Modification by preoperative beta-blockade of the renin response to infra-renal aortic cross-clamping

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The activity of the renin-angiotensin system was measured before, during, and after infrarenal aortic cross-clamping in 13 patients. Five of the patients studied were taking propranolol preoperatively and formed a subgroup. Intraoperative blood loss, volume of crystalloid and colloid infused, haemodynamic parameters and urine output were similar for the two groups.

In eight patients who were not taking propranolol mean plasma renin activity was 2.24 $ng \cdot ml^{-1} \cdot hr^{-1}$ prior to induction, 3.78 $ng \cdot ml^{-1} \cdot hr^{-1}$ during surgery prior to cross-clamping and 4.42 $ng \cdot ml^{-1} \cdot hr^{-1}$ 15 minutes after the aorta was cross-clamped (increases not statistically significant). Mean plasma renin activity measured ten minutes prior to release of the cross-clamp (5.02 $ng \cdot ml^{-1} \cdot hr^{-1}$), 15 minutes after clamp release (5.47 $ng \cdot ml^{-1} \cdot hr^{-1}$), and 30 minutes after reaching the recovery room (5.84 $ng \cdot ml^{-1} \cdot hr^{-1}$) were significantly greater than pre-induction levels. Four patients developed postoperative hypertension (mean blood pressure greater than 120 mmHg); there was not a correlation between the elevated plasma renin activity observed postoperatively and the occurrence of postoperative hypertension.

The five patients taking propranolol had a markedly attenuated renin activity response during and after surgery; the mean plasma renin activity was less than 1.5 $ng \cdot ml^{-1} \cdot hr^{-1}$ at all sampling times. Two of these five patients did develop postoperative hypertension.

It is concluded that surgery involving infrarenal aortic cross-clamping is associated with increased plasma renin activity with peak levels occurring postoperatively. The observed increases in renin activity do not correlate the development of hypertension postoperatively. Preoperative beta-blockade attenuates the response of the renin angiotensin system, but does not prevent postoperative hypertension.

Key words
SURGERY: cardiovascular, aortic clamping, renin response; ANAESTHESIA: cardiovascular; SYMPATHETIC NERVOUS SYSTEM: sympatholytic agents, propranolol.

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Haemodynamic instability and postoperative hypertension occur commonly in patients undergoing major surgery of the abdominal aorta.[1-4] It has been suggested that increased activity of the renin-angiotensin system might be the cause of postoperative hypertension in these patients, but this possibility has not been thoroughly investigated. Conflicting results concerning the response of the renin-angiotensin system to infrarenal aortic clamping have been reported in various animal studies.[5,6] Until recently, only a single clinical study had been published concerning the changes in plasma renin activity in man occurring with abdominal aortic surgery. Gal *et al.* demonstrated that aortic cross-clamping was associated with an increase in plasma renin activity in man.[7] Similar results were reported by Grindlinger *et al.* in a recent publication.[13]

The renin-angiotensin system plays a role in the maintenance of blood pressure and fluid and electrolyte balance during anaesthesia.[8,9] Elevations of

TABLE Patient characteristics

Patient #	*Age*	*Sex*	*Pertinent history*	*Aneurysm*	*Propranolol*
1	59	F	Hypertension	No	No
2	48	F	None	No	No
3	37	F	None	No	No
4	73	M	None	No	No
5	69	M	Previous MI	No	No
6	58	M	Previous MI	Yes	No
7	66	M	None	Yes	No
8	55	M	Hypertension	Yes	No
9	63	F	None	No	60 mg/day
10	61	M	Hypertension	No	160 mg/day
11	71	M	Hypertension	Yes	40 mg/day
12	60	M	Previous MI – recent aortocoronary bypass	Yes	40 mg/day
13	54	M	Previous MI – hypertension	Yes	80 mg/day

renin activity have been reported in man during controlled hypotension with sodium nitroprusside, and may be partly responsible for the rebound hypertension seen with the discontinuation of a nitroprusside infusion.[10]

The present study was carried out to assess the response of the renin-angiotensin system in patients undergoing abdominal aortic surgery and to see if there was a relationship between postoperative hypertension and renin activity. The effects of preoperative treatment with propranolol were also studied.

Methods and patient characteristics

Thirteen patients were studied. There were nine males and four females in the series; age ranged from 37 to 73 years. Six patients underwent resection and grafting of abdominal aortic aneurysm and seven patients had aortofemoral bifurcation grafting for aortoiliac stenotic disease. Five patients were receiving propranolol preoperatively in varying dosage regimens (Table).

Four patients had had previous myocardial infarctions, but none reported angina pectoris for three months prior to surgery. No patient had signs or symptoms of congestive heart failure.

All patients were premedicated with a benzodiazepine and sodium citrate 15 ml or cimetidine 300 mg by mouth. All patients who had been taking propranolol were given their usual oral dose of this drug 90 minutes preoperatively with the premedication.

Prior to induction of anaesthesia, a #20-gauge catheter was placed percutaneously in a radial artery. Blood pressure was monitored directly with an Electronics for Medicine or Saturn 5 cardiac monitor. Anaesthesia was induced with fentanyl, 2 to 5 $\mu g \cdot kg^{-1}$, diazepam, 5 to 10 mg, and thiopental, 2 to 4 $mg \cdot kg^{-1}$. Pancuronium, 80 to 100 $\mu g \cdot kg^{-1}$ was given and ventilation controlled while N_2O 50 per cent and halothane, 0.5 to 1.0 per cent was administered. Tracheal intubation was performed after two to three minutes.

Following intubation, a #16-gauge catheter was placed in the right internal jugular vein, and was connected to a CVP manometer. Anaesthesia was maintained with nitrous oxide, oxygen, halothane, 0–1.5 per cent and increments of fentanyl. All patients received 15 to 30 mg of morphine intravenously in increments during the last hour of surgery so as to provide some analgesia during emergence from anaesthesia.

Ringer's lactate and five per cent dextrose was administered to maintain the CVP at 8–15 cm of H_2O pressure. Transfusion with red blood cells or whole blood was commenced once an estimated 10–15 per cent of blood volume had been lost and further losses were expected. All intravenous fluids and blood products were warmed to body temperature during administration.

Peripheral arterial blood samples for assay of plasma renin activity were obtained at the following times: (1) prior to induction of anaesthesia, (2) intraoperatively, prior to infrarenal aortic cross-clamping, (3) 15 minutes after aortic cross-clamping, (4) 10 minutes prior to clamp release, (5) 30 minutes after clamp release, and, (6) 30 to 45 minutes after admission to the recovery room.

Blood samples were placed in EDTA tubes and centrifuged at 3,000 rpm for ten minutes. Plasma was then removed, transferred to sealed plastic tubes and quick frozen on dry ice. All specimens were kept frozen until such time as plasma renin activity was measured using the radioimmunoassay technique of Wilkins and Powell.[11] Renin activity was recorded as nanograms (ng) of angiotensin I generated per ml per hour. Normal values for the renin activity assay used are up to one $ng \cdot ml^{-1} \cdot hr^{-1}$ after one hour in the supine position and from one to

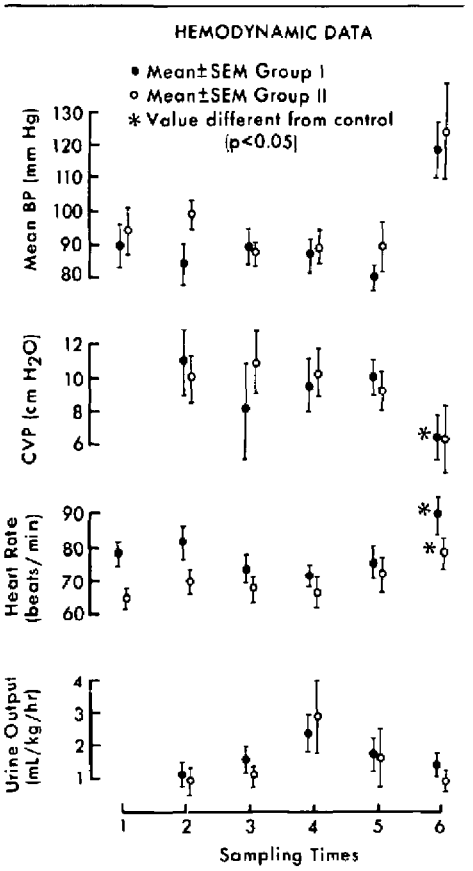

FIGURE 1 Haemodynamic data.
Group I : patients not taking propranolol (n = 8).
Group II: patients taking propranolol (n = 5).

Sampling times:
1. preinduction.
2. intraoperatively, prior to aortic clamping.
3. 15 minutes after aortic cross-clamping.
4. 10 minutes prior to clamp release.
5. 30 minutes after clamp release.
6. 30 to 45 minutes after admission to the recovery room.

four $ng \cdot ml^{-1} \cdot hr^{-1}$ after two hours in the upright position.

At each sampling time heart rate, blood pressure, central venous pressure, urine output and temperature were noted. Two patients who were not receiving propranolol became oliguric during the cross-clamp period (urine output less than 15 ml/hr) and were treated with 40 mg of furosemide and 60 mg furosemide plus 20 grams of mannitol respectively. These two patients were not included in the analysis of urine output (Figure 1).

Nitroglycerine, 50 to 100 μg by bolus or titrated by infusion was administered to four patients whose mean blood pressure increased to greater than 120 mmHg following application of the cross-clamp. Three of the four patients who received nitroglycerine had aortic aneurysms. In the two cases where nitroglycerine was administered by infusion, the infusion was discontinued within ten minutes. No other vasodilators were used.

Nine patients were extubated at the end of surgery and four received a short period of mechanical ventilation (less than six hours in all cases).

Results

Renin activity data were analyzed utilizing Tukey's minimum range statistic, a repeated measure analysis, and Pearson correlation coefficients. Haemodynamic data and urine output were analyzed with the two-tailed paired Student's t-test.

Haemodynamic and urine output data are summarized in Figure 1. At each sampling time the mean values for BP, CVP, heart rate, and urine output for those patients in Group I (not receiving propranolol) were compared to the mean values for those patients in Group II (receiving propranolol preoperatively). There were no significant differences between the two groups for the parameters measured. Within each group, the first value for each parameter was compared to later measurements. Heart rate was significantly greater in the recovery room for both Groups I and II. Central venous pressure was significantly lower in the recovery room than it was intraoperatively prior to cross-clamping for those patients in Group I.

Blood loss for Group I (1300 ± 253 ml) was not significantly different than blood loss for Group II (1590 ± 307 ml) ($p = 0.48$). The amounts of blood transfused (925 ± 248 ml) and crystalloid administered (3568 ± 178 ml) to patients in Group I were similar to the amounts transfused to patients in Group II (980 ± 215 ml and 3770 ± 347 ml respectively). Blood loss for patients with abdominal aneurysms (1792 ± 289 ml) was greater than for patients with aortoiliac occlusive disease (1085 ± 196) but not significantly so ($p = 0.074$).

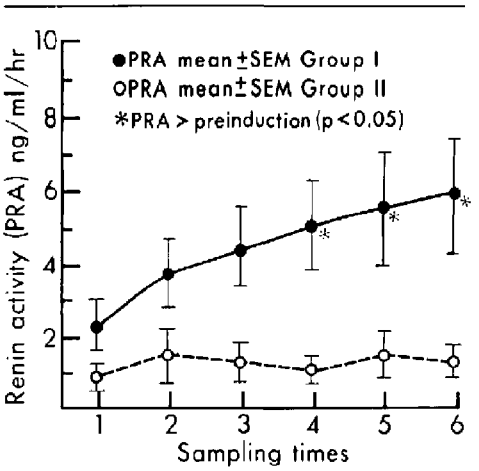

FIGURE 2 Renin activity before, during and after surgery.
Group I : patients not taking propranolol (n = 8).
Group II: patients taking propranolol (n = 5).

Sampling times:
1. preinduction.
2. intraoperatively, prior to aortic clamping.
3. 15 minutes after aortic cross-clamping.
4. 10 minutes prior to clamp release.
5. 30 minutes after clamp release.
6. 30 to 45 minutes after admission to the recovery room.

Results of plasma renin activity are shown in Figure 2. For the eight patients not receiving propranolol preoperatively, mean preinduction renin activity was 2.24 ± 0.71 $ng \cdot ml^{-1} \cdot hr^{-1}$ and increased to 3.78 ± 0.96 with anaesthesia and surgery alone. Aortic cross-clamping was associated with a further increase in mean renin activity to 4.42 ± 1.07 $ng \cdot ml^{-1} \cdot hr^{-1}$. Mean renin activity at sample times (2) and (3) (see Figure 2), although greater than the preinduction level, do not reach statistical significance. Renin activity at sample times (4), (5), and (6), however, are all greater than the preoperative level ($p < 0.05$). Thus, aortic cross-clamping was associated with a significant increase in mean renin activity for those eight patients in the study who were not receiving β-blockers.

Mean renin activity was greater during the cross-clamp period and after unclamping than during surgery prior to cross-clamping, but not significantly so.

Also shown in Figure 2 are the mean renin activity levels for those five patients who were maintained on propranolol preoperatively. There was no change in mean renin activity for this group of patients throughout the perioperative period. Renin activity was significantly greater in the non-beta-blocked patients at all sample times ($p < 0.05$).

Six patients (46 per cent) became hypertensive in the postoperative period (defined as mean blood pressure ≥120 mmHg) and required treatment. Two of these six patients were receiving propranolol operatively. Two of the six patients who became hypertensive were ventilated mechanically in the recovery room and the presence of an endotracheal tube during emergence from anaesthesia may have contributed to the development of hypertension.

Six patients, four of whom were treated with propranolol preoperatively, were treated with propranolol in the recovery room for hypertension and/or tachycardia. The final specimen for measurement of plasma renin activity was obtained prior to administering propranolol in all cases.

Although renin activity reached its maximum level in the recovery room in those patients not taking propranolol, there was not a correlation between mean arterial blood pressure and renin activity at this time (Pearson correlation coefficient = 0.11, p = 0.4).

Within the group of eight patients who were not receiving propranolol preoperatively, the patients who remained normotensive postoperatively (n = 4) were compared to those who became hypertensive (n = 4). As can be seen in Figure 3, there was no difference in renin activity between these two groups throughout the study period.

As mentioned, two of the patients who became hypertensive postoperatively were in the propranolol group. Renin activity in the recovery room for both these patients was actually below the lowest level of analysis of the assay.

There was not a significant correlation between the development of postoperative hypertension and any of the following parameters: (i) preoperative history of hypertension, (ii) intraoperative blood loss, (iii) postoperative body temperature, (iv) presence or absence of abdominal aortic aneurysm. (Pearson correlation coefficients, $p > 0.10$ for all correlations.)

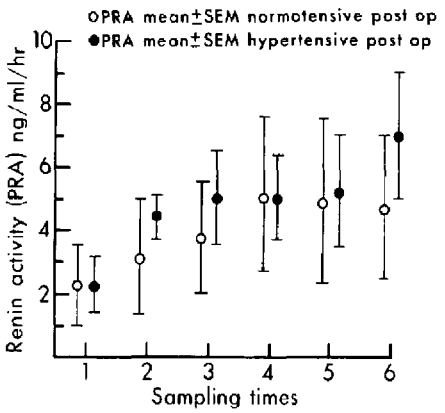

FIGURE 3 Renin activity before, during and after surgery for those patients not taking propranolol (n = 8). Patients who became hypertensive postoperatively (n = 4) are compared to those who did not (n = 4).

Sampling times:
1. preinduction.
2. intraoperatively, prior to aortic clamping.
3. 15 minutes after aortic cross-clamping.
4. 10 minutes prior to clamp release.
5. 30 minutes after clamp release.
6. 30 to 45 minutes after admission to the recovery room.

Discussion

The response of the renin-angiotensin system to anaesthesia and to anaesthesia/surgery has been well documented. Halothane or enflurane with nitrous oxide anaesthesia produced a slight increase in renin activity with no further increase after the start of surgery.[12] Spinal anaesthesia produced no change in plasma renin activity and no change occurred after the start of surgery.[12]

In the rat, Miller *et al.* showed that anaesthesia with halothane, ketamine, or fluroxene failed to produce a significant change in renin activity.[8,9] Infusion of saralasin, a competitive inhibitor of angiotensin II, produced a significant decrease in mean blood pressure in those animals anaesthetized with halothane or enflurane, but not in those animals anaesthetized with ketamine or fluroxene, suggesting that the renin-angiotensin system may play a role in blood pressure regulation during halothane and enflurane anaesthesia.

Conflicting results have been reported by different groups studying renin activity in dogs undergoing aortic cross-clamping. Berkowitz and Shetty found that aortic cross-clamping in the dog produced a significant increase in renin activity above that associated with surgery and anaesthesia (pentobarbital) alone.[5] They suggested that the increased renin activity may have caused the corticomedullary redistribution of intrarenal blood flow observed in their study.

Cronenwett and Lindenauer, however, used a different method (microsphere technique) and failed to observe any redistribution of intrarenal blood flow; they furthermore failed to observe any increase in renin activity with aortic cross-clamping for 90 minutes. These authors suggested that more aggressive fluid replacement in their experimental animals may have explained the differences in results compared to those of Berkowitz and Shetty.[6]

Gal *et al.* studied renin activity in 21 patients undergoing abdominal aortic surgery, and found an increase in renin activity after aortic cross-clamping, compared to renin activity during surgery prior to cross-clamping.[7] These authors noted that postoperative hypertension did not correlate with renin activity in the recovery room.

Recently, Grindlinger *et al.* reported their findings in 17 patients undergoing repair of abdominal aneurysm.[14] Peak renin activity was noted in the postoperative period, as was the case in our study; renin activity was significantly greater during the cross-clamp period than preoperatively. Grindlinger *et al.* noted that 43 per cent of their patients became hypertensive postoperatively and that postoperative hypertension was not correlated with renin activity, also in agreement with the present study.

Contrary to our results, in which beta-blockage markedly attenuated the renin response to aortic clamping, Grindlinger *et al.* noted that their patients who were taking propranolol preoperatively did not have a suppressed renin response to aortic clamping. The results of the present study are more in keeping with the fact that beta-blockade inhibits renin release from the kidney.[15] Grindlinger *et al.* fail to mention whether or not their patients taking propranolol received their usual dose immediately preoperatively, as was the case in our study. Discontinuation of propranolol more than 12 to 24 hours preoperatively may explain the conflicting results as the elimination half-life of propranolol is four hours during chronic oral administration.[15]

Although propranolol inhibited the renin response to anaesthesia, surgery and aortic clamping in the five patients in our study, postoperative hypertension was still a problem in two of these five patients. Heart rate was below 90/minute throughout the study in both patients who became hypertensive, suggesting that they were reasonably well beta-blocked.

The cause of postoperative hypertension in patients undergoing abdominal aortic surgery remains unclear. Fluid overload, postoperative hypothermia with resultant vasoconstriction, and vascular hyper-reactivity in this frequently hypertensive patient population are all possible contributing factors. Although increased renin activity has been associated with rebound hypertension following discontinuation of sodium nitroprusside,[11] in patients undergoing abdominal aortic surgery the observed increase in renin activity does not appear to be the cause of postoperative hypertension. Furthermore, beta-blockade, which does prevent the increase in renin levels secondary to aortic surgery, fails to protect against the development of postoperative hypertension.

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Résumé

L'activité du système rénine-angiotensine a été mesurée avant, pendant et après la mise du clamp aortique infra-rénal chez 13 patients. Cinq prenaient du propranolol en pré-opératoire. Les pertes sanguines per-opératoires, la quantité des colloïdes et des crystalloïdes administrée, les profils hémodynamiques et le débit urinaire étaient similaires pour les deux groupes.

Chez huit patients qui ne prenaient pas de propranolol, l'activité moyenne de la rénine plasmatique était de 2.24 $ng \cdot ml^{-1} \cdot hre^{-1}$ avant l'induction, 3.78 $ng \cdot ml^{-1} \cdot hre^{-1}$ pendant la chirurgie avant la mise en place du clamp et de 4.42 $ng \cdot ml^{-1} \cdot hre^{-1}$ quinze minutes après avoir clampé l'aorte (augmentation non statistiquement significative).

L'activité de la rénine plasmatique dix minutes avant le relâchement du clamp (5.02 $ng \cdot ml^{-1} \cdot hre^{-1}$), 15 minutes après le relâchement du clamp (5.47 $ng \cdot ml^{-1} \cdot hre^{-1}$) et 30 minutes après l'arrivée en salle de réveil (5.84 $ng \cdot ml^{-1} \cdot hre^{-1}$) était significativement plus élevée qu'avant l'induction. Quatre patients ont développé une hypertension post-opératoire (pression artérielle moyenne >120 mmHg). Il n'y avait pas de corrélation entre l'activité de la rénine plasmatique en post-opératoire et l'incidence d'hypertension post-opératoire.

Les cinq patients prenant du propranolol avaient une activité de la rénine plasmatique nettement abaissée durant et après la chirurgie; tous les échantillons prélevés montraient une activité inférieure à 1.5 $ng \cdot ml^{-1} \cdot hre^{-1}$. Deux des cinq patients ont développé une hypertension post-opératoire.

On conclut que l'obstruction aortique sous les rénales est associée à une augmentation de la rénine plasmatique atteignant son maximum en post-opératoire. Il n'y a pas de corrélation entre l'augmentation de l'activité de la rénine et le développement d'hypertension. Les bêta-bloqueurs administrés en pré-opératoire atténuent la réponse du système rénine-angiotensine mais ne préviennent pas l'hypertension post-opératoire.