ROLE OF SYMPATHOADRENAL AND RENIN-ANGIOTENSIN SYSTEM IN HEMODYNAMIC STATE AFTER CORONARY ARTERY BYPASS GRAFTING

SHOOHEI HAYASE, M.D., TAKESHI SHIMIZU, M.D.,* MASAMICHI NAKAJIMA, M.D.*

Department of Surgery, The Japanese Red Cross, Nagoya First Hospital
Department of Thoracic and Cardiovascular Surgery, Kanazawa Medical University*

ABSTRACT

To evaluate the role of the sympathoadrenal and renin-angiotensin systems in postoperative hemodynamic state, plasma concentrations of catecholamines, renin activity, angiotensin, and aldosterone as well as hemodynamics were studied following coronary artery bypass grafting in 55 patients. The patients were divided into four groups: 1) uneventful, 2) hypertension (HT), 3) hypotension for which catecholamines were administered (CAT), and 4) perioperative myocardial infarction (POMI). The mean cardiac index in the HT group was higher than that in the Uneventful group and some patients in the HT group showed high adrenaline level. A group of patients who had a hypertensive episode and then sustained low cardiac output state (HT-to-LOS group) showed marked elevation of systemic vascular resistance index and noradrenaline level. These findings suggest that the hypertensive episodes in the HT-to-LOS group may be primarily caused by the activation of the sympathetic nerve system and that those of some patients in the HT group may be caused by marked adrenal medullary secretion. Five patients (56%) in the HT group showed plasma renin activity of more than 5.0 ng/ml/hr. and three patients (33%) showed angiotensin II of more than 100 pg/ml. Thus, postoperative hypertension seems to be multifactorial in nature. The POMI group represented significant elevation of plasma adrenaline concentration and significantly low sensitivity to catecholamines of the ventricle accompanied with impaired left ventricular performance. Although the mean aldosterone level in the CAT group was significantly higher than that in the Uneventful group, only a few patients of the CAT group demonstrated marked elevation of aldosterone concentration which might cause a vicious circle to develop. Clinical significance of modest increase of aldosterone concentration in other patients in the CAT group is questionable.


Coronary artery bypass grafting (CABG) can be performed with acceptably low morbidity and mortality. However, both hemodynamic and metabolic instability have been demonstrated in the early postoperative period despite utilization of myocardial preservation technique1-4. Postoperative hypertension and perioperative myocardial infarction are potentially dangerous complications during this period of vulnerability. Hypertension might increase postoperative bleeding, risk of acute cerebrovascular accidents, and myocardial oxygen demands which, in the presence of a fixed coronary blood supply, might lead to regional ischemia. Both the sympathoadrenal5-7 and renin-angiotensin systems5,8,9 have been implicated as possible biochemical mediators of postoperative hypertension. The appearance of perioperative myocardial infarction increased hospital mortality with worsened left ventricular performance and occurrence of dysrythmia10,11. Analysis of the differential contribution of postoperative hypertension, perioperative myocardial
infarction, and low cardiac output state with respect to activation of the sympathoadrenal and renin-angiotensin systems has not been well documented, although there are a few data on the correlation between the sympathoadrenal and renin-angiotensin system and hemodynamic changes in the immediate postoperative period\textsuperscript{5-8,12}.

This study was undertaken to correlate hemodynamic alterations in response to postoperative hypertension, perioperative myocardial infarction and low cardiac output state with concomitant changes in plasma concentrations of noradrenaline, adrenaline, and the renin-angiotensin system, so that the importance of each component as an imposed stress could be delineated.

METHODS

Patient population

The study population was composed of 55 patients (48 men and 7 women, aged 27 to 69 years with mean age of 54.4 ± 8.9 years) among 82 patients who underwent elective CABG at the Kanazawa Medical University. All patients were informed about and consented to the study. Patients who had associated cardiac procedures such as valve replacement or ventricular aneurysm resection were excluded. The patients were divided into four groups: 1) a group of patients with CABG operations who had uneventful postoperative course (Un/eventful group), 2) a group of patients who had postoperative hypertension (HT group), 3) a group of patients in whom intravenous administration of catecholamine such as dopamine and/or noradrenaline was utilized to maintain hemodynamic state (CAT group), and 4) a group of patients who had perioperative myocardial infarction (POMI group). There were 9 patients in the Un/eventful group, 9 in the HT group, 26 in the CAT group, and 11 in the POMI group. Analysis of preoperative data revealed no significant differences among the four groups with regard to age, history of myocardial infarction, ejection fraction, left ventricular end-diastolic pressure, and number of diseased coronary arteries. Nine of the CAT group patients had a hypertensive episode immediately after CABG and then sustained low cardiac output state (HT-to-LOS group). To analyze the mechanism of postoperative hypertension, changes of sympathoadrenal system, renin-angiotensin system and hemodynamic state in this group were compared with those of the HT group.

Hypertensive patients were defined as those in whom a systolic pressure of more than 150 mmHg or a diastolic pressure of more than 90 mmHg developed, provided that this rise was not reversed by simple sedation and that there was no evidence of hypoxia, hypercarbia, shivering, or fighting the ventilator. Perioperative myocardial infarction was diagnosed by means of the following criteria: Based on values of serum enzymes and electrocardiogram changes, scores were determined as follows: score 1 = creatine kinase (CK) > 300 units/l; score 1 = glutamic oxaloacetic transaminase (GOT) > 100 units/l; score 1 = lactic dehydrogenase (LDH) > 500 units/l; score 2 = appearance of new persistent Q wave on the electrocardiogram; and score 1 = appearance of ST-T changes on the electrocardiogram. A sum of these scores greater than four suggested perioperative myocardial infarction. Development of new Q wave on the electrocardiogram, elevation of serum cardiac enzymes, and the finding of myocardial uptake of technetium-99 pyrophosphate have been proposed as diagnostic criteria for POMI, but the clinical significance of a single abnormal test result is debated, particularly when the results of several tests are discordant. As Fennell et al.\textsuperscript{11} found that total CK, GOT, and LDH values are valuable in determining whether or not a new infarction has occurred, we utilized the multiple criteria described above for diagnosis of perioperative myocardial infarction.

Protocol of surgery and postoperative care

Reverse saphenous vein bypass surgery was performed utilizing cardiopulmonary bypass with
systemic hypothermia at 25°C. Multiple doses of a crystalloid solution were infused into the aortic root to lower the myocardial temperature below 15°C every 30 minutes during ischemic arrest. After operation, patients were monitored in the intensive care unit. Respiration was assisted by a volume cycle ventilator to maintain normal arterial blood gases. Patients were sedated with diazepam or morphine sulfate as needed to relieve pain. Blood or fresh frozen plasma was administered to maintain left arterial pressure and central venous pressure within normal limits. Intravenous nitroglycerin administration was routinely started immediately after discontinuance of cardiopulmonary bypass and continued until the second postoperative day or longer until the hemodynamics were stabilized. Sublingual nifedipine therapy was added in the intensive care unit to prevent coronary artery spasm. Systolic arterial pressure of less than 80 mmHg was treated with an intravenous bolus injection of calcium chloride. If this regimen was not effective, intravenous dripping of dopamine and/or noradrenaline was started.

Measurements

Hemodynamic variables, which consisted of cardiac output, cardiac index (CI), stroke volume index (SVI), systemic vascular resistance index (SVRI), and left ventricular stroke work index (LVSWI), were calculated. Cardiac output was determined in triplicate by the thermodilution method. Venous blood was withdrawn from the peripherial vein for analysis of plasma concentrations of adrenaline, noradrenaline, angiotensin I and II, and aldosterone as well as plasma renin activity. The above measurements were made sequentially according to the following schedule: 1) before induction of anesthesia, 2) immediately after operation, 3) 3 hours and 6 hours after operation, 4) 3°, 6°, 12°, 18°, and 24° on the first postoperative day, and 5) 6° and 18° on the following five days. Hemodynamic variables were usually observed until the second postoperative day. In some patients they were calculated until the third day. Measurements of catecholamines, renin activity, angiotensin and aldosterone were usually done until the fourth postoperative day. In some patients, they were done until the sixth day. Measurements of catecholamines were done only in 4 patients of the Uneventful group, 5 of the HT group, 13 of the CAT group, and 4 of the POMI group by a high performance liquid-chromatographic method. Patients with noradrenaline dripping were excluded. Plasma renin activity and angiotensin concentration were measured by a radioimmunoassay with dextran charcoal. Plasma aldosterone level was measured by a radioimmunoassay with polyethylene glycol.

Data analyses

The data were reported as mean ± one standard error of the mean. Analyses comparing the groups at specific time periods were performed using student’s t test. Correlation coefficients were determined between the variables and their significance was analysed by t test.

RESULTS

1) Differences in hemodynamics (Fig. 1)

In the Uneventful group, the mean CI was 2.50 ± 0.40 l/min/m² immediately after operation. It increased gradually to 3.30 ± 0.27 l/min/m² 18 hours postoperatively and then fell to 2.64 ± 0.30 l/min/m² two days postoperatively. In contrast to CI, the mean SVRI decreased gradually from 2713 ± 397 dynes-sec-cm⁻⁵-m² three hours postoperatively to 1835 ± 251 dynes-sec-cm⁻⁵-m² 18 hours postoperatively and then showed a slight increase two days postoperatively. The mean CI in the HT group was greater than that in the Uneventful group at every test time, whereas the mean SVRI in the HT group was less than that in the Uneventful group. The trends of CI and SVRI were the same as those in the Uneventful group and there was no significant difference in either mean CI.
or SVRI between the two groups. The mean CI and SVRI in the CAT group were maintained at about 2.5 l/min/m² and 2,400 dynes-sec-cm⁻¹-m⁻², respectively. In the POMI group, marked decrease of CI and marked increase of SVRI were seen as compared with the other groups during the first 24 hours. There was significant difference in the mean CI 18 hours postoperatively between the POMI group and the Uneventful group. The mean SVI revealed the same trend as the mean CI in all the groups.

![Graph showing changes in cardiac index and systemic vascular resistance index](image-url)

**Fig. 1** Changes in mean cardiac index and systemic vascular resistance index after CABG
2) Plasma noradrenaline (Fig. 2)

The preoperative mean concentration of plasma noradrenaline was $167 \pm 28$ pg/ml. This level is within the levels reported for normal supine adults. Although postoperative mean levels remained within normal limit in all the groups, 7 patients who comprised 1 in the HT group, 4 in the HT-to-LOS group, and 2 in the POMI group had a level of more than 400 pg/ml during the postoperative period. There was no significant difference in mean levels between the four groups.

---

**Plasma Noradrenaline**

![Graph showing changes in mean plasma noradrenaline concentration after CABG](image-url)

Legend:
- **Catecholamine (+)**
- **P.O.M.I. (+)**
- **Catecholamine (-)**
- **P.O.M.I. (-)**

**P.O.M.I.** = Perioperative Myocardial Infarction

**Graph Caption:** Changes in mean plasma noradrenaline concentration after CABG
3) Plasma adrenaline (Fig. 3)

The preoperative mean concentration of plasma adrenaline was 17.5 ± 2.5 pg/ml. This level is within the levels reported for normal supine adults. Both the Uneventful and the CAT groups showed no significant increase in mean level. Two patients in the HT group and two in the POMI group revealed plasma levels of more than 100 pg/ml during the postoperative period, especially from 12 to 24 hours postoperatively. There were significant differences between the Uneventful group and the POMI group in mean levels 18 hours (p < 0.05) and 24 hours (p < 0.02) postoperatively.

Fig. 3 Changes in mean plasma adrenaline concentration after CABG
4) LVSWI/plasma adrenaline (Fig. 4)

Ratios of LVSWI to simultaneous plasma adrenaline concentration were utilized as an index of sensitivity of heart to plasma adrenaline on the basis of Okamura's idea. The ratios in the POMI group remained low until the third postoperative day. There was significant difference ($p < 0.02$) six hours postoperatively between the POMI group and the Uneventful group.

![Graph showing changes in left ventricular stroke work index to plasma adrenaline concentration after CABG](image)

Fig. 4 Changes in ratio of left ventricular stroke work index to plasma adrenaline concentration after CABG
5) **Plasma renin activity** (Fig. 5)

The preoperative mean renin activity was 1.98 ± 0.41 ng/ml/hr. This level is similar to those measured for normal supine adults\(^\text{16}\). The mean renin activity in the Uneventful, CAT, and POMI groups remained within normal limits during the postoperative period. The mean renin activity in the HT group increased from two days to six days postoperatively, but there was no significant difference between the HT group and the other three groups. Patients who had plasma renin activity of more than 5.0 ng/ml/hr. comprised 1 in the Uneventful group, 5 in the HT group, 4 in the CAT group, and 2 in the POMI group. Fifty-six percent of the HT group patients had high renin activity and had been on nitroglycerin and nifedipine therapy for a long time. The rest of the HT group patients did not have high renin activity and had a short hypertensive episode.

![Plasma Renin Activity Graph](image)

**Fig. 5** Changes in mean plasma renin activity after CABG
6) **Plasma angiotensin**

The preoperative mean concentrations of angiotensin I and II were 819 ± 289 pg/ml and 82 ± 21 pg/ml, respectively. Analyses of trends of mean levels could not be meaningfully performed because the levels varied widely. Six patients who showed angiotensin II level of more than 100 pg/ml comprised 3 in the HT group, 1 in the Uneventful group, 1 in the POMI group, and 1 in the CAT group.

7) **Plasma aldosterone** (Fig. 6)

The mean plasma concentration of aldosterone was 58.3 ± 8.2 pg/ml preoperatively. After operation, the mean level in the Uneventful group decreased gradually to the lowest point of 12.0 ± 2.1 pg/ml on the fourth postoperative day. Although the mean levels in the CAT group did not show marked elevation, there were significant differences between the CAT group and the Uneventful group from the first postoperative day to fourth day. The mean levels in the HT and the POMI groups revealed almost the same trends as those in the Uneventful group. Plasma aldosterone level of more than 200 pg/ml was demonstrated in 1 patient of the HT group, 4 of the CAT group, and 1 of the POMI group.

![Plasma Aldosterone](image)

**Fig. 6** Changes in mean plasma aldosterone concentration after CABG
8) Correlation between plasma renin activity, angiotensin, and aldosterone
Although there were significant correlations ($p < 0.001$) between renin activity and angiotensin I as well as between angiotensin I and II, no significant correlation between angiotensin II and aldosterone was demonstrated.

9) Correlation between angiotensin II and SVRI
There were significant correlations between angiotensin II and SVRI in the Uneventful ($p < 0.01$) and CAT ($p < 0.05$) groups, but not in the HT or POMI group.

10) Correlation between noradrenaline and SVRI
There were significant correlations between noradrenaline and SVRI in the Uneventful ($p < 0.01$) and CAT ($p < 0.02$) groups, but not in the HT or POMI group.

11) Comparison of HT-to-LOS group with HT group (Fig. 7, 8)
The mean concentrations of plasma noradrenaline in the HT-to-LOS group were higher than those in the HT group during the postoperative period although no significant differences were demonstrated. In contrast, the mean concentrations of plasma adrenaline showed marked increase only in the HT group from the first to second postoperative day. The HT-to-LOS group showed higher mean SVRI and lower mean SVI during the postoperative period as compared with those in the HT group. A significant difference between these groups was apparent only immediately after operation. Trends of both renin activity and aldosterone in the HT-to-LOS group were similar to those in the HT group.

Fig. 7 Comparison of sympathoadrenal system between HT-to-LOS group and HT group after CABG
DISCUSSION

Hypertension after CABG has been reported to occur in 33% to 61% of patients. The low incidence (22%) of hypertension in our patients may be the result of intravenous nitroglycerin therapy, which started immediately after discontinuance of cardiopulmonary bypass, and sublingual nifedipine therapy. These drugs may play a role in reducing SVRI and in preventing the occurrence of postoperative hypertension. The pathophysiological mechanism of postoperative hypertension is uncertain, although many attractive hypotheses have been offered.

General anesthesia is known to suppress baroreceptor sensitivity. In other studies, there was no significant difference in the blunting of the reflexes between the patients who remained normotensive and those who became hypertensive after operation. It would, therefore, seem that postoperative hypertension was not the result of reduced baroreceptor control. However, the reduction of baroreceptor sensitivity in the postoperative period might help set the stage for the development of hypertension from other causes. Postoperative pain, anxiety, hypoxia, hypercarbia, shivering, and fighting the ventilator are obvious causes of the postoperative hypertension. All hypertensive patients in our study had no evidence of these signs. Their hypertensive episodes were not reversed by simple sedation. Therefore, hypertension could not be attributed to any of these factors. The role of an improved myocardial function, caused by a successful restoration of blood flow to a previously ischemic myocardium, has been considered and ruled out as a possible pathogenic mechanism, because myocardial function improved also in patients who remained normotensive. Although Whelton et al. demonstrated a significant fall in CI and stroke volume in the hypertensive patients, other investigators showed normal CI. In our results, the mean CI in the HT group was higher than that in the Uneventful group during the test period. One may speculate that, in certain cases, an increase in CI may play a role in maintaining the elevated blood pressure. 

Fig. 8 Comparison of renin-angiotensin system and hemodynamic state between HT-to-LOS group and HT group after CABG.
pressure. The hypothesis that increased CI may be secondary to relative hypervolemia is denied because right and left arterial pressure have been maintained to adequate levels in our patients. Whelton et al. suggested that postoperative hypertension might be related to excessive sympathetic stimulation in the presence of continued beta-adrenergic blockade, or to the occurrence of a rebound hyperreninemic state or hyperkinetic state resulting from excess beta-adrenergic activity following abrupt cessation of therapy. However, this possibility seems unlikely in our patients because they had not received beta-adrenergic blockade preoperatively. Fouad et al. presented that blood pressure was reduced consequent to the unilateral stellate block, being associated with a reduction in systemic vascular resistance. This finding might suggest that postoperative hypertension could be due to an efferent sympathetic reflex originating from the heart, great vessels, or coronary arteries. Especially, the paroxysmal nature of this hypertension and its temporal relation to manipulation of the heart are in favor of a reflex mechanism. The efferent sympathetic limb of this reflex could contribute to the increase in circulating adrenaline and noradrenaline.

Increased SVRI had been found to be associated with increased plasma catecholamine levels, because a strong positive correlation had been observed between blood pressure and plasma catecholamines in hypertensive patients. However, we could not demonstrate any significant correlation between SVRI and catecholamines in the HT group. Some patients in the HT group showed elevated catecholamine concentrations, but there was no significant difference in the mean adrenaline and noradrenaline levels between the HT group and the Uneventful group. These findings are consistent with Whelton's report. The HT-to-LOS group showed marked elevation of SVRI and low SVI immediately after operation. Since the mean concentrations of plasma noradrenaline in the HT-to-LOS group were higher than those in the HT group, high SVRI in the HT-to-LOS group seems to result from noradrenaline release. Conversely, two patients in the HT group showed plasma adrenaline concentration of more than 100 pg/ml, while no patient in the HT-to-LOS group showed high adrenaline level. These findings suggest that the hypertensive episodes in the HT-to-LOS group may be primarily caused by the activation of the sympathetic nerve system and that those of some patients in the HT group may be caused by marked adrenal medullary secretion, based on the fact that circulating adrenaline is derived from adrenal medullary secretion whereas noradrenaline results primarily from overflow of noradrenaline released from sympathetic neurons. It is known that the marked elevation of SVRI increases myocardial oxygen consumption and plays an important role in depression of left ventricular performance during the postoperative period when there is hemodynamic and metabolic instability. This phenomenon may result in low cardiac output state as experienced in the HT-to-LOS group.

Although Taylor et al., Roberts et al., and Niarchos et al. demonstrated that the renin-angiotensin system was an important mediator of the increased vascular resistance observed in patients with postoperative hypertension, Wallach et al., Fouad et al., and Whelton et al. showed that there was no correlation between postoperative blood pressure and renin activity. Our results showed no significant difference in the mean plasma renin activity, angiotensin I or II between the HT group and the other three groups. However, the findings that five patients (56%) in the HT group showed renin activity of more than 5.0 ng/ml/hr. and that three patients (33%) showed angiotensin II of more than 100 pg/ml may imply that there is a correlation between the renin-angiotensin system and postoperative hypertension in some patients. Niarchos et al. demonstrated the existence of two types of postoperative hypertension in relation to the renin-angiotensin system: a renin-dependent form responsive to the angiotensin II blockade with the converting enzyme inhibitor, and a nonrenin-dependent form that is unresponsive to the inhibitor. The etiology of the elevated renin activity in the HT group from the second to sixth postoperative day is uncertain from our study. Higher mean level of adrenaline and lower mean level of noradrenaline accompanied with higher mean renin activity in the HT group as compared with those
in the HT-to-LOS group might support the theory of the dominance of beta-receptor mechanism in the adrenergic control of renin release\textsuperscript{16}. It is also possible that a variety of drugs, including diuretics, spironolactone, and vasodilating antihypertensive drugs, stimulate renin activity\textsuperscript{16}. The fact that the patients with high renin activity needed long-term vasodilating therapy supports this possibility. Further investigation would be necessary to elucidate these mechanisms.

Thus, hypertensions after CABG seem to be multifactorial in nature. They are not due to the same causes and do not necessarily develop by the same mechanism, hence, there is an urgent need for accurate definition of their various types to facilitate correct identification and therapy.

There are several reports which investigated plasma catecholamines in acute myocardial infarction\textsuperscript{22,23}, but we could not find any reports on plasma catecholamine after perioperative myocardial infarction. Nadeau et al.\textsuperscript{22} and Vetter et al.\textsuperscript{23} showed that circulating catecholamine levels remained elevated during the first day after onset of acute myocardial infarction, but that these levels gradually decreased during the second 24 hours. Concomitantly, our results showed that there were significant elevations of the mean adrenaline levels in the POMI group from 18 hours to 24 hours postoperatively as compared with those in the Uneventful group. The patients with perioperative myocardial infarction also had lower CI, higher SVRI, and lower ratio of LVSWI/plasma adrenaline as compared with those in the other groups. It is likely that superimposition of the stimuli of perioperative myocardial infarction upon the sympathoadrenal system activated by CABG elicits a marked sympathoadrenal response which is associated with deterioration of myocardial performance, elevated SVRI, and low sensitivity to catecholamines of the ventricle.

It is generally accepted that aldosterone secretion is primarily regulated by the renin-angiotensin system\textsuperscript{24,25}. However, our results showed no significant correlation between angiotensin II and aldosterone. This implies a dissociation phenomenon of the renin-angiotensin-aldosterone system\textsuperscript{16,26}. It means that many factors other than the renin-angiotensin system, such as adrenocorticotropic hormone\textsuperscript{24,25}, concentration of sodium and potassium\textsuperscript{24,27}, metabolic clearance rate of liver\textsuperscript{28}, and influence from administration of dopamine\textsuperscript{29} play a role in controlling the plasma aldosterone concentration. Normal levels of mean renin activity and angiotensin in the CAT group might be related to adequate CI which was maintained by administering inotropic agents and nitroglycerin during the early postoperative days. Many investigators\textsuperscript{8,26-30} observed that the activation of the renin-angiotensin-aldosterone system in the patients with low cardiac output state adversely affected the hemodynamic state with volume retention and interstitial edema of myocardium instead of controlling the homeostasis. Marked elevation of aldosterone level, which was demonstrated in only a few patients of the CAT group, may cause a vicious circle to develop. Clinical significance of modest increase of plasma aldosterone in other patients in the CAT group is uncertain from or results, even though there were significant differences in the mean aldosterone levels between the CAT group and the Uneventful group. To determine the most important factor for aldosterone secretion after CABG and to evaluate its clinical significance, further investigation will be required.

Although our results were obtained from a relatively small group of patients, they can provide accurate data with which further studies on sympathoadrenal and renin-angiotensin systems may be compared in the future.

REFERENCES


Abbreviations: CABG, coronary artery bypass grafting; HT, hypertension; CAT, hypotension for which catecholamines were administered; POMI, perioperative myocardial infarction; HT-to-LOS group, a group of patients who had a hypertensive episode and then sustained low cardiac output state; CK, creatine kinase; GOT, glutamic oxaloacetic transaminase; LDH, lactic dehydrogenase; CI, cardiac index; SVI, stroke volume index; SVRI, systemic vascular resistance index; LVSWI, left ventricular stroke work index.