

A Preliminary Study of the Effect of Continuing Angiotensin-Converting Enzyme Inhibitors on Plasma Concentration of Bradykinin During Cardiopulmonary Bypass*

Teo Li-Ming *MBBS, MMed*, Hwang Nian Chih *MBBS, FFARCSI*, Lai Oi Fah *BSc, MSc*,¹ Sie Ming Yao *MB BCh, FRCA*,² Kong Chee Seng *MBBS, FRCA*, Leong Choy Kuen *MBBS, MMed*

Department of Anaesthesia and Surgical Intensive Care, SGH

¹Department of Clinical Research, SGH

²Department of Anaesthesiology, University Malaya Medical Centre, Malaysia

ABSTRACT

Background. Patients on angiotensin-converting enzyme inhibitors (ACEi) undergoing cardiopulmonary bypass (CPB) have been reported to have increased vasoconstrictor use in the period after separation from CPB. Angiotensin-converting enzyme prevents generation of angiotensin II and blocks the breakdown of bradykinin, a potent vasodilator. We examined if the vasodilatory effect, observed after separation from CPB, in patients who had ACEi continued until the morning of cardiac surgery, can be attributed to the effect of circulating bradykinin. We compared the plasma concentrations of bradykinin during and after CPB in patients who had ACEi continued or omitted on the day of cardiac surgery.

Methods. Forty patients were randomised to either continue ACEi or to omit ACEi on the day of coronary artery bypass surgery (CABG) which would have required the use of CPB. Another 10 patients undergoing similar operations were recruited as controls. Blood samples were taken before induction of anaesthesia, after sternotomy, 30 mins and 60 mins after commencing CPB, and 30 mins after separation from CPB. From the plasma, bradykinin was extracted and the concentration measured using competitive enzyme immunoassay. At the 2 time points during CPB when blood samples were obtained, the cardiac output of the extra-corporal circuit was recorded and systemic vascular resistance (SVR) calculated. Vasoconstrictor use during CPB was noted.

Results. There was no difference in the plasma concentrations of bradykinin among the 3 groups at the first 3 time points. The differences in plasma bradykinin concentrations at the fourth and fifth time points did not achieve statistical significance. No significant difference was also detected in the SVR among the 3 groups ($p > 0.05$) during the 2 time points within CPB. The slight difference in the dosages of vasoconstrictor usage during CPB did not reach statistical significance.

Conclusion. In patients treated with ACEi and undergoing CPB, the vasodilatory effect observed in the post-CPB period after ACEi therapy is probably not attributed to increases in plasma bradykinin concentration, as continuing or omitting ACEi on the day of cardiac surgery does not appear to have the expected impact on the plasma bradykinin concentrations in these patients. It is possible that the inability to generate angiotensin II may have a more important role in the observed increased vasoconstrictor use post-CPB.

Keywords: angiotensin-converting enzyme inhibitors, bradykinin, cardiopulmonary bypass

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INTRODUCTION

Angiotensin converting enzyme inhibitors (ACEi) are widely prescribed for patients who have heart failure, hypertension and in those who had myocardial infarction because ACEi therapy has been shown to

reduce mortality and adverse cardiovascular events and also to improve the quality of life.¹

Patients presenting for coronary artery bypass surgery continue to take ACEi up to the time of surgery. However, there have been reports of adverse effects particularly hypotension during the peri-operative period.^{2,3} Deakin and colleagues have shown that pre-operative therapy decreases systemic vascular resistance during the rewarming phase of cardiopulmonary bypass (CPB) and increases post-bypass vasoactive drug requirements.⁴ For these reasons, some practising clinicians would omit the ACEi before surgery.^{3,5}

Angiotensin converting enzyme, also known as kininase II, degrades bradykinin. Cugno *et al* have shown that the plasma bradykinin concentrations are raised during CPB.⁶ As bradykinin is a potent vasodilator, this may contribute to the hypotension during bypass, and for a period after separation from bypass. There are no studies on the effect of ACEi on circulating plasma bradykinin concentration. The aim of this study is to examine if the vasodilatory effect, observed after separation from CPB, in patients who had ACEi continued until the morning of coronary artery bypass surgery (CABG), can be attributed to the effect of circulating bradykinin. We compared the plasma concentrations of bradykinin during and after CPB in patients who had ACEi continued or omitted on the day of cardiac surgery.

METHODS

Local hospital Ethics Committee approval was obtained for this study and written consent was obtained from patients. We recruited 40 patients, who had been taking ACEi to control hypertension or symptoms of heart failure for at least a week, scheduled for elective CABG requiring the use of CPB. The patients were randomised either to continue or to omit ACEi on the day of surgery. Another 10 patients who had never been on ACEi who were also undergoing CABG requiring the use of CPB were recruited as controls. All regular medications were continued on the day of surgery.

The anaesthesiologist conducting the anaesthetic and the perfusionist were blinded to which group the patient belonged. Besides standard monitoring, intra-arterial blood pressures and central venous pressures were monitored. As to the method of conduct of anaesthesia, the patients received propofol 5-6mg/kg/hr while on CPB. The vasoconstrictor used was metaraminol while glyceryl trinitrate (GTN) was

the vasodilator. If required, adrenaline was used for inotropic support. Otherwise, the anaesthesiologist was free to conduct the anaesthetic as he or she normally would. The extracorporeal circuit (ECC) consisted of a closed system hollow fibre membrane oxygenator with integral heat exchanger CX* SX25 (Terumo Corporation, Japan), a separate cardiotomy reservoir BCR3538 (Baxter, USA), a Stockert III arterial roller pump (Munich, Germany), an arterial blood filter D732 (Dideco, Italy) and a custom pack non-heparinised polyvinylchloride tubing set (CSS, Singapore).

Blood samples for plasma bradykinin concentrations were drawn from the central venous catheter at 5 different time points: before induction of anaesthesia, after sternotomy, 30 minutes and 60 minutes after commencement of CPB, and 30 minutes after separation from CPB. At each time point, after drawing 3mls of blood ("dead space") from the central venous catheter, 6mls of blood was drawn using a ice-chilled 10ml syringe. Into 2 propylene tubes containing 3 mg ethylene diamine tetraacetic acid (EDTA) (to constitute 1 mg/ml of blood after the addition of blood) and 0.2ml aprotinin (500KIU/ml of blood), 3mls of the patient's whole blood was placed into each and immediately stored at 0°C. Samples were then centrifuged at 1600xg for 15 minutes at 0°C and the plasma transferred to a fresh propylene tube. These were then stored at -70°C (temperature for maximum stability) and the samples thawed when sufficient numbers had been collected to perform the assays.

From the plasma samples, bradykinin was first extracted using solid phase extraction. Thereafter, the samples were measured for bradykinin concentration using the competitive enzyme immunoassay technique. This was performed using a commercially available kit (Bradykinin High Sensitive EIA kit, Cat no.: S-1135, Peninsula Laboratories, USA). The average bradykinin concentration at each time point was then noted. The bradykinin concentration values obtained at 30 minutes and 60 minutes into CPB were further multiplied by the haemodilution factor after initiation of CPB to obtain the final plasma bradykinin concentration.

Haemodynamic parameters were noted during the time of blood sampling. The total dose of vasoconstrictor (metaraminol) or other inotropic agents used were also recorded. Systemic vascular resistance (SVR) during the 2 time points of CPB was calculated in absolute units using the following equation: (mean arterial pressure minus pressure in right atrium)/blood flow $\times 80$. Blood flow in litres/minute was obtained from the steady state cardiac output of the ECC at those points in time.

Table 1. Patient characteristics and type of ACE inhibitor therapy in the groups.

Patient's characteristics	Control (n=10)	ACEi omitted (n=20)	ACEi given (n=20)
Age (years)*	61 (8)	62 (9)	64 (8)
Gender: Males	7	18	17
Females	3	2	3
Weight (kg)*	66.4 (12.5)	62.2 (11.2)	65.0 (9.4)
Height (m)*	1.59 (0.10)	1.50 (0.50)	1.52 (0.39)
BSA (m ₂)	1.70 (0.21)	1.69 (0.18)	1.69 (0.16)
Ejection fraction (%)*	49 (13)	41 (18)	49 (11)
Starting haematocrit (%)*	40 (6)	39 (5)	38(6)
Type of ACEi used:			
Nil	10		
Captopril		8	9
Enalapril		6	5
Lisinopril		3	3
Others		3	3

*: Mean (SD)

The differences were not statistically significant.

Table 2. Total dose of metaraminol administered (mg) (median (range)) during anaesthesia.

Event	Control group	ACEi omitted group	ACEi given group
Pre-bypass	0.48 (0–1.00)	0.68 (0–3.00)	1.16 (0–3.5)
On bypass	2.31 (1.00–6.30)	3.01 (0–7.00)	3.74 (0.25–7.00)
Post-bypass	0.46 (0–1.00)	0.45 (0–3.00)	0.79 (0–6.00)

The differences were not statistically significant.

Our data was analysed using SPSS version 11.0. Normally distributed continuous data are expressed in mean (SD). Analysis of variance (ANOVA) was used to determine the significance between the groups. Non-normally distributed continuous data like doses of vasoactive drugs are expressed in median (range) and analysed with the Mann-Whitney U test and Kruskal-Wallis H for non-parametric data. $P < 0.05$ was considered the level of significance.

RESULTS

Table 1 shows the patients' characteristics and the type of ACEi therapy that they were taking. Other than the gender, the 3 groups of patients showed similar demographics ($p > 0.05$).

There was no statistical difference in the plasma bradykinin concentrations among the 3 groups at all time points ($p > 0.05$). Figure 1 shows the trend of the plasma bradykinin concentrations throughout the operation.

Mean arterial blood pressure (MAP) for all three groups is shown in figure 2. There was no significant difference in the MAP throughout the operation between the 2 groups of patients who had been on chronic ACEi therapy. At 30 minutes into CPB, SVR was calculated to be 1055 (248) dynes·second·cm⁻⁵ for the ACEi omitted group and 1218 (376) dynes·second·cm⁻⁵ for the ACEi given group. For the control group, this was 1095 (212) dynes·second·cm⁻⁵. At 60 minutes into CPB, SVR was 1088 (265) dynes·second·cm⁻⁵ in the ACEi omitted group, 1190 (295) dynes·second·cm⁻⁵ in the ACEi given group and 1180 (310) dynes·second·cm⁻⁵ in the control group. At both time points, there was no difference among the 3 groups ($p > 0.05$).

Table 2 shows the dose of metaraminol administered during the operation. The differences in vasoconstrictor usage before, during, and after separation from CPB were not statistically significant. The peri-operative infusion rates of glyceryl trinitrate and adrenaline were similar among the 3 groups ($p > 0.05$).

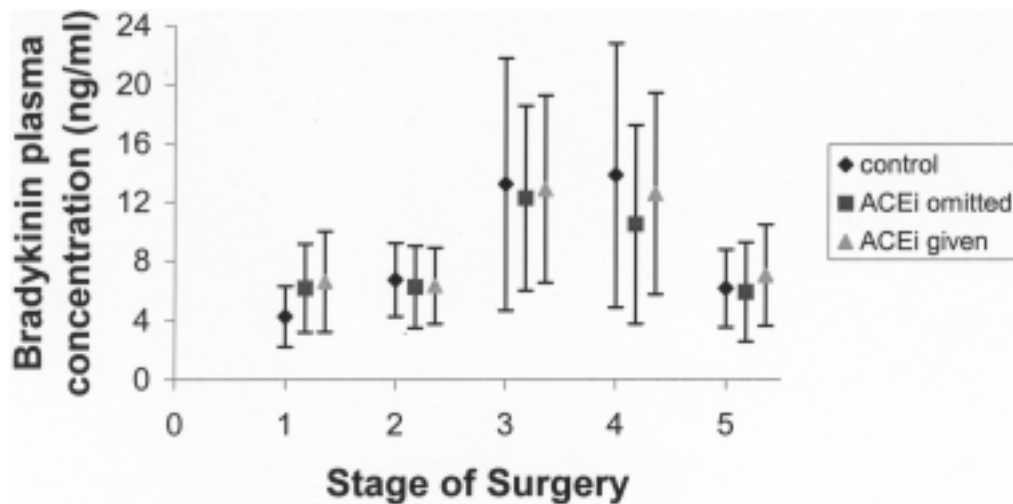


Fig 1. Plasma bradykinin concentrations during surgery. Along the x-axis, 1=pre-induction, 2=post sternotomy, 3=30 minutes into CPB, 4=60 minutes into CPB and 5=30 minutes after separation from CPB.

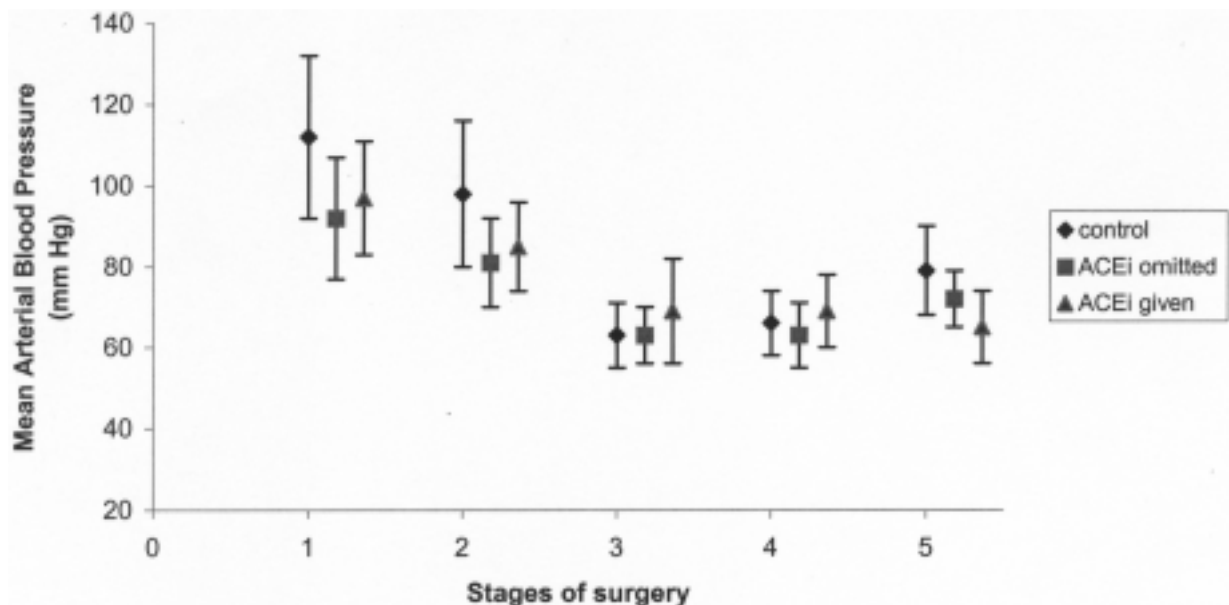


Fig 2. Mean arterial blood pressures throughout surgery. Along the x-axis, 1=pre-induction, 2=post sternotomy, 3=30 minutes into CPB, 4=60 minutes into CPB and 5=30 minutes after separation from CPB.

DISCUSSION

In our protocol, we used syringes chilled in ice to draw blood from the patients. The tubes containing the blood were then plunged into ice. This was done to inactivate any enzymes in the circulation that might break down bradykinin although the primary site of bradykinin degradation was in the lungs. Ethylene diamine tetraacetic acid in the tubes served as an anticoagulant while aprotinin functioned as a protease inhibitor, preventing the conversion of high molecular weight kininogen in the blood to bradykinin. This prevented any further elevation of plasma bradykinin concentration.

Blood samples taken before induction of anaesthesia served as a baseline. We were curious whether a particularly painful stimulus would trigger bradykinin formation. Hence, the blood sample was taken post-sternotomy.

At initiation of CPB, the perfusionists manipulated the cardiac output of the ECC and used varying amounts of vasoconstrictors, like metaraminol, to achieve a MAP of between 60 mm Hg to 80 mm Hg. Subsequent administration of cardioplegia caused a fall in MAP which was treated with either increasing the speed of the roller pump and hence cardiac output; or

administering more metaraminol. By 30 minutes after the initiation of CPB, a steady state would have been reached and deemed appropriate for measuring plasma bradykinin concentration. Weaning the patient off CPB is again potentially eventful. We felt that at half an hour after separation from CPB, a steady state would most likely have been achieved. That was when we took the last blood sample.

Bradykinin is composed of 9 amino acids and is formed from the action of kallikrein on high molecular weight kininogen. Its formation is triggered by any cause that results in inflammation. A series of enzymatic reactions culminates in bradykinin formation. Bradykinin binds to receptors on nearby endothelial cells which liberate vasoactive prostaglandins or nitric oxide, resulting in vasodilatation. Bradykinin is efficiently degraded in the pulmonary vascular bed by ACE. In patients treated with ACEi, it would be expected that the plasma bradykinin concentration might be raised.

In their study, Cugno *et al* excluded patients who had been treated with ACEi. They showed that from the beginning of CPB, plasma bradykinin concentration rises and is increased fourfold at the end of CPB and returns to normal by 24 hours. They attributed this partly to reduced degradation as CPB completely bypasses the pulmonary circulation. They did not show any correlation between the increase in plasma bradykinin concentration with the activation of the contact coagulation system. As far as we know, there have been no other studies that have measured plasma bradykinin concentration in patients treated with ACEi undergoing cardiac surgery requiring cardiopulmonary bypass. As such, our study group of patients could be considered a pilot study.

Compared to Cugno's study, all groups of patients in our study did not show the same fourfold increase in plasma bradykinin concentrations while on CPB. An increase in bradykinin concentration, albeit small, was seen in the 3 groups of patients 30 minutes into CPB. In the control and the ACEi given group, this slightly increased further at 60 minutes into CPB and decreased at 30 minutes after separation from CPB. However, in the ACEi omitted group, plasma bradykinin concentration was lower at 60 minutes into CPB. It further decreased at 30 minutes after separation from CPB. The differences observed at these time points between all 3 groups were not statistically significant. A small sample size may be a reason. A larger series of patients needs to be studied in order to determine if there is indeed no difference.

In spite of the small sample size, it is possible that ACEi therapy alters normal bradykinin physiology such that the same rise in bradykinin concentration is not seen. This effect may continue even after the morning dose of ACEi is stopped. In our study, no significant difference is demonstrated in the plasma bradykinin concentrations in both study groups. It is likely that the practice of omitting the morning dose of ACEi just prior to cardiac surgery is not sufficient to completely eliminate the plasma ACEi concentrations from the system. This is especially so with the increase in usage of long-acting ACEi such as the lisinopril and the pro-drug, enalapril. As such, the practice of omitting the morning dose of ACEi especially long acting ACEi may not have the desired effect on plasma bradykinin concentration.

Cugno *et al* utilised a different assay in the measurement of bradykinin concentrations. Plasma bradykinin concentrations were measured specifically by radio-immunoassay after liquid-phase extraction and subsequent high-performance liquid chromatography.⁷ In our study, we utilised a competitive enzyme immunoassay after solid-phase extraction. There might be differences in the sensitivity and specificity between the 2 methods. Hence, a direct comparison between the 2 studies might not be possible.

Tuman showed that the peri-operative use of ACEi increased the need for 2 or more vasopressors as the patients separated from CPB.⁸ It is perhaps due to the small sample size that the slight differences in the dosages of metaraminol, nitroglycerin and adrenaline administered in our study did not achieve statistical significance, whether or not ACEi had been continued. As the haemodynamic status of the patient after separation from CPB might have been unstable, in order not to complicate the anaesthetic, the anaesthetic administered during that period was left to the judgement of the anaesthetist. This might have played in a role in the results.

CONCLUSION

In patients treated with ACEi, omitting ACEi on the morning of cardiac surgery involving CPB failed to show the expected impact on plasma bradykinin concentrations. The vasodilatory effect observed in the post-CPB period after ACEi therapy is probably not attributed to increases in plasma bradykinin concentration. The inability to generate angiotensin II may have a more important role in the observed increased vasoconstrictor use post-CPB.

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