Effects of enalaprilat infusion on hemodynamics and renal function in patients undergoing cardiac surgery

Kalp cerrahisinde kullanılan enalaprilat infüzyonunun hemodinamik değişkenlere ve böbrek fonksiyonlarına etkisi

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ABSTRACT

Objective: This study was undertaken to evaluate the effect of Enalaprilat infusion on hemodynamics and renal function during cardiopulmonary bypass (CPB).

Methods: Thirty adults undergoing CPB were randomly allocated into 2 groups. All patients received the same anesthetic protocol and same dopamine infusion protocol (2 mg/kg -1/min-1) during the study. In addition to dopamine infusion 15 patients received enalaprilat infusion (0.06 mg/kg-1/hr-1) during CPB. Blood creatinine, urea levels, and creatinine clearance (CLcr) were measured and cardiac output (CO) was calculated by echocardiography preoperatively and on the 6th postoperative day. Mean arterial pressure (MAP), central venous pressure (CVP), systemic vascular resistance (SVR) measurements were recorded during the operation and during postoperative 24 hours.

Results: In the control group postoperative blood creatinine and urea levels were significantly higher and CLcr measurements were significantly lower than the preoperative values ($p<0.05$). These values did not change in the enalaprilat group. Mean arterial pressure was similar in both groups ($p>0.05$), but SVR was lower ($p<0.05$) and CVP was higher ($p<0.05$) in the enalaprilat group than in the control group. In the enalaprilat group postoperative CO measurements were higher than the preoperative values ($p<0.05$).

Conclusion: Our results demonstrate that enalaprilat infusion during CPB improves renal function and CO measurements in the early postoperative period. *(Anadolu Kardiyol Derg 2004; 4: 296-300)*

Key words: Cardiopulmonary bypass, enalaprilat, renal function, hemodynamics

ÖZET

Amaç: Kardiyopulmoner baypas (KPB) sırasında kullanılan enalaprilat infüzyonunun hemodinamik değişkenlere ve böbrek fonksiyonlarına etkisini araştırmak.

Yöntemler: Kardiyopulmoner baypas yapılacak 30 erişkin hasta rastgele olarak iki gruba ayrıldı. Tüm hastalarda standart anestezi yöntemi ve çalışma süresince dopamin infüzyonu kullanıldı (2 mg/kg–1/dak-1). Birinci grup hastalara (n=15) KPB sırasında enalaprilat infüzyonu (0.06 mg/kg-1/st-1) uygulandı. Preoperatif dönemde ve postoperatif 6. günde serum kreatinin ve üre düzeyleri ile kreatinin klirensleri (KLkr) ölçüldü ve ekokardiyografi ile kalp debileri hesaplandı. Ameliyat sırasında ve postoperatif 24 saat boyunca ölçülen ortalama arter basıncı (OAB), santral venöz basınç (SVB) ve sistemik vasküler rezistans (SVR) değerleri kaydedildi.

Bulgular: Kontrol grubunun postoperatif dönemdeki kreatinin ve üre düzeyleri preoperatif döneme kıyasla anlamlı olarak yüksek, KLkr ölçümleri ise anlamlı olarak düşük bulundu ($p<0.05$). Enalaprilat grubunda bu ölçümler benzerdi. Her iki gruptaki OAB değişiklikleri benzer iken ($p>0.05$) enalaprilat grubunun SVR ölçümleri kontrol grubuna kıyasla anlamlı olarak düşük ($p<0.05$), SVB ölçümleri ise anlamlı olarak yüksekti ($p<0.05$). Enalaprilat grubunun postoperatif kalp debisi ölçümleri preoperatif döneme kıyasla anlamlı olarak yüksek bulundu ($p<0.05$).

Sonuç: Bulgularımız, KPB sırasında kullanılan enalaprilat infüzyonunun erken postoperatif dönemdeki böbrek fonksiyonlarını ve kalp debisi ölçümlerini iyileştirdiğini göstermektedir. *(Anadolu Kardiyol Derg 2004; 4: 296-300)*

Anahtar kelimeler: Kardiyopulmoner baypas, enalaprilat, böbrek fonksiyonları, hemodinami

Introduction

Renal dysfunction and/or acute renal failure can occur after open-heart surgery with an incidence of 3-29 % regardless of age or cardiac condition (1). Inadequate perfusion is thought to be the leading cause of renal dysfunction, and this can occur before, during, or after cardiopulmonary bypass (CPB). Hemolysis, perioperative administration of nephrotoxic drugs, and low cardiac output syndrome may be the other causes (1).

The increased sympathetic activity during CPB results in re-

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nal hypotension by which the renin-angiotensin system is activated. Activation of the renin-angiotensin system may be both beneficial in sustaining blood pressure, and harmful in compromising renal hemodynamics (2). In recent years, angiotensin-converting enzyme inhibitors (ACE-I) have become widely used in the treatment of hypertension, congestive heart failure and for prevention of diabetic and nondiabetic nephropathy (3). There are few studies investigating the effects of ACE-I during CPB. Colson et al. (2) showed that short-term pretreatment with captopril does not influence blood pressure and renal function in patients undergoing CPB. Boldt et al. (4) demonstrated acute iv administration of enalaprilat has some beneficial effects on endocrine regulators of the circulation. There is also a study investigating the effects of ACE-I on hemodynamic and renal function in patients with preoperative cardiac dysfunction (5). Our study was undertaken to evaluate the effects of Enalaprilat infusion on hemodynamics and renal function during CPB in patients with normal preoperative cardiac and renal functions.

Material and Methods

After obtaining institutional approval, which covers ethical and scientific issues, and an informed consent, we studied 30 patients prospectively who were scheduled for elective coronary artery bypass graft surgery with median sternotomy. Preoperative exclusion criteria were patients older than 70 years, a past medical history of renal vascular stenosis, diabetes mellitus, cardiac failure, blood creatinine levels greater than 2 mg/dL^{-1} and ejection fractions less than 35%. Individuals who experienced excessive bleeding, low cardiac output, or respiratory problems postoperatively were also excluded from the study.

After premedication with 0.1 mg/kg^{-1} intramuscular morphine sulfate and 10 mg oral diazepam, anesthesia was induced with 0.05 mg/kg^{-1} midazolam, 2 mg/kg^{-1} fentanyl, 0.3 mg/kg^{-1} etomidate, and 0.1 mg/kg^{-1} vecuronium. Anesthesia was maintained with 0.5% isoflurane and 50% N_2O in O_2. Doses of fentanyl 2 $\mu g/kg^{-1}$ and vecuronium 0.05 mg/kg^{-1} were administered as required. All patients were subjected to the same anesthetic and surgical protocols, and received the same dopamine infusion (2 $\mu g/kg^{-1}min^{-1}$) during the study. Patients were randomly allocated into 2 groups. Group 1 (15 patients) received an enalaprilat (Vasotec®) infusion (0.06 $mg/kg^{-1}hr^{-1}$) in addition to dopamine infusion during CPB. The enalaprilat infusion was started with initiation of CPB and ended with the termination of CPB. Group 2 was a control group (n=15). Mean arterial pressure (MAP) was maintained between 55-65 mmHg and changes in mean arterial pressure were controlled with nitroglycerine, phenylephrine, and pump flow adjustments.

Cardiopulmonary bypass was performed using a membrane oxygenator with prime volumes of 35 ml/kg^{-1}. Pump flow and hematocrit were maintained at 2.5 to 3.0 L $min^{-1}/m2^{-1}$ and 30% respectively. The standard CPB procedure under moderate hypothermia (32°C) was performed in all patients. Perioperative fluid therapy and blood transfusions were administered according to changes in central venous pressures (CVP). After surgery, each patient was returned to the cardiothoracic intensive care unit (ICU) while still intubated and on ventilatory support. All patients received 20 % mannitol (0.2 g/kg^{-1}) before the termination of CPB.

In each patient, MAP, and CVP were recorded during CPB at 15-minute intervals and at 24 hours postoperatively, and systemic vascular resistance (SVR) was calculated (MAP-CVP/pump flow) during CPB at 15-minute intervals. Serum creatinine, blood urea nitrogen, creatinine clearance (CLcr) (24 hours), and urinary protein loss were measured preoperatively and on postoperative day 6. Cardiac output (CO) was calculated by echocardiography preoperatively and on postoperative day 6 by a cardiologist who was blinded to the study protocol and to the medications given to individual study patients. Echocardiographic assessment: all subjects were placed in the left lateral decubitus position and underwent a complete same investigation. An Acuson 128 XP ultrasound system (Acuson Corp., Mountain echocardiographic examination by the View, CA, USA) and a 3.5-MHz transducer were used. Classical echocardiographic windows with electrocardiogram monitoring were used. Complete two dimensional (2D), M-mode and Doppler echocardiographic examinations were performed according to the methods previously described (6,7). End-diastolic and end-systolic volumes of left ventricle were measured from two orthogonal apical windows (apical 4-chamber and apical 2-chamber views). Measures of LV systolic function were determined by Simpson's modified biplane formula. Left ventricular stroke volume and cardiac output were calculated by the formulas represented below. Three consecutive beats were measured and averaged for each measurement (6,7).

Stroke volume (ml) = Left ventricular end-diastolic volume-Left ventricular end-systolic volume

Cardiac output (l/min) = Stroke volume x Heart rate

The use of vasodilators, inotropic drugs, and diuretics after the termination of bypass and during the first 24 hours in ICU was recorded for each patient. The indication for use of inotropic agents was to maintain the systolic blood pressure above 85 mmHg in the presence of an adequate cardiac output.

All results are presented as the mean ± SD. Statistical analyses of differences between and within groups were performed using the Mann-Whitney U test and the Wilcoxon test, respectively. Differences in inotropic, diuretic and vasodilator agents requirements were analyzed by Chi-square testing and MAP, CVP, SVR and heart rate findings were investigated by the analysis of variance. P values < 0.05 were considered significant.

Results

The demographic data, duration of CPB, and cross-clamp times are shown in the Table 1. The groups were similar with re-

Table 1. Demographic data, duration of cardiopulmonary bypass and cross-clamp times

	Enalaprilat (n=15)	Control (n=15)
Gender (M/F)	13/2	11/4
Age (years)	58.1±6.9	59.7±5.8
Weight (kg)	70.9±18.2	68.7±18.2
Duration of CPB (min)	79.4±22.8	59.1±22.1*
Duration of cross-clamp (min)	41.9±18.2	29.9±15.9*
Number of grafts	3.7±0.9	2.6±1.1*

CPB: cardiopulmonary bypass, F: female, M: male
* p< 0.05 significantly different as compared to the Enalaprilat group

gard to age and weight. Same surgical team operated all patients. Duration of CPB and cross-clamp times were significantly longer in the Enalaprilat group. The postoperative period was uneventful in all cases, and none of the patients experienced cardiac, respiratory, or renal failure, and excessive bleeding.

In the control group, postoperative serum creatinine and blood urea nitrogen were significantly higher and Clcr measurements were significantly lower than the preoperative values ($p<0.05$). In the Enalaprilat group these values remained steady from the pre- to postoperative stage (Table 2). Postoperative cardiac output was higher than the preoperative output level in the Enalaprilat group ($p<0.05$) (Table 2). Comparison of urinary protein loss between and within the groups revealed no significant differences ($p>0.05$) (Table 2). Both groups' MAP values were similar throughout the study. Although the findings were not clinically important, SVR was significantly lower and CVP was significantly higher in the Enalaprilat group than in the control group ($p<0.05$) (Table 3).

showed that, compared to controls, the Enalaprilat-infused patients had better renal function and higher CO in the early postoperative period.

The renin-angiotensin system plays an important role in cardiovascular homeostasis. As mentioned above, activation of this system during open-heart surgery can be both beneficial and deleterious, in that it helps maintaining blood pressure but may compromise renal hemodynamics (2). During CPB, increased sympathetic activity leads to renal hypoperfusion, while ACE inhibition limits renal vasoconstriction and improves renal perfusion. In a cohort study consisting of 6.400 low- or high-risk cardiac patients, Rady and Ryan (8) found that preoperative therapy with ACE-I did not appear to influence the clinical outcome. However, they defined renal dysfunction as a postoperative serum creatinine of 3.8 mg/dL, a doubling of serum creatinine value if the preoperative value was >1.9 mg/dL, or requirement of renal replacement therapy. These criteria are different from those

Table 2. Preoperative and postoperative changes in biochemical and echocardiographic parameters

	Enalaprilat (n=15)		Control (n=15)	
	Preoperative	Postoperative	Preoperative	Postoperative
Creatinine (mg/dL-1)	0.83±0.11	0.89±0.15	0.87±0.11	1.10±0.19*
BUN (mg/dL-1)	18.5±2.7	19.6±4.4	17.8±3.1	22.7±6.2*
Clcr (mg/dL-1/min-1)	93.2±15.1	91.6±14.7	99.7±15.5	90.1±22.8*
Proteinuria (mg/dL-1)	118.6±82.8	116.0±81.6	120.8±83.9	106.0±123.0
CO (L/min-1)	3.79±0.67	4.66±1.20	4.19±1.35	4.77±1.23

BUN: Blood urea nitrogen, CLcr: Creatinine clearance, CO: Cardiac output,
* p<0.05 different from Enalaprilat group
+ p< 0.05 different from preoperative measurements

Table 3. Perioperative changes in hemodynamic parameters

	MAP (mmHg)		**CVP** (mmHg)		**SVR** (dyne/sn-1/cm5)	
	Enalaprilat (n=15)	**Cntrol (n=15)**	**Enalaprilat (n=15)**	**Control (n=15)**	**Enalaprilat (n=15)**	**Control (n=15)**
Before CPB	100.0 ± 18.2	99 ± 17.8	7.6 ± 2.3	6.8 ± 3.9		
CPB (5 min)	61.1 ± 11.1	66.3 ± 10.8	10.2 ± 4.3	7.8 ± 3.9*	887 ± 29.0	1084 ± 37*
CPB (15 min)	56.6 ± 8.9	57.3 ± 10.0	8.06 ± 3.8	6.6 ± 4.1*	822 ± 22.8	974 ± 24*
CPB (30 min)	57.9 ± 8.1	58.4 ± 5.4	9.4 ± 3.9	7.8 ± 3.8*	814 ± 21.3	969 ± 30
After CPB	62.9 ± 10.5	61.3 ± 11.6	9.4 ± 3.8	8.3 ± 4.1*		

CPB: Cardiopulmonary bypass, CVP: Central venous pressure, MAP: Mean arterial pressure, SVR: Systemic vascular resistance
* p<0.05 different from Enalaprilat group

The requirements for vasodilators, inotropes, and diuretics after the termination of CPB and during the first 24 hours in the intensive care unit (ICU) are summarized in the Table 4. The use of inotropic agents was significantly higher in control group than in the Enalaprilat group ($p<0.05$) after the termination of CPB.

Discussion

The present study examined the effects of Enalaprilat infusion during CPB on hemodynamics and renal function. The results

Table 4. Number of patients requiring vasodilators, inotropics, and diuretics after the termination of cardiopulmonary bypass and during the first 24 hours in the intensive care unit

	Enalaprilat (n=15)		Control (n=15)	
	After CPB	24 hr Postop	After CPB	24 hr Postop
Vasodilators	1	9	4	8
Inotropics	0	4	4*	2
Diuretics	3	5	4	1

CPB: Cardiopulmonary bypass, ICU: Intensive care unit, postop: postoperatively
* p<0.05 different to Enalaprilat group

described in literature. Lower creatinine values are considered as sign of renal dysfunction by most authors (9,10). Different definitions used for renal dysfunction may be the reason for different results. It has been demonstrated that Enalaprilat can reduce the rate of decline in kidney function in patients with nephropathy (11,12). Our findings in patients undergoing CPB were in accordance with these results. Although postoperative blood urea nitrogen and creatinine levels increased, and Clcr decreased significantly in the control group, the findings for these parameters remained steady in the Enalaprilat group. This renalprotective effect may be due to the positive effect of enalaprilat on tissue perfusion and renal blood flow.

Enalaprilat has been shown to have an antiproteinuric effect that is independent of its effect on systemic blood pressure (3,11). However, we observed no difference between groups regarding urinary protein loss. The antiproteinuric effect of ACE inhibitors is known to be reversible (13). We administered enalaprilat for a relatively short period only during CPB, and its antiproteinuric effect may have been lost in the early postoperative period.

Boldt et al. (4,14) showed a decrease in both SVR and filling pressures with intravenous enalaprilat administration in their two different studies. However our results were discordant with their findings. We observed lower SVR but higher CVP values in the enalaprilat group during infusion. Ryckwaert and co-workers (5) also found lower SVR and higher CVP values in the Enalaprilat group when 1 mg of enalaprilat was used at intervals of 6 h for 2 days. It is not easy to explain this increase in CVP. It can be speculated that the higher CVP values in the Enalaprilat group is due to the higher intravascular volume, which might have been used during CPB to compensate the decrease in SVR in these patients.

Studies have indicated that preoperative use of ACE-I is associated with hypotension and increased vasoconstriction requirements at separation from CPB (15,16). However, many investigators (8,17,18) have reported that preoperative therapy with ACE-I is not associated with low systemic vascular resistance syndrome, and does not affect clinical outcome after cardiovascular surgery. Despite longer cross-clamp and CPB durations in the enalaprilat group in our study, the need for inotropic support at the termination of CPB was significantly lower than the need in the control group. Boldt et al. (19) demonstrated that administration of Enalaprilat before the initiation of CPB protects the heart against ischemia/reperfusion injury. Even though the duration of cross-clamping and CPB were coincidentally longer in the Enalaprilat group in our study (number of grafts were 3.7 and 2.6 in the Enalaprilat and control groups, respectively), the need for inotropic support was lower. This indicates that enalaprilat may help prevent or minimize ischemia/reperfusion injury in the myocardium.

Research has also revealed that ACE inhibitors have cardioprotective effects when they are given prior to ischemia (19). It has been demonstrated that administration of intravenous enalaprilat before myocardial ischemia preserved myocardial tissue (19,20). Sirivell et al. (21) have demonstrated that early-postoperative administration of ACE-I agents to patients with severe postcardiotomy dysfunction improves in tissue perfusion and reduces mortality, morbidity, and length of hospital stay. Boldt et al (4) demonstrated vascular dilatation and improved microcirculation with enalaprilat, and concluded that the drug may be of benefit for patients with heart failure. Our findings of lower requirements for inotropic support and statistically higher cardiac output in the Enalaprilat group in the postoperative period also indicate that this drug has cardioprotective effects.

Conclusion

In summary, one of the major aims in cardiac surgery is the prevention of damage to organs such as the heart and kidneys. Our results show that enalaprilat infusion administered during CPB results in better cardiac output and better renal function in the early postoperative period. In view of our promising findings with enalaprilat patients with normal preoperative renal function, we would recommend further randomized controlled trials with enalaprilat, in patients with compromised renal and cardiac functions during CPB.

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