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Role of renin-angiotensin system in cardiopulmonary bypass hypertension

The role of the renin-angiotensin system in the aetiology of perioperative hypertension was studied in 15 previously normotensive patients undergoing coronary artery surgery and anaesthetized with fentanyl. Measurements of plasma renin activity were made at intervals before and during cardiopulmonary bypass (CPB). In addition, angiotensin II blockade with saralasin was used in an attempt to treat hypertension during CPB.

Nine of the patients became hypertensive (increase in systemic pressure of more than 20 per cent) before CPB and although the mean plasma renin activity was higher in this group than in the normotensive patients it was within normal limits for each group. Hypertension during CPB (mean blood pressure greater than 100 mmHg at $1.8 \text{ l} \cdot \text{m}^{-2}$ flow), occurred in seven patients but was not associated with increased renin activity and did not respond to saralasin in doses up to $20 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. It is concluded that cardiopulmonary bypass associated hypertension is not mediated by activation of the renin-angiotensin system.

Key words

ANAESTHESIA: cardiac; HYPERTENSION: cardiopulmonary bypass, renin-angiotensin, saralasin.

The aetiology of the hypertension which develops during cardiopulmonary bypass (CPB) is uncertain. It has been attributed to the release of catecholamines but changes in blood pressure (BP) do not correlate with circulating concentrations of epinephrine and norepinephrine.¹ The role of other pressor hormones such as vasopressin² and angiotensin II^{3,4} has also been suggested but not proved.

The present study was designed to determine whether activation of the renin-angiotensin system correlated with BP increases before and during CPB. Blood was collected intermittently throughout surgery for estimation of plasma renin activity (PRA) which was correlated with elevation of systolic blood pressure. In addition, attempts were made to reduce hypertension during CPB with infusion of the angiotensin II antagonist, saralasin.

Methods

The protocol was approved by the Hospital Ethics Committee. After informed consent, 15 patients undergoing CPB for coronary artery disease were studied. Before operation, they were normotensive, BP of 160/100 or less and free of renal dysfunction as determined by normal serum creatinine and blood urea concentrations. Preoperative angiography demonstrated severe (>50 per cent) obstruction of the left main coronary artery in all patients and most had multiple vessel disease. Medications (Table I), were continued up to the night before surgery except for propranolol which was also given on the morning of operation. Premedication consisted of flurazepam, 30 mg, as night sedation and diazepam $0.15 \text{ mg} \cdot \text{kg}^{-1}$ orally, morphine $0.15 \text{ mg} \cdot \text{kg}^{-1}$ IM and scopolamine, 0.4 mg IM, 60 to 90 minutes before surgery.

On arrival in the operating room, an electrocardiogram was attached to the patient and a modified V5 lead was monitored throughout surgery. Cath-

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TABLE 1 Demographic data (Mean $\pm$ SEM)

	Pre bypass		During bypass	
	Hypertensive	Normotensive	Hypertensive	Normotensive
n	9	6	7	8
Age (yr)	55.1 $\pm$ 3.6	55.5 $\pm$ 4.6	52.7 $\pm$ 3.9	57.5 $\pm$ 3.8
Ht (cm)	175 $\pm$ 1.7	163.4 $\pm$ 4.0	171 $\pm$ 1.9	169.2 $\pm$ 4.3
Wt (kg)	77.3 $\pm$ 4.0	64.5 $\pm$ 4.4	74.1 $\pm$ 2.9	70.5 $\pm$ 5.9
BSA (m ²)	1.92 $\pm$ 0.04	1.7 $\pm$ 0.07	1.86 $\pm$ 0.03	1.79 $\pm$ 0.08
Sex	9 M	4 M, 2 F	7 M	6 M, 2 F
Grafts (n)	2.8 $\pm$ 0.3	2.7 $\pm$ 0.6	3.4 $\pm$ 0.3	2.9 $\pm$ 0.7
Medication:				
Nitrates	8/9	6/6	6/7	8/8
β block	8/9	6/6	7/7	8/8
Diuretics	1/9	1/6	1/7	1/8

ters for haemodynamic measurements were inserted under local anaesthesia. An arterial line was positioned in a radial artery and a Swan Ganz thermidilution catheter in the pulmonary artery. These enabled measurements to be made of left and right heart filling pressures, systemic and pulmonary arterial pressures, and cardiac output.

All patients were anaesthetized with fentanyl which was given in a dose of 75–150 $\mu\text{g}\cdot\text{kg}^{-1}$. After induction of anaesthesia the patients received pancuronium to a total of 0.15 $\text{mg}\cdot\text{kg}^{-1}$, were intubated and ventilated with 100 per cent oxygen to maintain normocarbida.

Intravascular volume was maintained by infusion of crystalloid and blood to keep pulmonary artery diastolic pressure at 10–15 mmHg. Total crystalloid infused varied between 2650–7550 ml which included 1750 ml of bypass priming fluid. Systolic and pulmonary blood pressures and EKG were recorded continuously. During non-pulsatile CPB the flow was maintained at 2.41 $\text{m}^3\cdot\text{min}^{-2}$ at normothermia and 1.81 $\text{m}^3\cdot\text{min}^{-2}$ when the temperature was decreased to 26–28°C. Normothermia was restored at the end of CPB. The heart was protected with cardioplegic solution (Ringer's lactate, 500 ml, 10 meq KCl, 12.5 ml lidocaine two per cent, 12.5 meq NaHCO_3 , 17 ml 50 per cent dextrose at less than 5°C) during CPB.

Control haemodynamic data were recorded after insertion of cannulae before induction of anaesthesia and were repeated at the following times; after induction of anaesthesia, skin incision, sternotomy and aortic dissection. Mean blood pressure (BP)

was recorded 10 minutes after starting CPB and at 30-minute intervals. Blood was taken for estimation of PRA, before operation and also at the same times as the recording of haemodynamic data. Renin activity was estimated by a modification of the method described by Haber *et al.*⁵ using New England Nuclear reagents. Plasma was incubated for two hours to generate angiotensin I which was estimated by radioimmunoassay and the plasma renin activity was reported as $\text{ng}\cdot\text{ml}^{-1}\cdot\text{hr}^{-1}$ of angiotensin I generated.

Hypertension occurring before CPB was defined as an increase in systolic blood pressure of more than 20 per cent of the pre-anaesthetic control value. During CPB it was defined as a mean BP greater than 100 mmHg at a flow of 1.81 $\text{m}^3\cdot\text{min}^{-2}$. It was treated before CPB with addition of an inhalational anaesthetic agent, halothane or enflurane, which was discontinued at the start of CPB. During CPB initial treatment of hypertension was attempted with saralasin administered in an initial dose of 7.5 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and, if ineffective, increased incrementally to 10, 12.5, 15 and 20 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ at three-minute intervals.

The data are presented as mean values $\pm$ SEM. Student's *t* test was applied where indicated, paired (STp) for within group and unpaired (STu) for between group comparisons. Bonferroni's modification was used for multiple comparisons and the null hypothesis was rejected when $p < 0.05$. Regression lines were constructed by the least squares regression method and correlation coefficients calculated where necessary.

FIGURE 1 Mean changes in systemic vascular resistance (SVR), systolic blood pressure (BP) and plasma renin activity (PRA) at specific times before cardiopulmonary bypass. The solid line represents those patients who became hypertensive and the dotted line those who did not. (* $p < 0.05$).

Results

The demographic data are shown in Table I with the patients divided according to the presence or absence of hypertension before and during CPB. The hypertensive and normotensive groups were similar in their preoperative medication regimens and physical characteristics except that neither of the two women became hypertensive.

Before CPB, increases of systemic vascular resistance (SVR) and BP occurred in 9 patients who were then given additional volatile anaesthetic. Significant differences in BP were demonstrated between those patients who became hypertensive and those who did not only at sternotomy and aortic dissection (STu). Failure to demonstrate further statistical differences either within (STp) or between (STu) these two groups was mainly because of the treatment imposed when the BP exceeded predetermined limits. Plasma renin activity remained within the normal range ($0.5\text{--}3.8\text{ ng}\cdot\text{ml}^{-1}$

FIGURE 2 Mean haemodynamic responses and plasma renin activity during cardiopulmonary bypass in those patients who became hypertensive (solid line) or remained normotensive (dotted line). (* $p < 0.05$; ** $p < 0.01$).

hr^{-1}) and was not statistically different between the two groups (STu) at any time (Figure 1).

During CPB, BP and SVR increased in seven of the 15 patients, four of whom had developed pre-CPB hypertension (Figure 2). Mean BP exceeded 100 mmHg at a mean time of 57.3 ± 5.9 minutes. There was no difference between the groups in mean PRA which remained within the normal range. Saralasin was infused incrementally in doses from 7.5 to $20\text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ but failed to decrease BP or SVR in any of the seven subjects. In fact, at low infusion rates ($7.5\text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$), there was a temporary increase in BP in all treated subjects (Figure 3). There was no correlation between PRA and BP elevation during CPB.

Discussion

The reported incidence of perioperative hypertension varies from 33 to 75 per cent in patients undergoing coronary artery revascularization^{6,7} but

this may be affected by the choice of anaesthesia. McIlvaine *et al.*⁸ showed in a retrospective study that the use of high-dose morphine reduced the incidence of hypertension compared with halogenated volatile agents. High dose fentanyl anaesthesia, as an alternative to morphine, provides haemodynamic⁹ and hormonal^{10,11} stability during cardiac surgery. We have found previously that although high dose fentanyl does not eliminate hypertension, supplementary anaesthesia readily controls it.¹² Furthermore, the incidence of hypertension can be correlated with plasma fentanyl concentration.¹³ In the present study patients were anaesthetized with high dose fentanyl and ventilated with 100 per cent oxygen. A non-pulsatile pump was used during CPB despite earlier reports that this might encourage the development of hypertension¹⁴ and stimulate renin release.¹⁵ These findings were not confirmed by Salerno *et al.*¹⁶ but their patients received greater beta blockade.

The mechanism involved in the production of hypertension may be different before, during and after CPB and may not be the same for all patients. In particular, renin secretion is reduced by sympathetic blockade¹⁷ and thus its role will be modified by propranolol therapy. Renin release is also reduced during hypothermia¹⁸ so that, during CPB, PRA will depend upon the degree of cooling. Ninety per cent of converting enzyme is found in the lungs¹⁹ which are isolated from the circulation during CPB so that conversion of angiotensin I to angiotensin II is inhibited and the pressor effects of any renin released will not be seen. The renin secretion which may be influenced by hypovolemia and sodium balance was avoided in the present study by using crystalloid fluids to maintain filling pressures and to prime the pump. Despite these theoretical considerations, high PRA has been found during CPB⁴ and this has been blamed for postoperative hypertension.³

We observed hypertension in nine of 15 patients between induction of anaesthesia and the onset of CPB and in seven patients during CPB. Such hypertension has been associated with elevated plasma concentrations of several pressor hormones; catecholamines,¹ vasopressin² and renin-angiotensin.³ Of these three, the renin-angiotensin system is unique because angiotensin II inhibitors have been synthesized so that not only can plasma renin

FIGURE 3 Haemodynamic responses to saralasin infusion during cardiopulmonary bypass.

activity be measured but also indices of the importance of angiotensin II can be obtained to determine its role in hypertension.

The mean PRA was not increased significantly in the groups of patients who became hypertensive either before or during CPB. Indeed, the mean values during CPB tended to be lower in the hypertensive group. The infusion of saralasin in the CPB hypertensive group did not decrease either BP or SVR in any patient. Indeed, a short-lasting agonist effect was seen at the lowest dose (Figure 3). Therefore, the absence of a hypotensive response to saralasin infused in doses sufficient to antagonize angiotensin II²⁰ suggests that the renin-angiotensin system does not have an aetiological role in CPB-hypertension. It is possible that it may be responsible for the hypertension which develops either before the start of, or after the conclusion of CPB. Landymore *et al.*¹⁸ showed that, in similar patients, propranolol therapy reduced PRA but had no influence on the incidence of hypertension in the immediate postoperative period but Niarchos *et al.*²¹ demonstrated that post-CPB hypertension responded to therapy with converting enzyme in-

hibitor in eight of 13 patients. Thus it seems that the renin-angiotensin system is not the primary mediator of hypertension occurring during coronary artery surgery but that it may be responsible for postoperative hypertension in some patients.

The considerable increases in PRA, 4 to 15 ng·ml⁻¹·hr⁻¹, reported by Bailey *et al.*⁴ were not seen in the present study. It is interesting that recent investigators²² have also failed to confirm that plasma vasopressin concentrations increase to the hyperphysiological, hypertensive range previously reported by Philbin *et al.*² Thus it seems that CPB associated hypertension is not a consequence of activation of these pressor systems. Consequently, specific antagonist therapy is unlikely to be effective treatment. We conclude that the renin-angiotensin system is not the primary mediator of CPB-associated hypertension, at least during fentanyl anaesthesia.

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Résumé

Nous avons étudié la participation du système rénine-angiotensine dans l'étiologie de l'hypertension péri-opératoire chez 15 patients normotensifs soumis à une chirurgie coronaire sous anesthésie au fentanyl. Les mesures de l'activité de la rénine plasmatique ont été effectuées à intervalles avant et durant la circulation extracorporelle (CEC). En plus, on a utilisé la saralasin, un bloqueur de l'angiotensine II pour tenter de traiter l'hypertension durant la CEC.

Neuf patients ont présenté de l'hypertension (augmentation des pressions systémiques de plus de 20 pour cent) avant la CEC: l'activité de la rénine plasmatique était plus élevée dans ce groupe que chez les patients normotendus cependant elle demeurait dans les limites de la normale.

Durant la CEC, sept malades ont présenté de l'hypertension (pression moyenne plus grande que 100 mmHg à $1.8 \text{ l} \cdot \text{m}^{-2}$ de débit), mais cette hypertension n'était pas associée avec une augmentation d'activité de la rénine plasmatique et elle n'a pas répondu à la saralasin à des doses qu'on a montées jusqu'à $20 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. On a conclu que l'hypertension survenant au cours de la CEC n'est pas attribuable à l'activation du système rénine-angiotensine.