 ± 3	87 ± 3	59 ± 2†	65 ± 4†	72 ± 3†	81 ± 3†
	ACEI	93 ± 2	82 ± 2	61 ± 3†	58 ± 3†	70 ± 3†	84 ± 2†
HR (beats · min^{-1})	Control	60 ± 3	58 ± 2.3	NA	NA	84 ± 5	87 ± 5†
	ACEI	67 ± 2*	64 ± 2.4	NA	NA	86 ± 2	93 ± 4†
CI (L · min^{-1} · m^{-2})	Control	3.11 ± 0.15	2.58 ± 0.16†	2.17 ± 0.06†	2.52 ± 0.06†	3.15 ± 0.14	2.64 ± 0.14†
	ACEI	3.19 ± 0.09	2.55 ± 0.07†	2.18 ± 0.05†	2.68 ± 0.08†	3.22 ± 0.13	2.70 ± 0.13†
SVRI (dynes · s · cm^{-5} · m^{-2})	Control	2,326 ± 116	2,533 ± 164	1,839 ± 122†	1,883 ± 184†	1,793 ± 64†	2,457 ± 141
	ACEI	2,222 ± 91	2,335 ± 124	1,752 ± 111†	1,742 ± 106†	1,701 ± 58†	2,444 ± 117

Data are mean ± SEM of 19 (control group) and 22 (ACEI group) patients.

ACEI = angiotensin-converting enzyme inhibitor; CPB = cardiopulmonary bypass; MAP = mean arterial pressure; HR = heart rate; CI = cardiac index; SVRI = systemic vascular resistance index; NA = not applicable.

* $P < 0.05$ *versus* control group.

† $P < 0.05$ *versus* preanesthesia period.

of SVRI/norepinephrine log dose was significantly steeper in the former condition (table 4).

The vasopressor and constrictor responses to norepinephrine were markedly attenuated during hypothermic CPB and during the normothermic post-CPB period in the ACEI group compared to the control group; the pressor dose-response curves were shifted to the right (figs. 2B and 2C), the slopes (SVRI/log norepinephrine dose) were diminished by 73% and by 82% (figs. 3B and 3C) and the dose of norepinephrine required to raise MAP by 20% (PD_{20}) were increased by a factor of 2.5 and 2.6, respectively, during and after CPB (table 4). In the ACEI group, the norepinephrine-induced hemodynamic response was not significantly different between patients receiving captopril (n = 5) or enalapril (n = 8) During hypothermic CPB however, the pressor effects of norepinephrine were greater in patients undergoing CABG compared to the patients undergoing MVR (median values of PD_{20}: 0.05 μg/kg in ACEI-CABG patients [n = 8] *vs.* 0.19 μg/kg in ACEI-MVR patients [n = 5], $P = 0.013$).

Discussion

The results of the current study demonstrate that the vasopressor and constrictor responses to norepinephrine infusion are significantly attenuated by more than 50% during and immediately after CPB in adult patients receiving long-term treatment with ACE inhibitors. The discrepancy between appropriate hemodynamic and hormonal profiles that are not affected by ACE inhibitor therapy and the norepinephrine-induced increase in MAP and SVR, which is clearly attenuated with ACE inhibition, indicates that the RAS plays a secondary role in blood pressure regulation during surgical stress but that it yet may markedly influence the response to vasopressor agents such as norepinephrine.

It is well established that perioperative hemodynamic control is principally determined by the interplay between the sympathetic nervous system, the RAS, the hypothalamic release of arginine vasopressin, and, finally, the end-organ responsiveness within the cardiovascular system.[16] Because of redundancy among their mechanisms of action, removal of one of these defense lines usually will not threaten blood pressure control under physiologic conditions.[17] Accordingly, the sympathetic nervous system is considered the organism's main defense against arterial hypotension in humans. In patients with autonomic dysfunction and/or limited cardiovascular reserve such as in heart failure or after

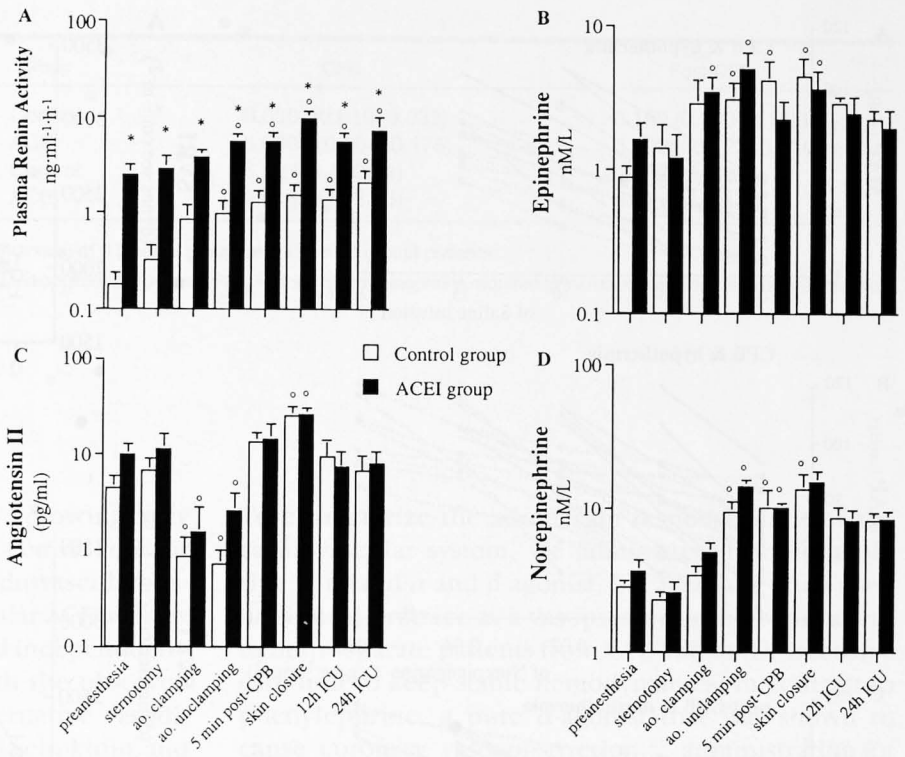

Fig. 1. (*A*) Plasma renin activity, (*B*) plasma concentrations of angiotensin II, (*C*) epinephrine, and (*D*) norepinephrine measured before, during, and up to 24 h after surgery. Data are expressed as mean ± SEM; *$P < 0.05$, significantly different between the control and ACEI groups; °$P < 0.05$, significantly different compared with preanesthesia values.

myocardial infarct, superimposition of pharmacologic RAS blockade is thought to precipitate unstable hemodynamics. Because most inhaled and intravenous anesthetics are responsible for blunting of sympathetic reflexes and for myocardial depression, patients whose RAS is inhibited, are prone to sudden decreases in blood pressure during anesthesia induction or when acute intraoperative hemorrhage occurs. Some of these conditions were actually encountered in the clinical and anecdotal reports relating hypotensive events in ACE inhibitor-treated patients.[9–12] We studied patients with coronary artery disease and mitral valve regurgitation who were free of severe cardiac insufficiency, peripheral neuropathy, and autonomic dysfunction. A "smooth" anesthesia induction resulted in similar and uneventful hemodynamic responses in the two groups. Interestingly, whereas in the control group, patients tolerated the usual loading doses of fentanyl (25–30 μg/kg) and midazolam (0.05–0.07 mg/kg), ACEI-treated patients were given significantly lesser amount of anesthetics to maintain a desired stable blood pressure. Sensitivity to the circulatory depressant effects of anesthetics after chronic RAS blockade also has recently been documented by Coriat *et al.* who observed up to 100% hypotensive episodes requiring phenylephrine administration when a fixed anesthetic dosage regimen (5 μg/kg fentanyl and 0.15 mg/kg midazolam) was given in patients chronically treated with enalapril.[11] The lower incidence of hypotension encountered in the current study was most likely attributed to lower midazolam dosage and to slow titration of anesthesia induction that allowed counterregulatory mechanisms to progressively compensate for the circulatory depressant effects of anesthetics.

Systemic hemodynamics, fluid requirements, inotropic and vasopressor support, as well as neuroendocrine responses did not differ between the two groups intraoperatively and postoperatively. We therefore hypothesize that partial preservation of systemic RAS and intact sympathoadrenal activation both contributed to maintain perioperative cardiocirculatory homeostasis in ACEI-treated patients.

During each study period, higher PRA were found in the ACEI group compared with the control group, that resulted from enalapril- or captopril-induced suppression of angiotensin II generation (mostly at the renal juxta-glomerular site) and hence, from interruption of the negative feedback mechanism controlling renin synthesis. As reported by others,[18–20] circulating angiotensin II concentrations usually are not reduced in patients receiving long-term ACE inhibitors and do not correlate with any antihypertensive effects. Because

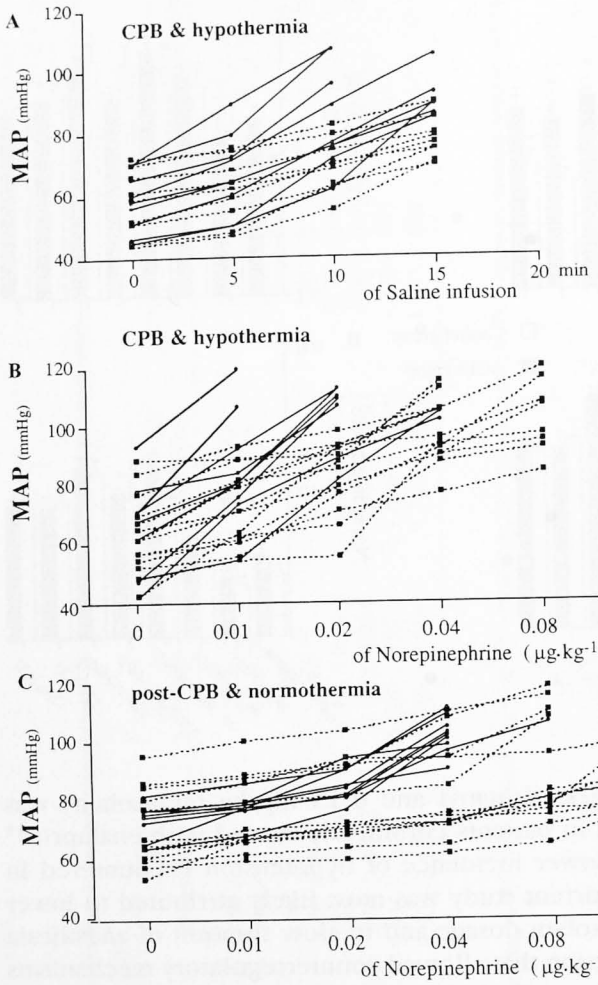

Fig. 2. Individual changes in mean arterial pressure occurring spontaneously after institution of hypothermic cardiopulmonary bypass (*A*), after infusion of incremental doses of norepinephrine during the hypothermic cardiopulmonary bypass (*B*) and the normothermic postcardiopulmonary bypass periods (*C*) in the control (open circles) and ACEI (closed squares) groups.

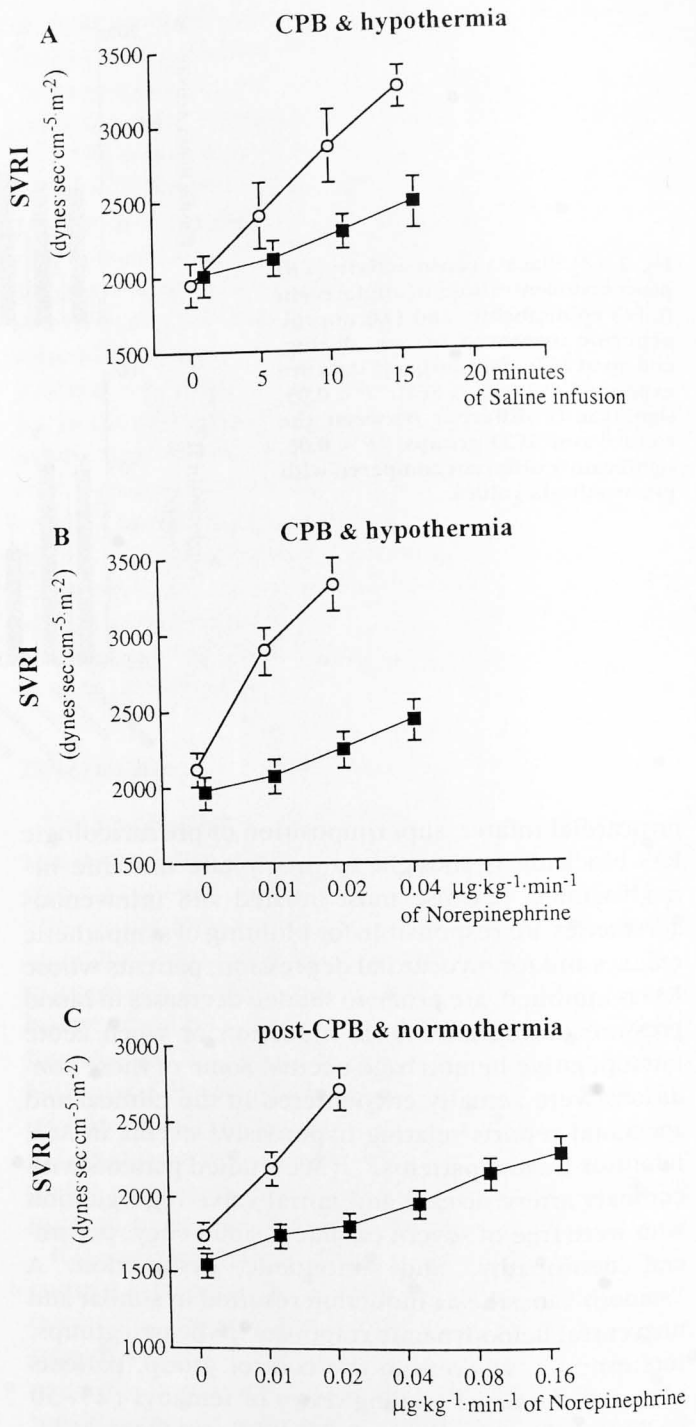

Fig. 3. Changes in systemic vascular resistance index occurring during and after hypothermic cardiopulmonary bypass in the control (open circles) and the ACEI (closed squares) groups: "spontaneous" increase in systemic vascular resistance index over 15 min after the institution of hypothermic cardiopulmonary bypass during saline infusion (*A*), increase in SVRI after the infusion of incremental doses of norepinephrine during the hypothermic cardiopulmonary bypass (*B*) and the normothermic postcardiopulmonary bypass (*C*) periods. Data are expressed as mean ± SEM.

angiotensin II regulates renin and ACE gene transcription *via* a negative feedback mechanism, synthesis of pulmonary ACE and prorenin substrates are rapidly induced after initiation of ACE inhibitor treatment, leading to increases in PRA and in serum ACE activity and ultimately to restoration of plasma angiotensin II levels.[21] However, it cannot be excluded that the true biologically active plasma angiotensin II concentrations were overestimated in the current study because we used an antibody that cross-reacted with other angiotensin peptides that could have been generated by some other proteolytic enzymes (cathepsines) released by

Table 4. Norepinephrine Dose–Responses

Variable	Group	CPB	Post-CPB
PD_{20} (μg/kg)	Control	0.030* (0.019–0.039)	0.150 (0.100–0.165)
	ACEI	0.080† (0.004–0.175)	0.520† (0.122–0.810)
Slope (ΔSVR/logNE dose)	Control	75.2‡ (41.5–93.1)	46.6 (28.3–59.2)
	ACEI	19.6*§ (9.5–33.6)	8.1§ (3.7–11.9)

PD_{20} and slope expressed as median (90% confidence intervals) of 9 (control group) and 13 (ACEI group) patients.

ACEI = angiotensin-converting enzyme inhibitor; CPB = cardiopulmonary bypass; PD_{20} = dose of norepinephrine required to increase baseline mean arterial pressure by 20%.

* $P < 0.01$ *versus* post-CPB.

† $P < 0.05$ *versus* control group.

‡ $P < 0.05$ *versus* post-CPB.

§ $P < 0.01$ *versus* control group.

activated leukocytes. Currently, there is a growing body of experimental evidence supporting a central role for RAS blockade within the brain, the cardiovascular system, and the kidney; in particular, vascular ACE activity has been demonstrated to be suppressed independently of plasma RAS and correlates well with the observed hypotensive effects.[22] In addition, alternative vasodilatory mechanisms involving the kallikrein-kinin and prostaglandin pathways appears to be implicated: ACE is a nonspecific enzyme structurally similar to kininase II, hence, ACE inhibition is expected to result in accumulation of endogenous bradykinin with vasorelaxant properties.[23]

The similar changes in plasma catecholamines within the two groups reflected appropriate sympathoadrenal responses to surgery and hypothermic CPB, that helped to maintain stable hemodynamics. In response to other acute stressful events, such as tracheal intubation,[7] postural changes,[24] and exercise,[25] the blood pressure-heart rate relationship has been demonstrated to be preserved in patients chronically treated with ACE inhibitors; this could be attributed to normal or enhanced sympathetic reflexes, as indicated by a resetting or an increased sensitivity of the baroreflex activity[26] and by an even greater release of catecholamines during postural changes.[27] Furthermore, the direct stimulatory effects of bradykinin on the release of norepinephrine and epinephrine may partly compensate for the loss of the facilitatory influences of angiotensin II on the sympathetic nervous system.[28]

Although the hemodynamic and neuroendocrine time course was indistinguishable between patients with and without chronic ACE inhibitors, the adrenergic responsiveness to exogenously infused norepinephrine differed markedly between the two treatment groups. To characterize the adrenergic responsiveness of the cardiovascular system, we administered norepinephrine, a mixed α and β agonist, because it is often used in clinical practice as a vasopressor or inotropic agent to help separate patients from CPB and in the intensive care unit to keep stable hemodynamics. In contrast to phenylephrine, a pure α-agonist that was shown to cause coronary vasoconstriction,[29] administration of norepinephrine after completion of surgery, has been associated with unchanged or increased blood flows through venous and arterial coronary bypass grafts. Mean arterial pressure and SVR were chosen as hemodynamic markers: MAP as an end-point of pressor responsiveness and determination of SVR to integrate the simultaneous changes in cardiac output and vascular pressure that were measured during norepinephrine infusion.

To assess the hemodynamic (and neuroendocrine) effects of hypothermic CPB and surgery, we studied patients in the control and ACEI groups receiving intravenous saline instead of norepinephrine. In both groups, baseline hemodynamics remained stable for at least 20 min after complete rewarming and separation from bypass whereas a gradual increase in SVR occurred shortly after institution of hypothermic CPB. Increased plasma viscosity, elevated plasma catecholamines, and tissue metabolic factors related to hypothermia have all been incriminated in increasing peripheral vascular resistance either directly or through enhancement of the sensitivity to endogenous and exogenous vasoconstrictors.[30] Of note, exclusion of the lung from the circulatory compartment was expected to prolong the biologic half-life of norepinephrine because pulmonary endothelium is the predominant clearance pathway of this catecholamine.[31]

The hemodynamic responses associated with hypothermic CPB and those induced by norepinephrine infusion were both markedly attenuated in patients receiving ACE inhibitors on a long-term basis as indicated by reduced values for the regression slopes of the time-response (SVR/time) and dose-response relationships (SVR/norepinephrine log dose) as well as by increased PD_{20} (amount of norepinephrine required to increase MAP by 20%). In support of our results, Tuman and colleagues observed a twofold increased vasoconstrictor requirement immediately after CPB in the presence *versus* absence of chronic preoperative ACE inhibitors.[32] Attenuation of the vasoconstricting effects of norepinephrine also has been observed in isolated arteries pretreated with various ACE inhibitors[33,34] as well as in normotensive and hypertensive subjects receiving a single 50-mg dose of captopril.[35] Interestingly, blunting of norepinephrine responses was more pronounced in chronically treated patients and reversal of adrenergic "hyporesponsiveness" could be achieved when low doses of angiotensin II or bradykinin type 2 antagonists were administered.[36] Taken together, the rightward shift and the reduced slopes of the vasoconstrictor and vasopressor dose-response are compatible with ACE inhibitors acting as noncompetitive antagonists that blunt the norepinephrine pressor effects through removal of angiotensin II and enhancement of vasorelaxant mediator(s).

Vascular ACE activity is mostly localized within the endothelial layer and adventitia of large and small arteries where it is involved in angiotensin II synthesis and in bradykinin inactivation.[37] Besides its powerful vasoconstrictor effects, angiotensin II acts as a growth factor that may lead to cardiac and vascular hypertrophy and that ultimately results in increased vascular resistance (arteriolar vessels), decreased arterial compliance (large arteries) and nonspecific enhancement of vasoconstrictor responses.[38] Regression of these structural and functional cardiovascular changes has been documented, independently of any blood pressure lowering effect, after a 3–6-month treatment with ACE inhibitors.[13,22,39] Furthermore, the enhanced bradykinin-induced relaxation associated with ACE inhibition is thought to result from the accumulation of endogenous kinins within the endothelium and the secondary release of potent direct vasodilators such as nitric oxide, prostacyclin, and a putative hyperpolarizing factor. The same vasodilatory factors also are released after activation of endothelial α_2-adrenergic receptors,[40] hence, we may speculate that norepinephrine-induced α_1-constriction was more strongly opposed by α_2-mediated vasorelaxation in the ACEI group than in the control group during the norepinephrine challenge.

From the above data, *in vivo* attenuation of pressure responses to norepinephrine in patients receiving ACE inhibitors can be viewed as a "resetting" of adrenergic sensitivity secondary to vascular RAS blockade that is characterized by: (1) depletion of angiotensin II, (2) regression of smooth muscle hypertrophy and "normalization" of arterial medial thickness, and (3) improvement of the endothelial vasodilatory function (increase in endogenous bradykinin stores).

Several aspects of the study design deserve further comment because a nonrandomized mixed population comprising patients undergoing CABG or MVR and who were treated preoperatively either with ACEI (captopril or enalapril) or with non-ACEI medications were studied.

First, although systemic hemodynamic and neuroendocrine responses behaved similarly in CABG and MVR patients, we observed greater pressor responses to norepinephrine in patients undergoing coronary artery surgery compared with patients undergoing valvular surgery; this could be related to the higher prevalence of arterial hypertension and diffuse atherosclerotic lesions in patients with coronary artery disease whereas those with mitral regurgitation often are seen with isolated inflammatory, infectious, or degenerative valvular abnormality. There is experimental evidence suggesting that the reactivity, but not the sensitivity, to humoral agents is increased in hypertensive patients because of endothelial dysfunction, reduced arteriolar density, and increased ratio of wall thickness to lumen diameter.[38,41] Second, β-blockers and calcium-channel blockers were prescribed more often as antihypertensive, antianginal, or antiarrhythmic agents in the control group. Continuation of these medications has been found to be associated with reduced incidence of myocardial ischemia, blunting of the hemodynamic response to surgery but also with increased needs for vasopressor support after CPB.[42] It is conceivable that a greater degree of β-blockade could account for some attenuation of the sympathetically induced release of renin and for reduced inotropic response to the β-stimulatory effects of norepinephrine, during and after surgery.[43] However, it is unlikely that an increase in the relative ratio of α- to β-receptor activity due to chronic β-blockade contributed to relevant differences in vascular α_1-responsiveness, because the hemodynamic re-

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sponse to phenylephrine during surgery has been shown to be unaltered after chronic propranolol therapy.[44] Because the vasorelaxant and antiadrenergic effects of ACE inhibition were expected to be amplified or potentiated by calcium channel blockade, we excluded patients pretreated with calcium channel blockers from the norepinephrine dose-response study. In fact, prolonged treatment with these medications also may lead to regression of vascular and cardiac hypertrophy in hypertensive patients as well as to reduced pressure response to phenylephrine during cardiac surgery.[45]

Third, the type of ACE inhibitor does not seem to affect the perioperative hemodynamic changes and norepinephrine-induced pressor responses, because comparable results were observed in patients receiving captopril—a lipophilic compound bearing a sulfhydryl group—or enalapril, which is 10–30 times more potent. Although differential access to tissues and differential inhibition of angiotensin-converting isoenzyme by various ACE inhibitors could account for some discrepant effects, these were probably not relevant in the settings of the current investigation. In a large prospective study,[32] similar vasoconstrictor requirements were found after CPB in patients pretreated with enalapril or captopril, supporting the finding that pooling the data of these two subpopulation of patients has most probably not affected the current results in a significant manner. Yet, it is possible that the variable duration of preoperative ACE inhibitor treatment (4–24 months) is implicated in time-related regression of the cardiovascular hypertrophic changes that would secondarily influence adrenergic responsiveness.

In summary, long-term treatment with ACE inhibitors in patients with preserved ventricular function is associated with stable hemodynamics and appropriate hormonal responses during cardiac surgery as indicated by activation of the sympathoadrenal and renin angiotensin systems. We hypothesize that the attenuated responsiveness to adrenergic stimulation more likely results from vascular angiotensin II depletion, "normalization" of the vascular structure, and enhanced endothelial vasodilatory function.

Based on these results, it appears that preoperative withdrawal of treatment with ACE inhibitor is not justified. However, the anesthesiologist should be aware of the greater sensitivity of patients receiving ACE inhibitors to anesthetic-induced circulatory depression, caution should also be exercised during surgery involving major fluid losses or when autonomic nervous and endocrine responses are obtunded secondary to disease processes or some drug therapies. Clinicians should keep in mind that continuation of ACE inhibitor treatment is potentially associated with beneficial effects: prevention of hypertension,[46] improved renal function,[6] and attenuation of coronary vasoconstriction.[47] In the future, it might be worthwhile to devote further clinical scrutiny to detect cardiac and renal protective effects associated with the use of ACE inhibitors, in patients undergoing cardiac or noncardiac surgery.

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