

Effect of Angiotensin Converting Enzyme Inhibition on Blood Pressure and Renal Function during Open Heart Surgery

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Activation of the renin-angiotensin system during open heart surgery may have consequences both beneficial in sustaining blood pressure and deleterious in compromising renal hemodynamics. The influence of short-term pretreatment with captopril on blood pressure and renal function was assessed double-blind *versus* placebo in 18 patients without pre-existing cardiac or renal failure, and undergoing coronary artery bypass. No difference in blood pressure and fluid requirement during the surgical period was observed between groups receiving captopril or placebo. Effective renal plasma flow and glomerular filtration rate decreased in the placebo group whereas they remained unaltered in the captopril group; during cardiopulmonary bypass, urinary excretion of sodium was greater in patients receiving captopril than those receiving placebo. These results suggest that captopril pretreatment does not compromise the control of blood pressure and renal function during open heart surgery; additional studies on the protective value of angiotensin-converting enzyme inhibitors are warranted in patients at higher risk for developing renal failure. (Key words: Kidney: renin-angiotensin system. Pharmacology: captopril. Surgery, cardiac: cardiopulmonary bypass.)

THE OCCURRENCE OF RENAL FAILURE following open heart surgery is not uncommon. Up to 30% of such patients may develop a transient decline in renal function,¹⁻³ resulting in postoperative azotemia, sodium retention, and impairment in renal concentrating mechanisms, a picture generally viewed as a form of prerenal failure.⁴ Intrinsic acute renal failure requiring dialysis is observed in only 3% of all patients but carries a very poor prognosis. Postoperative renal failure is thought to be hemodynamically mediated⁴ and various factors have been implicated in its pathogenesis. It appears that a prominent role is played by the decrease in left ventricular function and systemic blood pressure either during^{1,2,5} or in the days following⁶ the surgical procedures. Protective measures of incompletely documented value have been adopted during recent years and include extracellular fluid volume expansion, hypothermia, hemodilution, and intermittent mannitol administration.⁷

It has been suggested that the renin-angiotensin system is involved in the maintenance of normal blood pressure during anesthesia.⁸ On the other hand, renin may have a role during the course of acute renal failure.⁹ Since a marked activation of the renin-angiotensin system has been observed during cardiopulmonary bypass (CPB),¹⁰ the question arises of whether this stimulated renin-angiotensin system may exert a beneficial or a deleterious effect during CPB. In recent years, angiotensin-converting enzyme inhibitors (CEI) have been increasingly used in the treatment of hypertension and congestive heart failure, and a number of patients receiving such treatments are candidates for some type of thoracic surgery; the lack of a reactive renin-angiotensin system in such patients may have both desirable and undesirable effects regarding the variations in blood pressure and renal function associated with cardiopulmonary surgery. The present studies were undertaken to evaluate the influence of pretreatment with the converting-enzyme inhibitor captopril on blood pressure and renal function in patients undergoing coronary artery surgery.

Methods

The study population consisted of 18 men scheduled for coronary artery bypass surgery. Patients with prior renal dysfunction (serum creatinine > 1.7 mg/dl) or cardiac failure (ejection fraction < 50% as estimated by ventriculography) were not included. The protocol was approved by the Committee for Ethics in Clinical Research of our institution and informed consent was obtained from each patient. Two days before surgery, patients were allocated in a randomized double-blind fashion to the treatment group (captopril, 100 mg bid, n = 8) or the control group (placebo tablet bid, n = 10). The last dose of either captopril or placebo was given at the time of preanesthetic medication, about 2 h before the beginning of surgical procedures. Both treatments were well tolerated. Antianalgesic therapy was maintained until the day before surgery: all patients were given a calcium channel blocking drug and three subjects in each group also received a β -adrenergic blocking drug.

Preanesthetic medication consisted of 200 mg hydroxyzine and 100 mg meperidine im. Anesthesia was induced and maintained with dextromoramide (0.2–0.3 mg/kg), droperidol (0.1–0.3 mg/kg), diazepam (0.3–0.5 mg/kg), and pancuronium (0.15 mg/kg). Ventilation was

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controlled using 50% nitrous oxide and oxygen, except during CPB when 100% oxygen was used. In all patients a peripheral vein was cannulated prior to anesthesia, then a central venous catheter was inserted *via* the internal jugular vein; a radial artery catheter and a Foley urinary bladder catheter were inserted after the induction of anesthesia. The heart was approached *via* a median sternotomy and cannulation for CPB was made *via* the ascending aorta and both vena cava through the right atrium. CPB was instituted with a Bentley BOS 10 bubble oxygenator, primed with 25–30 ml/kg of a crystalloid solution to reach a 25–30% hemodilution (calculated from the change in hematocrit (Hct) as $(1 - (\text{Hct}_{\text{CPB}}/\text{Hct}_{\text{basal}})) \times 100$). The aorta was clamped and a cardioplegic solution was infused into the aortic root until myocardial temperature fell to 15° C or less. General body temperature was reduced to 25–30° C during cardiac arrest.

A first series of measurement (period 0) was made just before entering the operating room, about 1 h after pre-anesthetic medication and administration of the last dose of pretreatment. Then, three periods of measurements of renal function (clearance periods), 20–30 min duration each, were made as follows: during surgical approach but before CPB (period 1), during CPB (period 2), and during surgical closure, 30–60 min after CPB (period 3). Mean arterial pressure (MAP, mmHg) was obtained through electronic monitoring. Volumes administered during CPB were computed as a total volume load, including the priming solution and all solutes added to ensure MAP above 60 mmHg and a nonpulsatile pump flow rate (PFR) greater than $2.5 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$. Total vascular resistance during CPB (TVR , $\text{mmHg} \cdot \text{l}^{-1} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$) was calculated as MAP/PFR .

Blood samples were obtained at the midpoint of each clearance period. Glomerular filtration rate (GFR, $\text{ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$) was measured through the endogenous creatinine clearance. Fractional excretion of sodium (FE_{Na}) and potassium (FE_{K}) were calculated as: $\text{Na clearance}/\text{creatinine clearance} \times 100$, and $\text{K clearance}/\text{creatinine clearance} \times 100$, respectively. Effective renal plasma flow (ERPF, $\text{ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$) was estimated from the clearance of ^{131}I -orthoiodohippuran, using the continuous infusion technique as previously described for this laboratory.¹¹ Plasma renin activity (PRA) was evaluated by radioimmunoassay (CEA Sorin kit); the hormone concentration was corrected for the hemodiluting effect of CPB according to the changes in hematocrit: $\text{PRA} \times \text{Hct}_{\text{basal}}/\text{Hct}_t$, where $\text{Hct}_{\text{basal}}$ is the value of pre-CPB hematocrit and Hct_t the hematocrit at the time of sampling.

Data are expressed as mean \pm SEM. Two-way repeated measures ANOVA and Student's *t* test with Dunnett's correction were used to assess significance between and within groups. $P < 0.05$ was considered the minimum level of significance.

Results

The two groups of patients did not differ in any demographic data or details of surgical procedures (table 1). The total dose of anesthetic medications was similar in the two groups. No vasopressor was given in any group.

Period 1 (Prebypass). Figure 1 shows that following induction of anesthesia and sternotomy, blood pressure decreased slightly (but not significantly) in captopril-treated patients, while PRA increased by $31 \pm 13\%$ ($P < 0.05$). Both MAP and PRA remained unchanged in the control group.

Period 2 (Cardiac bypass). During CPB, blood pressure decreased to the same extent in the two groups (85 ± 4 to 69 ± 4 and 86 ± 5 to 66 ± 3 mmHg, respectively; both $P < 0.05$). As indicated in table 1, PFR was set at the same level in the two groups, so that calculated TVR were similar (0.248 ± 0.014 in captopril-treated patients and 0.256 ± 0.016 in controls, respectively; $P = \text{NS}$). In addition, the volume load required to obtain the desired blood pressure and pump flow rate in the captopril group was identical to that in the control group. However, ERPF and GFR remained stable in captopril-treated patients, whereas both parameters decreased (by 33.7 ± 12.7 and $33.9 \pm 11.6\%$, respectively; both $P < 0.05$) in patients receiving placebo. Similar differences were observed in urinary excretion rates of sodium and potassium, which increased in the captopril group (68 ± 8 to 210 ± 52 and 44 ± 8 to $89 \pm 19 \mu\text{mol}/\text{min}$, respectively; both $P < 0.05$) but not in the control group. PRA rose further in the captopril group ($P = 0.06$ when compared to period 1) and remained unchanged in the control group.

Period 3 (Postbypass). When CPB was stopped and the patients rewarmed, blood pressure increased in both groups, without reaching pre-CPB levels in the control group ($P = 0.05$). During this period, volume load and central venous pressure were similar between groups (data not shown). GFR increased slightly ($P = \text{NS}$) above baseline values in the captopril group and returned to pre-bypass levels in the control group (fig. 1). Urinary excretion rate of sodium and potassium increased significantly

TABLE 1. Demographic and Perioperative Characteristics in 18 Patients Undergoing Coronary Artery Bypass after a 48-Hour Treatment by Captopril or Placebo

Demographic and Perioperative Data	Placebo-Treated	Captopril-Treated
Number of patients	10	8
Age (yr)	60 \pm 2	56 \pm 3
Body weight (kg)	71.8 \pm 1.9	71 \pm 3.8
Azotemia (g/dl)	20.5 \pm 4.1	19.3 \pm 5.2
Plasma creatinine (mg/dl)	1.17 \pm 0.15	1.23 \pm 0.18
Duration of CPB (min)	55 \pm 6	55 \pm 5
Duration of aortic cross-clamp (min)	18 \pm 3	21 \pm 2
Temperature during CPB (°C)	28.8 \pm 0.9	28.1 \pm 0.8
Pump flow rate ($\text{l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$)	2.61 \pm 0.06	2.78 \pm 0.07
Volume load during CPB (l/m)	1.94 \pm 0.36	1.81 \pm 0.24

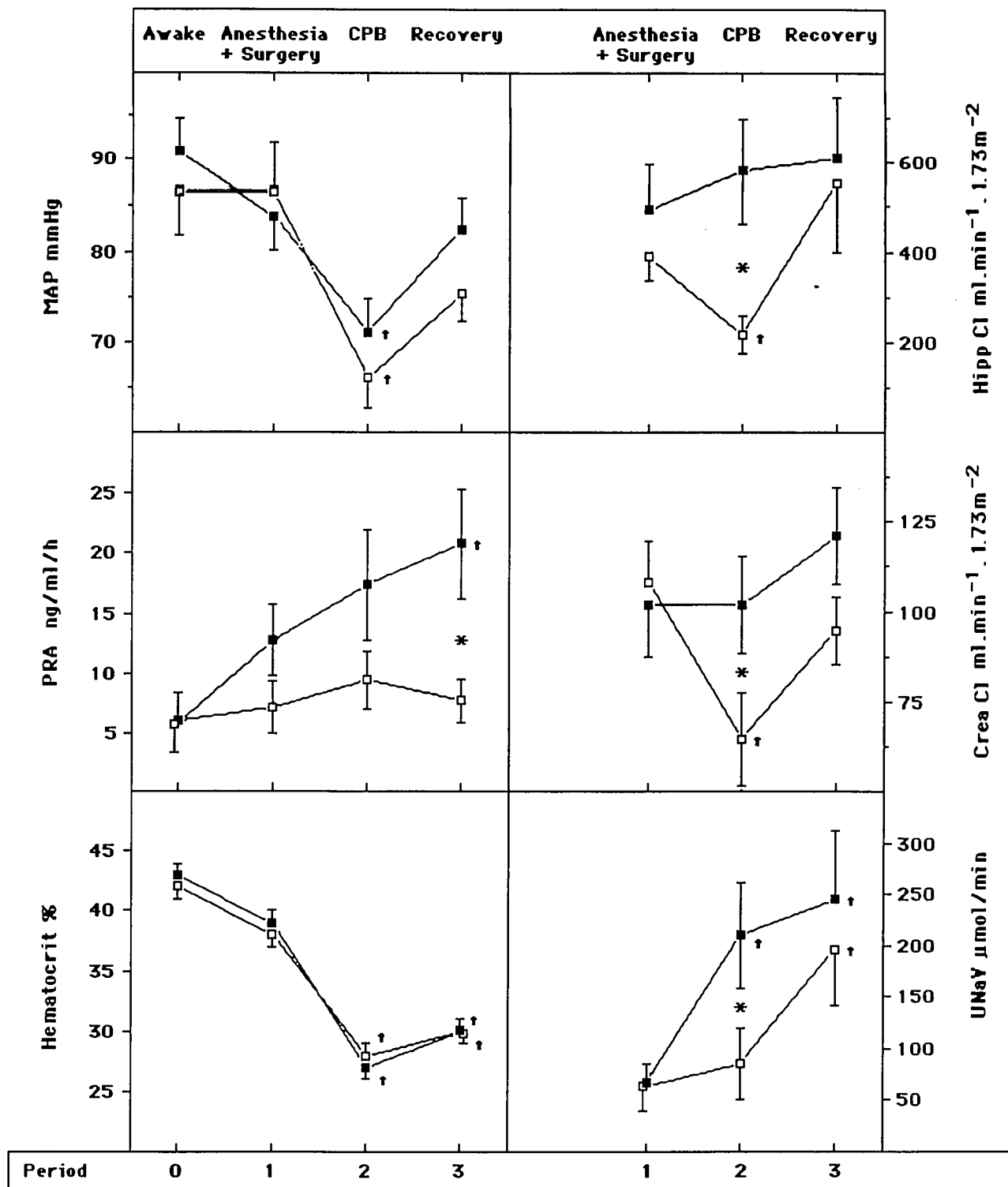


FIG. 1. Effect of captopril (closed squares, $n = 8$) and placebo (open squares, $n = 10$) pretreatment on mean arterial pressure (MAP), plasma renin activity (PRA), renal plasma flow (Hippuran clearance), glomerular filtration rate (Creatinine clearance), and urinary sodium excretion (UNaV) during cardiopulmonary bypass (CPB) ($P < 0.05$: † within- and * between-group).

in the control group only ($P < 0.05$ when comparing periods 2 and 3), so that final values of FE_{Na} and FE_K were identical in both groups (1.37 ± 0.34 vs. $1.49 \pm 0.39\%$ and 31.5 ± 9.7 vs. $32 \pm 3\%$ for FE_{Na} and FE_K , respectively; $P = NS$).

Discussion

The present studies indicate that administration of captopril for 2 days before surgery did not impair blood pressure control and attenuated the transient renal dysfunction associated with cardiac bypass surgery in normotensive patients without heart failure.

Large doses of angiotensin-converting enzyme inhibitors, such as those used in the present studies, are expected to suppress circulating levels of angiotensin II.¹² Plasma angiotensin II concentrations were not actually measured, but inhibition of angiotensin conversion was demonstrated by the rise in PRA during anesthesia, surgery, and cardiac bypass, indicating a lack of negative feedback on renin release. Presumably the differences observed in renal function between the groups could be accounted for by suppression of angiotensin II generation. However, other effects of captopril cannot be eliminated, due to possible stimulatory influence of captopril on prostaglandin synthesis¹³ and interference of converting enzyme blockade with the metabolism of other vasoactive substances.¹⁴

An important finding of this study is that blood pressure of captopril-treated patients remained stable, and similar to that of patients with an unimpaired renin-angiotensin system, during anesthesia, surgery, and cardiopulmonary bypass. Previous studies in humans have shown that PRA is barely stimulated by anesthesia per se⁸ or surgery,¹⁵ but rather by volume depletion.¹⁶ The renin system, however, may contribute to the normal maintenance of blood pressure during uncomplicated anesthesia. Taylor *et al.*¹⁰ observed that plasma angiotensin II concentration rose markedly during CPB and remained increased for several hours. In addition, although PRA failed to increase in rats anesthetized with halothane, acute administration of the angiotensin antagonist saralasin was associated with a decrease in blood pressure.¹⁷

Blockade of the renin system may interfere with the immediate regulation of systemic hemodynamics. Administration of captopril to rats¹⁸ or teprotide to dogs¹⁹ after hemorrhage impaired the recovery of blood pressure. These results contrast with reports of a beneficial effect of angiotensin inhibition in cats, when pretreatment by saralasin²⁰ or captopril²¹ was instituted before hemorrhage. Thus, the time schedule of renin blockade relative to the volume variation may be critical to the consequences on circulatory homeostasis. The determinants of blood pressure regulation in CEI-pretreated animals has not been fully explored for the moment. Previous

data from this laboratory²² indicate that blood pressure become markedly volume-dependant in normal subjects or those with essential hypertension receiving captopril for 4–8 days. However, in the present study, the maintenance of blood pressure in CEI-treated patients did not require a higher pump flow rate or a larger fluid intake when compared with the control group.

Although no instance of renal failure occurred post-operatively in either group, the present observations suggest that captopril pretreatment may have beneficial consequences on renal dysfunction associated with cardiopulmonary bypass. No decrease in renal plasma flow or glomerular filtration rate was observed in the captopril group during cardiopulmonary bypass, and urinary sodium excretion was significantly higher during this period when compared with the control group. Cardiopulmonary bypass has been likened to controlled shock, but only mild and transient renal impairment is usually observed, as in the present studies, presumably because of routine protective measures² including the induction of water diuresis,^{23,24} the maintenance of high flow rate,⁵ and perfusion pressure.¹ Recent data also suggest that the use of calcium antagonists (as in all our patients) possibly affords some additional protection against the vascular and cellular consequences of the more severe ischemic insult.²⁵

In the present studies, glomerular filtration rate was estimated by the clearance of endogenous creatinine, which has been shown to correlate closely with inulin clearance under the hemodynamic and metabolic conditions of CPB.^{23,24} Admittedly, the use of hippuran clearance as an index of effective renal plasma flow is more debatable, since some authors²³ have reported a 25% decrease in PAH extraction during hypothermia. This adds to the difficulties in clearance measurements due to hemodynamic instability, oliguria, and postoliguric washout of clearance markers during CPB. However, the operative procedures and the course of anesthesia were very similar in both groups, thus suggesting that captopril pretreatment was specifically associated with a preserved glomerular filtration rate and a decreased tubular reabsorption of sodium at the time of CPB.

Additional studies are needed to determine whether renal vasodilatation and natriuresis observed in captopril-treated patients will be associated with some protection of the renal areas with high susceptibility to hypoxia, which may be responsible for complete renal failure.²⁶ It is conceivable that the attenuation of ischemia and subsequent fluctuations in renal blood flow may blunt reperfusion cellular injury. We think that patients undergoing coronary surgery provide a useful model to test this hypothesis by monitoring systemic and renal hemodynamics. However, it is known that renal failure prior to, and marked hypotension during treatment by angiotensin-converting enzyme inhibitors, may be associated with ex-

acerbation of renal dysfunction. Thus, the issue of a protective effect of CEI in patients at high risk of cardiac surgery-associated renal failure requires specific studies in such patients.

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