Reports of Investigation

Chronic angiotensin converting inhibition does not influence renal hemodynamic and function during cardiac surgery

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Purpose: Treatment with angiotensin-converting enzyme (ACE) inhibitors affects the autoregulation of renal blood flow and glomerular filtration and provides renal protective effects. The purpose of this case-control study was to investigate the effects of chronic ACE inhibition on perioperative renal hemodynamics and function.

Method: We prospectively studied renal function in two groups of patients, chronically treated or not, with ACE inhibitors (ACEI and control; n = 16, in each group) who underwent elective cardiac surgery under hypothermic cardiopulmonary bypass. Glomerular filtration rate, effective renal plasma flow, osmolar clearance and fractional excretion of sodium and potassium were determined before, during and after CPB. Additional measurements included plasma atrial natriuretic factor (ANF) as well as plasma and urinary cyclic GMP (cGMP), thromboxane B_2 (Tx B_2) and 6-keto-PGF_1.

Results: Renal functional and hemodynamic variables did not differ between the two groups, at any period. Cardiopulmonary bypass induced increases in urinary flow, osmolar clearance and fractional excretion of sodium and potassium in both groups. Plasma and urinary ratio of 6-keto-PGF_1 to Tx B_2 increased markedly and reflected a predominent systemic and renal release of vasodilatory prostaglandins. Intraoperatively, ANF was higher in ACEIs than in control patients.

Conclusions: Long term treatment with ACE inhibitors does not influence the perioperative changes in renal hemodynamics and function. During cardiopulmonary bypass, a transient impairment in solute reabsorption is associated with renal release of vasodilatory mediators (nitric oxide and prostacyclin).

Objectif : Le traitement avec les inhibiteurs de l'enzyme de conversion de l'angiotensine (ECA) agit sur l'autorégulation du débit sanguin rénal et la filtration glomérulaire et a un effet de protection rénale. L'objectif de cette étude cas-témoins est d'examiner les effets d'une inhibition de longue durée de l'ECA sur l'hémodynamie et la fonction rénales périopératoires.

Méthode : Nous avons réalisé une étude prospective de la fonction rénale chez les patients de deux groupes, traités ou non à long terme avec des inhibiteurs de l'ECA (IECA et témoin; n = 16 dans chacun), et qui subissent une intervention cardiaque élective avec circulation extracorporelle hypothermique. On a déterminé avant, pendant et après la CEC, la vitesse de filtration glomérulaire, le débit sanguin rénal efficace, la clairance osmolaire et la fraction excrétée du sodium et du potassium. D'autres mesures concernent : le facteur natriurétique auriculaire (FNA) et la guanosine monophosphate cyclique urinaire (GMPc), la thromboxane B_2 (Tx B_2) et la 6-céto- PGF

Résultats : À aucun moment, les variables rénales fonctionnelles et hémodynamiques n'ont présenté de différences intergroupes. La CEC a induit une hausse du débit urinaire, de la clairance osmolaire et de la fraction excrétée du sodium et du potassium dans les deux groupes. Les taux plasmatiques et urinaires de 6-céto-PGF_1 par rapport à la Tx B_2 ont beaucoup augmenté, reflet d'une libération systémique et rénale de prostaglandines vasodilatatrices. Le FNA peropératoire était plus élevé dans le groupe IECA que dans le groupe témoin.

Conclusion : Un traitement à long terme avec les inhibiteurs de l'ECA n'influence pas les changements périopératoires de l'hémodynamie et de la fonction rénales. Une altération transitoire de la réabsorption osmotique pendant la circulation extracorporelle est associée à la libération rénale de médiateurs vasodilatateurs (l'oxyde nitrique et la prostacycline).

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OVER the last two decades, angiotensin-converting enzyme (ACE) inhibitors have been successfully prescribed in an increasing number of patients with congestive heart failure, arterial hypertension and following myocardial infarct.[1] More recently, chronic inhibition of the renin-angiotensin system has been shown to delay the onset of end stage renal failure in several types of renal diseases.[2]

Angiotensin-converting enzyme is a non-specific metalloprotease and its inhibition leads not only to reduced angiotensin II formation but also to accumulation of bradykinin which triggers the release of prostacyclin and nitric oxide, from endothelial and renal tubular cells.[3]

During cardiac surgery, marked activation of the sympatho-adrenergic and renin-angiotensin systems is accompanied by the release of vasopressin, endothelin and thromboxane A_2.[4] These vasoconstricting and fluid retaining mechanisms are opposed by vasodilatory prostanoids and atrial natriuretic factor (ANF).[5] In such acute situations, inhibition of the RAS may impair the autoregulatory mechanisms aimed to control glomerular filtration and renal perfusion. Although short-term pretreatment with ACE inhibitors has been shown to preserve or enhance renal blood flow,[6,7] it remains unknown whether long term treatment with ACE inhibitors provides any renal protective or deleterious effects in patients undergoing cardiac surgery.

Thus, the purpose of the present study was to investigate the perioperative changes in renal function in patients chronically treated or not, with ACE inhibitors. In addition, we questioned whether the release of vasoconstrictor and vasodilatory prostanoids (thromboxane A_2 and prostacyclin) as well as plasma ANF and cyclic GMP (cGMP), its second messenger, was altered after chronic ACE inhibition.

Methods

Patients selection and management

After obtaining institutional Ethical Committee approval and informed consent, thirty-two patients scheduled for elective coronary artery bypass graft surgery, aortic valve replacement or mitral valve repair were investigated in an open prospective case-control study. All patients had moderate to well-preserved left ventricular function (ejection fraction $\geq$ 40%) and those referred with mitral regurgitation had no episode of congestive heart failure during the previous three months while receiving appropriate therapy. Patients with diabetes, recent myocardial infarction (< 30 days) and impaired renal function (creatinine clearance < 60 $ml \cdot ml^{-1}$) were excluded from the study. Cardiac catheterization with injection of radiocontrast materials was performed more than three days prior to surgery.

The usual cardiac medications, except diuretics and digoxin, were administered up to the morning of surgery. In the induction room, peripheral venous, radial arterial and central venous catheters were inserted for fluid and drug administration as well as for hemodynamic measurements. Preoperatively, 10 $ml \cdot kg^{-1}$ crystalloids were infused over 20 min. General anesthesia was standardized and consisted in fentanyl (40-60 $\mu g \cdot kg^{-1}$) and midazolam (0.03-0.06 $mg \cdot kg^{-1}$ followed by 0.10 $mg \cdot kg^{-1} \cdot hr^{-1}$) with pancuronium for muscular relaxation (0.15 $mg \cdot kg^{-1}$ at induction, 0.05 $mg \cdot kg^{-1}$ during bypass). Mechanical ventilation was adjusted to keep normocapnia and normoxia.

After aortic and right atrial cannulation, nonpulsatile CPB was instituted with a membrane oxygenator primed with two litres crystalloid and body temperature was decreased to achieve moderate hypothermia (26-30°C). After aortic clamping, myocardial protection was provided with St. Thomas's solution (600-900 ml) infused through the aortic root and repeated at 25-30 min intervals. During CPB, a pump flow > 2 $L \cdot min^{-1} \cdot m^{-2}$ was maintained during moderate hypothermia and was increased up to 2.4 $L \cdot min^{-1} \cdot m^{-2}$ during rewarming.

Study design

In our institution, 32% of patients referred for cardiac surgery are chronically treated with ACE inhibitors. Based on medical history, two groups of patients were investigated over a six months period: those treated with ACE inhibitors for at least three months (ACEI group, n = 16) and case controls matched for age and type of surgery who did not receive ACE inhibitors (control group, n = 16). During the first three months, data were only collected in ACEI-treated patients and, thereafter, case-controls were enrolled according to matching criteria. Renal function and blood samples were analyzed at the end of the six months period; the investigators and laboratory technicians were blinded to patient group allocation.

Before anesthesia, priming doses of 30 $mg \cdot kg^{-1}$ inulin (Inulin 10%; Laevosan Gesellschaft m.b.H., Linz, Austria) and 8 $mg \cdot kg^{-1}$ *p*-paraimmunohippurate (PAH, Merck, Sharp & Dohme, NJ) were injected *iv* followed by a continuous infusion of both drugs at 0.20 $mg \cdot kg^{-1} \cdot min^{-1}$ and 0.15 $mg \cdot kg^{-1} \cdot min^{-1}$, respectively, up to the end of surgery. An equilibration period of 60 min was allowed before baseline measurements. Diuretics, mannitol or dopamine, were not given during the

study. Treatment with ACE inhibitors was usually restarted in the ICU or, most often, on the surgical ward, i.e., two-three days after surgery.

Measurements

Glomerular filtration rate was assumed to equal creatinine or inulin clearances (C_{IN}, C_{creat}) and effective renal plasma flow was estimated as PAH clearance (C_{PAH}). Additional renal functional tests included osmolar clearance (C_{osm}) and fractional sodium and potassium excretion. Blood and urinary samples were obtained at the following times: 1) baseline measurement, 30 min before induction of anesthesia (preop), 2) before the start of bypass (pre-bypass), 3) after completion of the first cardioplegia (bypass), 4) after protamine administration (post-bypass) and, 5) on the fifth postoperative day. The urinary bladder was emptied through an indwelling Foley catheter after anesthesia induction, after inulin/PAH equilibration and prior to each measurement period. Intraoperatively, urine was collected over 30 min and arterial blood was collected in the middle of each sampling period. Pre- and postoperatively, urine was collected over 12 hr and mean of blood concentrations (for creatinine and electrolytes) at the beginning and the end of the clearance period, was calculated. Arterial blood was collected into cold tubes containing indomethacin, dipotassium ethylenediamino-tetraacetic acid or heparin and were immediately centrifuged at 4°C. C_{IN} and C_{PAH} were only determined intraoperatively. Urinary and plasma inulin and PAH concentrations were assayed spectrophotometrically. Serum and urinary sodium and creatinine were measured with a standard flame emission photometer. All clearance values were corrected for a standard body surface area of 1.73 m^2.

The plasma concentrations of ANF and its second messenger, cGMP, as well as the plasma and urinary concentrations of the stable metabolites of thromboxane A_2 (Tx B_2) and prostacyclin (6-keto-PGF_1) were determined before anaesthesia and during operation (pre-op, pre-bypass, bypass, post-bypass). Plasma ANF was extracted from a 2-ml plasma aliquot on a C-18 octadecylsilane cartridge (Sep-Pak, Waters Associates, Milfford, MA) and measured by a specific radioimmunoassay; intra- and interassay variations were 3.9% and 13.7%, respectively. After extraction by ethanol cGMP was measured using a commercial kit (Amersham, UK); intra- and interassay variations were 4.5% and 10%, respectively.

Prostanoids were measured in 100 µl plasma or urine aliquot containing indomethacin, by radioimmunoassay without extraction (Amersham, UK). The lower limit of sensitivity was 30 $pg \cdot ml^{-1}$ for both measurements. Excretion of urinary prostanoid metabolites was expressed as picograms per gram of creatinine (U creat).

Plasma concentrations of ANF, cGMP and prostanoids were corrected for the hemodiluting effects of CPB according to the change in hematocrit.

Statistical analysis

The sample size calculation was based on estimates of inulin and PAH clearances determined in a previous study including patients undergoing vascular surgery.[7] The calculations indicated that, to show a difference greater or equal to 1.2 standard deviation with a power of 90% and a significance of level of 5%, 16 patients should be evaluated in each group.

Data are expressed as means ± SD and differences are considered significant if $P < 0.05$. Two-way analysis of variance with Dunnett's test was used for within group comparisons with respect to baseline. A chi-square analysis with Yates's correction was used to compare percentages of patients. Simple linear correlation (Pearson) or regression analysis was used to

TABLE I Patient characteristics

	Control group (n = 16)	*ACEI group (n = 16)*
Age (yr)	64 ± 7	65 ± 6
Sex (M/F)	5/11	5/11
Height (cm)	172 ± 6	175 ± 5
Weight (kg)	76 ± 7	79 ± 10
Left ventricular ejection fraction (%)	61 ± 7	57 ± 9
Arterial hypertension	12	12
Preoperative medications (number of patients)		
ß-blockers	10	2*
calcium-channel antagonists	6	1
diuretics	4	3
nitrates	6	5
Serum creatinin ($mg \cdot dl^{-1}$)	94 ± 10	96 ± 11
Surgical procedures (number of patients)		
coronary bypass graft	10	10
aortic valve replacement	6	6
Cardiopulmonary bypass		
duration (min)	138 ± 20	152 ± 24
aortic cross-clamping (min)	92 ± 14	98 ± 18
lowest temperature (°C)	28.8 ± 0.7	28.2 ± 0.9
Inotropes / vasopressors; after cardiopulmonary bypass (number of patients)	3	13*

Data are expressed as mean ± SD, unless otherwise noted; * $P < 0.05$ between the two groups

TABLE II Renal functional data in patients undergoing cardiac surgery

	before surgery	*during surgery*			*5th postoperative day*
		pre-bypass	*bypass*	*post-bypass*	
Urinary flow ($ml \cdot min^{-1}$)					
Control group	0.9 ± 0.3	2.0 ± 1.1	6.7 ± 2.4*	4.2 ± 2.2*	1.2 ± 0.3
ACEI group	0.8 ± 0.3	1.2 ± 0.4	6.2 ± 3.8*	4.0 ± 1.9*	1.1 ± 0.4
Creatinine clearance ($ml \cdot min^{-1} \cdot 1.73\ M^{-2}$)					
Control group	79 ± 11	103 ± 34	83 ± 27	88 ± 32	81 ± 15
ACEI group	84 ± 19	97 ± 26	82 ± 30	81 ± 26	78 ± 21
Inuline, clearance ($ml \cdot min^{-1} \cdot 1.73\ M^{-2}$)					
Control group	-	64 ± 12	66 ± 14	62 ± 17	-
ACEI group	-	66 ± 14	59 ± 16	55 ± 15	-
PAH clearance ($ml \cdot min^{-1} \cdot 1.73\ m^{-2}$)					
Control group	-	228 ± 48	345 ± 71*	310 ± 94	-
ACEI group	-	234 ± 51	311 ± 62*	271 105	-
Filtration fraction (%)					
Control group	-	21.3 ± 4.1	18.6 ± 5.2	19.3 4.6	-
ACEI group	-	21.6 ± 3.7	17.8 ± 6.8	20.1 5.1	-
Osmolar clearance ($ml \cdot min^{-1} \cdot 1.73\ m^{-2}$)					
Control group	1.3 ± 0.2	2.3 ± 0.9	8.8 ± 3.7*	4.4 ± 2.1*	1.8 ± 0.4
ACEI group	1.5 ± 0.4	1.8 ± 0.8	7.8 ± 4.5*	4.8 ± 2.0*	1.7 ± 0.34
Fractional excretion of Na+ (%)					
Control group	0.9 ± 0.2	1.2 ± 0.4	8.1 ± 3.1*	3.4 ± 1.6*	1.4 ± 0.4
ACEI group	0.9 ± 0.3	0.8 ± 0.5	7.7 ± 3.9*	3.8 ± 1.8*	1.4 ± 0.9
Fractional excretion of K+ (%)					
Control group	14.2 ± 2.8	13.2 ± 2.7	28.5 ± 7.6*	33.9 ± 9.5*	7.6 ± 3.5
ACEI group	15.6 ± 3.7	12.5 ± 3.1	29.2 ± 8.1*	37.0 ± 12.3*	8.8 ± 3.7

Data are expressed as mean ± SD; * $P < 0.05$ compared with data obtained before surgery.

evaluate the relation among variables. For ANF, cGMP and prostanoid 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

Patients characteristics and outcome

Demographic data, left ventricular ejection fraction, surgical procedures and mean duration of CPB and cross- clamp were comparable in the two groups (Table I). In the control group, ß-blockers and calcium antagonists were prescribed more often in patients with hypertension. In the ACEI group, enalapril (six patients; 10-20 $mg \cdot day^{-1}$), captopril (five patients; 30-100 $mg \cdot dy^{-1}$), or lisinopril (five patients; 10-30 $mg \cdot dy^{-1}$) were administered over a median preoperative period of 12 mo (range, 6-36 mo). After weaning from CPB, infusion of catecholamines (adrenaline or noradrenaline at ≥ 0.01 $\mu g \cdot kg^{-1} \cdot h^{-1}$ for at least 60 min) was more often required to support blood pressure in the ACEI than in the control group (13 ACEI *vs* three control patients, $P < 0.05$). Perioperative fluid requirements were comparable between the two groups (3,224 ± 326 ml in the control group and 3,872 ± 528 ml in the ACEI group). There were no major postoperative complications, such as myocardial infarction, low cardiac output syndrome or excessive bleeding.

Renal hemodynamics and function

Renal functional and hemodynamic variables did not differ between the two groups, at any time period. Cardiopulmonary bypass was associated with increases in urinary flow, C_{osm} and fractional excretion of sodium and potassium (Table II). All these variables were still significantly elevated shortly after weaning from CPB and had recovered preoperative values at the fifth postoperative day. Creatinine and inulin clearances did not change during CPB whereas C_{PAH} increased in the control and ACEI groups (+56% and +36%, respectively). C_{creat} and C_{IN} were correlated with each other $r = 0.87$, $P < 0.05$).

TABLE III Plasma concentrations and urinary excretion of TxB_2 and 6-keto-PGF_1

	preoperatively	*prebypass*	*bypass*	*postbypass*
Plasma TxB_2 ($pg \cdot ml^{-1}$)				
Control group	406 ± 208	305 ± 107	502 ± 144	290 ± 117
ACEI group	576 ± 398	501 ± 375	826 ± 381	317 ± 139
Plasma 6-keto-PGF_1 ($pg \cdot ml^{-1}$)				
Control group	179 ± 113	342 ± 227	902 ± 567*	325 ± 237*
ACEI group	193 ± 96	322 ± 198	869 ± 328*	388 ± 149*
Plasma 6-keto-PF_{1a} / TxB_2				
Control group	0.46 ± 0.41	0.72 ± 0.61	1.84 ± 1.16*	1.12 ± 0.76*
ACEI group	0.37 ± 0.26	0.54 ± 0.28	1.05 ± 0.47*	1.22 ± 0.57*
Urinary TXB_2 ($Pg \cdot mg\ creat^{-1}$)				
Control group	21 ± 9	38 ± 12	958 ± 547*	875 ± 246*
ACEI group	23 ± 17	24 ± 20	1278 ± 789*	1253 ± 726*
Urinary 6-keto-PGF_1 ($pg \cdot mg\ creat^{-1}$)				
Control group	14 ± 5	20 ± 8	1964 ± 1171*	1142 ± 701'*
ACEI group	9 ± 7	13 ± 5	2752 ± 1542*	1549 ± 1089*
Urinary 6-keto-PF_{1a} / TXB_2				
Control group	0.42 ± 0.19	0.73 ± 0.51	2.53 ± 1.21*	1.22 ± 0.51*
ACEI group	0.39 ± 0.18	0.54 ± 0.23	2.34 ± 1.14*	1.70 ± 0.75*

Data are expressed as mean SD; * $P < 0.05$ compared with preoperative period.

Plasma ANF, plasma and urinary cGMP

In all the patients, plasma ANF increased after weaning from CPB (+70% in controls and +95% in ACEI patients) (Figure 1). Intra-operatively, ANF was higher in the ACEI than in the control group. Plasma ANF and cGMP were positively correlated r = 0.58 in controls and r = 0.79 in ACEIs patients) as well as plasma ANF and right atrial pressure r = 0.58 in controls and r = 0.73 in ACEIs patients).

The changes in plasma cGMP mimicked those of plasma ANF but did not reach statistical significance. In the two groups, urinary excretion of cGMP increased during bypass and postbypass periods and was positively correlated with C_{osm} (r=0.84 and 0.89, in control and ACEI groups, respectively).

Plasma and urinary Tx B_2 and 6-keto-PGF_1

Patients in the ACEI group did not differ from those in the control group with regard to plasma concentration and urinary excretion of 6-keto-PGF_1 and Tx B_2 and their respective ratios (Figures 2,3). After the start of CPB, the ratio of 6-keto-PGF_1 to Tx B_2 increased as a result of elevation in plasma 6-keto-PGF_1 while plasma Tx B_2 remained unchanged.

During and following CPB, urinary excretion of Tx B_2 and 6-keto-PGF_1 was increased in all patients and the ratio of 6-keto-PGF_1 to TxB_2 was increased as a result of larger urinary excretion of 6-keto-PGF_1 than Tx B_2. In the two groups, C_{osm} was directly related to urinary excretion of 6-keto-PGF_1 (r=0.67 and 0.82, in control and ACEI groups) and to the ratio of 6-keto-PGF_1 to TxB_2 (r=0.52 and 0.62, in control and ACEI groups).

Discussion

In patients with well-preserved renal function, we found that chronic treatment with ACE inhibitors did not produce either detrimental or beneficial changes in renal hemodynamics and function during cardiac surgery. Impaired solute reabsorption was induced by cardiopulmonary bypass and was associated with renal release of vasodilatory mediators (nitric oxide, prostacyclin) as evidence by the urinary excretion of cGMP and 6-keto-PGF_1.

Renal effects of ACE inhibitors

Short-term or single bolus administration of an ACE inhibitor has been shown to maintain glomerular filtration rate and to increase renal blood flow in hypertensive patients and during major surgical procedures.[6–8] Experimental studies suggest that these renoprotective effects might result from the removal of angiotensin II and local accumulation of kinins, prostanoids and nitric oxide.[9] In contrast, we found that during cardiac surgery, renal hemodynamics and function were not influenced by long term preoperative treatment with ACE inhibitors (> six months).

These discrepant renal effects between acute and chronic renin-angiotensin blockade could be explained by several reasons.

First, in agreement with our results, other investigators failed to demonstrate that prolonged ACE inhibition enhances prostacyclin and nitric oxide synthesis under clinical conditions.[10–12] These data support the hypothesis that a time-dependent decrease in renal synthesis of vasodilatory mediators (nitric oxide and prostacyclin) occurs after long-term blockade of ACE (kininase). Second, patients chronically treated with ACE inhibitors often require vasopressor support at the time of anesthesia induction and / or after weaning from bypass[13,14] whereas acute inhibition of the renin angiotensin system in normovolemic anesthetized patients is associated with hemodynamic stability and increased cardiac output.[7] Indeed, 13 of 16 patients in the ACEI group needed catecholamines infusion and such treatment could induce renal vasoconstriction or at least obliterate renal vasodilatation associated with ACE inhibitor treatment. Third, according to the nonrandomized study design, patients with hypertension, aortic stenosis or mitral valve regurgitation were selected by their own physician to be treated either with ACE inhibitors (captopril, enalapril and lisinopril) or with other cardiac drugs (ß-blockers and/or calcium-channel blockers). It is conceivable that such alternative treatment in control patients resulted in equi-effective preservation of renal function since ß-blockers attenuate the perioperative activation of plasma renin activity[15] and calcium- channel blockers tend to improve renal blood flow during aortic abdominal surgery.[16]

Renal dysfunction associated with CPB

Although earlier reports had raised concerns about cardiopulmonary bypass-induced renal vasoconstriction,[17] recent studies have shown that total renal plasma flow and glomerular filtration were either discretely decreased, unchanged or even increased during cardiac surgery.[18–20] In the present study, C_{PAH} and C_{creat} did not decrease throughout the study period. Improvement in surgical techniques, better control of circulatory homeostasis, maintenance of higher pump flow using a membrane oxygenator and an arterial filter have likely contributed to better preservation of renal function.

As reported by others, we found that extracorporeal bypass induced a transient tubular dysfunction characterized by impaired solute reabsorption, a brisk osmolar diuresis and increases in fractional excretion of sodium and potassium.[18,21] High C_{PAH} values which presumably

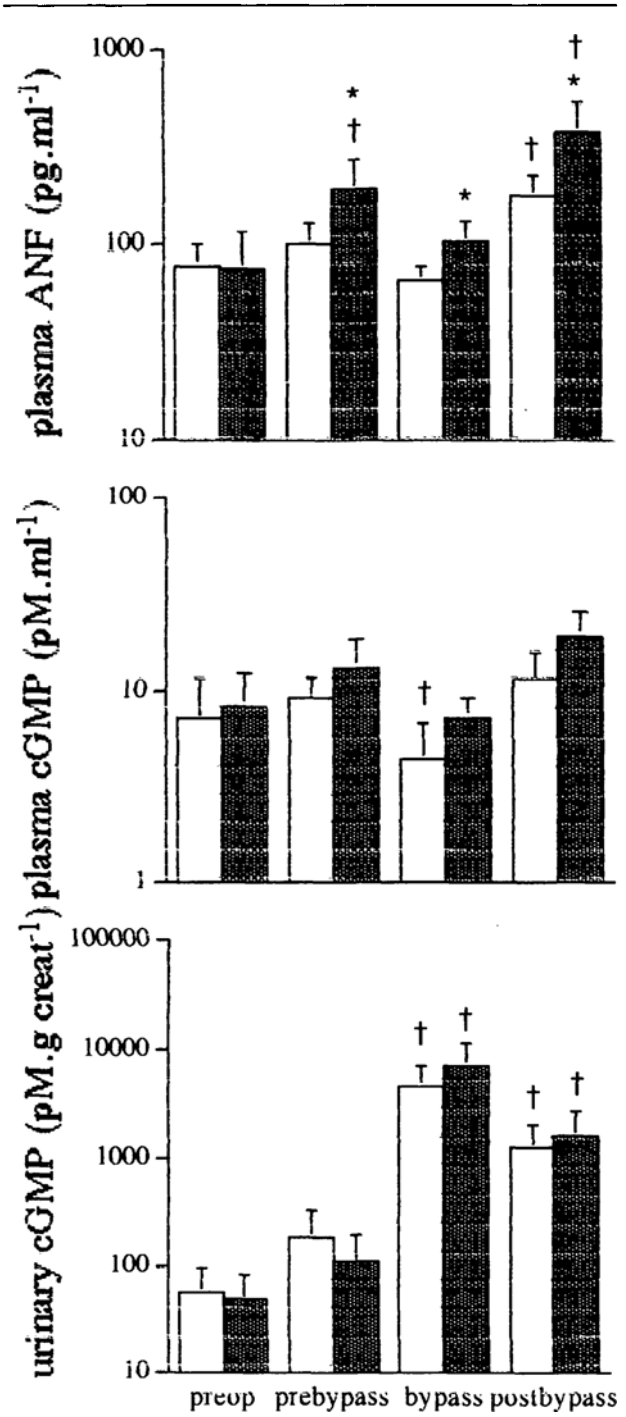

FIGURE Changes in plasma atrial natriuretic factor (ANF) and plasma and urinary cyclic guanidinomonophosphate (cGMP) concentrations in two groups of patients undergoing cardiac surgery (□, control group and ■, ACEI group). Data are presented as mean and SD. †Indicates significant differences from baseline (preoperative) at the indicated time period and *indicates differences between the two groups ($P < 0.05$).

reflect cortical blood flow, were likely attributed to hemodilution and reduced tubular extraction of PAH.[19,20] Hence, effective renal plasma flow was systematically overestimated in both groups since PAH is almost exclusively secreted in proximal tubular cells and the combined effects of hypothermia, non-pulsatile blood flow and redistribution of blood flow from the cortex to the medulla cause a 10-20% reduction in tubular extraction of PAH (and consequently a 10-20% false elevation in cortical blood flow).

Importantly, we observed a close relationship between osmolar diuresis and urinary excretion of 6-keto-PGF_1 and cGMP that reflected the renal formation of vasodilatory mediators (nitric oxide and prostacyclin).[22]

During CPB, whether enhanced salt and water excretion is a direct effect of prostanoids and nitric oxide on tubular cells or merely the result of redistribution of intra-renal blood flow, remains a matter of debate. Experimental studies have demonstrated that prostanoids antagonize the *in vivo* effect of antidiuretic hormone and inhibit Na^+/Cl reabsorption in the proximal and distal nephron and the loop of Henle.[10] On the other hand, papillary washout associated with medullary vasodilatation prevents the papillary Na^+/Cl^- countercurrent exchange by disrupting the hyperosmolar gradient.[23] Further impairment in tubular solute reabsorption involves the hypothermic-induced slowing of Na^+/Cl^- membrane pumps.

Plasma -ANF and ACE inhibition

The observed relationships between plasma concentration of ANF, plasma cGMP and right atrial pressure confirm that the atrial release of ANF, even during anesthesia, is partly triggered by changes in cardiac filling pressure[24] and that plasma ANF concentration largely determines the circulating level of its second messenger, cGMP.[25] Both ANF and nitric oxide activate guanylate cyclase and the release of cGMP within endothelial and renal tubular cells.[26] Besides cardiac filling, stress-related tachycardia and raised levels of circulating catecholamines play a minor role in atrial release of ANF.[27]

Interestingly, higher plasma concentrations of ANF were observed in patients receiving ACE inhibitors compared with controls, despite comparable heart rate and cardiac preload conditions. Similar results have also been reported in patients with chronic heart failure[28] that lend support to the hypothesis that the release of ANF could be reset at lower atrial distending tensions when the renin-angiotensin system is blocked.

The elevated ANF concentrations are not incriminated in causing greater urinary salt losses since ANF induced- natriuresis is blunted in patients receiving ACE inhibitors.[29] However, due to their potent vasodilatory effects, high ANF levels could partly account for the increased requirements in vasopressor agents after coming-off bypass, in the ACEI group. Such impaired perioperative adrenergic responsiveness is likely related to angiotensin II removal, regression of vascular hypertrophy, increased vascular synthesis of kinins and greater atrial release of ANF.[30]

Limitations of the study

We did not investigate patients with impaired cardiac and renal function who are at greater risk to develop perioperative renal insufficiency and who would benefit from a therapeutic intervention aimed to protect the kidney. In response to circulatory failure, the renal synthesis of thromboxane A_2 and the renin-angiotensin system are markedly stimulated and treatment with an ACE inhibitor has been demonstrated to restore the balance between vasoconstricting/vasodilator prostanoids while increasing renal blood flow.[12,31]

Given the small sample size of the study, we were unable to compare the effects of the three ACE inhibitors, i.e., captopril, enalapril and lisinopril. These drugs differ according to several structural and pharmacokinetic properties that may cause variable degree of ACE inhibition within tissues. Clinical data support that a greater renal blockade of ACE activity can be achieved with enalapril than with lisinopril.[32]

Conclusions

In summary, long-term preoperative treatment with ACE inhibitors did not impair or improve renal hemodynamics and function in patients undergoing cardiac operations, compared with controls receiving other anti-hypertensive medications. In all the patients, hypothermic bypass induced a transient tubular dysfunction characterized by impaired solute reabsorption that was likely related to enhanced renal synthesis of vasodilatory prostanoids and nitric oxide.

Due to the increasing use of ACE inhibitors, further studies should be focused on higher risk groups, i.e., patients with heart failure or renal insufficiency, in order to assess the risk/benefit ratio of such perioperative treatment in terms of cardiac and renal protection.

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