筑波大学

医学博士学位論文
PATHOPHYSIOLOGY OF HYPERTENSION FOLLOWING CORONARY ARTERY BYPASS SURGERY: AN EXPERIMENTAL DOG MODEL FOR POSTOPERATIVE HYPERTENSION

（冠状動脈バイパス術後高血圧の病態生理：術後高血圧実験犬モデル）

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筑波大学大学院博士課程医学研究科
山内 栄五郎

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PATHOPHYSIOLOGY OF HYPERTENSION FOLLOWING CORONARY ARTERY BYPASS SURGERY: AN EXPERIMENTAL DOG MODEL FOR POSTOPERATIVE HYPERTENSION

Eigoro YAMANOUCHI*, Hajime MAETA** and Motokazu HORI***

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*The University of Tsukuba Graduate School, Doctoral Program in Medical Sciences
Department of Surgery, Institute of Clinical Medicine.
**The University of Tsukuba, Tsukuba Ideopolis, Ibaraki, 305, Japan
## Contents

Summary................................................. 1  
Introduction.......................................... 3  
Material and methods................................. 4  
Results.................................................. 9  
Discussion............................................ 19  
Acknowledgment....................................... 24  
References............................................ 25
Immediate postoperative hypertension has been reported to occur during the first 3-6 hours in 30-75% of patients who have undergone aortocoronary bypass operations. Although some causes and potential predisposing factors of this type of hypertension have been cited, the mechanisms involved still remain unclear.

Some studies have implicated the involvement of nerve reflexes originating from the heart, great vessels, and coronary arteries, but they do not explain the exact role of such impulses. The paucity of data in humans is, needless to say, due primarily to the invasive nature of the experimental procedure. To further our knowledge on the involvement of nerve reflexes as a factor in initiating immediate postoperative hypertension, we used a dog model and devised a modified form of surgery by inserting a soft catheter into the left coronary artery to form a stenosis; we measured several factors usually involved in hypertension. We succeeded in performing this modified form of surgery in 10 of 81 dogs.

Our model showed that the mean aortic pressure significantly increased from 81 +/- 5.5 to 102 +/- 7.0 mmHg (P<0.05), systemic vascular resistance from 7604 +/- 833 to 9648 +/- 1101 dyn.sec.cm⁻⁵ (P<0.05), and plasma noradrenaline levels from 0.45 +/- 0.092 to 0.51 +/- 0.087 ng/ml (P<0.01) immediately after restoration of blood flow to the distal area behind the stenosis. These dynamic and humoral characteristics are similar to ones documented in current clinical reports.
To our knowledge, this is the first experimental animal model of hypertension after coronary artery bypass graft surgery.

Key words: Pathophysiology, Hypertension, Coronary artery bypass graft, Systemic vascular resistance, Noradrenaline
Introduction

Since it was first reported in 1973[1], hypertension following coronary artery bypass graft (CABG) surgery has come to be recognized as a major common postoperative complication. Studies have shown that it occurs in 30-75% of patients during the first 3-6 hours after CABG[1-5]. Postoperative hypertension not only affects the myocardium by increasing oxygen demand[6] but may also cause severe conditions such as cerebrovascular hemorrhage and bleeding from the suture site due to the increase in blood pressure[1,7]. Though there is still no agreement about the causes, treatment has been achieved by using strong, immediate-acting drugs like nitroprusside[8,9]. Pain, hypovolemia[10,11], hypoxia[12], shivering[13], serotonin[14-16], the renin-angiotensin system[2,3,13], arousal from anesthesia[12], and type of anesthetic method[4] have been hypothesized as contributing factors. Some reports indicate the involvement of sympathetic nervous activity[1] by citing high levels of catecholamines[3,17], dopamine beta hydroxylase[3], and unilateral stellate ganglion blockade[18,19], and they suggest that these effects may be mediated by way of reflexes originating from the heart, great vessels, and in particular the coronary arteries[3,10,12,17]. There has been no report, however, stating that nerve impulses do originate from these areas, because to detect nerve impulses directly would require procedures that are too invasive for the human body. To overcome the problems, we produced an experimental dog model of postoperative hypertension following CABG surgery.
Material and methods

The purpose of the experiment was first to determine whether there is a significant difference in blood pressure between the model group, in which the blood flow to the left coronary artery was restored 1-2 weeks after it had been reduced, and the control group, in which the blood flow was not restored, all other factors being constant. The second purpose was to determine whether the model group shows hemodynamic characteristics similar to ones commonly described.

Of a total of 81 dogs, ten survived surgery; of these, five made up the model group, and five the control group. The dogs were mongrels with an average weight of 16-25.5 kg and a mean weight of 20.2 +/- 1.39 kg. They were kept under controlled respiration in room air with a tidal volume of 20 ml/kg, respiratory rate of 20 /min, and a positive endoexpiratory pressure of 5 cm H₂O by intubation after being anesthetized by an intravenous injection of sodium pentobarbital at a concentration of 25 mg/kg. The chest was opened from the right side at the left lateral position. A soft catheter (16-18 G in size) was inserted through the right aortic wall into the left anterior descending branch (Fig. 1). A stenosis was created by allowing a thrombus to form around the catheter which extended 10-15 mm from the aortic orifice. The inside of this catheter was later used as a bypass pathway. Next, we inserted a flexible wire stylet into the catheter to ensure that it would not become obstructed by the thrombus and fixed the stylet to the aortic wall.
Figure 1. Schematic drawing of the modified operation. A soft catheter was inserted into the left coronary artery to make a stenosis by allowing a thrombus to form around the catheter. SVC: superior vena cava, IVC: inferior vena cava, Ao: aorta, LCA: left coronary artery, PA: pulmonary artery.
The ten experimental dogs had this catheter insertion for 8-12 days (average 9 days). During this period, antibiotics were administered intravenously and anticoagulant was not administered. After the chest was reopened in the same manner, 100 units/kg heparin was administered and the flexible wire stylet was removed. The bypass line was made by clamping one end of the catheter (3-mm internal diameter) filled with heparin-added saline solution and inserting it into the aorta through the left axillary artery. The other end of this bypass line was connected to the catheter which had been inserted earlier into the left coronary artery. In the model group, the blood flow beyond the stenosis was restored by releasing the clamp of the bypass line. In the control group, the blood flow was not restored and the clamp remained in place (Fig. 2). All these manipulations were done with as much care as possible so as not to stimulate the nerve reflex in the area around the left coronary artery. In the model group, "0 minute" was the time of clamp release, and in the control group, because we did not release the clamp, "0 minute" was a time arbitrarily chosen after the completion of the bypass.

Anesthesia and heparin concentration were kept constant at 5 mg/kg/h and 50 units/kg/h, respectively, by an infusion pump, and deep pharyngeal temperature was kept constant at around 36 °C by a bed-sheet warmer during the experiment. Administration of intravenous fluid was kept constant at the level of 10 ml/kg/h to compensate for perspiration and loss of body fluid during the experiment. Every manipulation was carefully performed, and even
Figure 2. Schematic drawing of the difference between the control group and the model group. In the model group, blood flow beyond the stenosis was restored by releasing the clamp of the bypass line. In the control group, blood flow was not restored and the clamp remained in place. Ao: aorta, LCA: left coronary artery.
though we observed some oozing, there were no major incidents of bleeding.

In both groups, heart rate, aortic pressure, cardiac output, central venous pressure, left atrial pressure, and deep pharyngeal temperature were measured every 15 min from "0 minute" to "360 minutes." Plasma adrenaline level, plasma noradrenaline level, and plasma renin activity were measured every 30 min. After the experiment, the bleeding volume and the intravenous fluid volume rate were measured. The stenosis was measured as polyethylene resin was injected into the left coronary artery with a pressure equal to the mean aortic pressure of the dog. After hardening, the left coronary artery was cut and its diameter was measured every 5 mm from the aortic orifice. The stenosis was measured as the point of maximum occlusion across the diameter.

The statistical significance of the results was assessed using the appropriate paired or unpaired Student's t-test. All results were expressed as a mean with +/- SEM.
Results

A total of 81 dogs were used in this series of experiments, though in only 33 of these were we able to implant the catheter into the left coronary artery. The other dogs died of massive bleeding during this operation. Of the 33 dogs, 14 died of heart failure before we reopened the chest. Two dogs died of infection and postoperative hemorrhage. In all of the 14 dogs that had died of heart failure, it was confirmed at autopsy that the inner lumen of the left coronary artery was completely obstructed by a thrombus which extended to the orifice at the aorta. One dog was removed from the experiment because massive hemorrhage occurred due to mismanipulation when we reopened the chest. Experimentation was discontinued in another six dogs because we could not observe any backflow from the catheter when we removed the wire stylet. This indicated that the left coronary artery had been completely obstructed. We used the remaining ten dogs as the experimental dogs.

Heart rate, aortic pressure, cardiac output, central venous pressure, left atrial pressure, plasma adrenaline level, plasma noradrenaline level, plasma renin activity, and weight measured at "0 minute" and the bleeding volume, intravenous fluid volume, and stenosis measured after the experiment did not show any significant difference (P<0.05) in the two experimental groups (Table 1). Furthermore, throughout each experiment, heart rate and left atrial pressure were stable in both groups.

The change in mean aortic pressure every 30 min from "0 minute" to "360 minutes" is shown in Fig. 3. We recognized two
Table 1. Values for several factors measured in each experimental dog.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Value 1</th>
<th>Value 2</th>
<th>Value 3</th>
<th>Value 4</th>
<th>Value 5</th>
<th>Mean</th>
<th>S.E.</th>
<th>pValues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Weight (kg)</td>
<td>23.0</td>
<td>20.0</td>
<td>16.0</td>
<td>17.5</td>
<td>20.5</td>
<td>19.4</td>
<td>1.32</td>
<td>NS</td>
</tr>
<tr>
<td>Heart Rate (t/min)</td>
<td>174</td>
<td>138</td>
<td>174</td>
<td>145</td>
<td>137</td>
<td>154</td>
<td>8.44</td>
<td>NS</td>
</tr>
<tr>
<td>Mean Aortic Pressure (mmHg)</td>
<td>70</td>
<td>110</td>
<td>82</td>
<td>105</td>
<td>67</td>
<td>87</td>
<td>8.9</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac Output (l/min)</td>
<td>0.91</td>
<td>1.35</td>
<td>0.81</td>
<td>0.91</td>
<td>0.74</td>
<td>0.94</td>
<td>0.11</td>
<td>NS</td>
</tr>
<tr>
<td>Central Venous Pressure (cmHg)</td>
<td>2.5</td>
<td>5.3</td>
<td>5.6</td>
<td>2.0</td>
<td>5.0</td>
<td>4.1</td>
<td>0.76</td>
<td>NS</td>
</tr>
<tr>
<td>Left Atrial Pressure (mmHg)</td>
<td>4.7</td>
<td>6.7</td>
<td>7.6</td>
<td>18.6</td>
<td>3.6</td>
<td>8.2</td>
<td>2.7</td>
<td>NS</td>
</tr>
<tr>
<td>Adrenaline (ng/ml)</td>
<td>0.01&gt;</td>
<td>0.01&gt;</td>
<td>0.03</td>
<td>0.05</td>
<td>0.02</td>
<td>0.02</td>
<td>0.0095 NS</td>
<td></td>
</tr>
<tr>
<td>Noradrenaline (ng/ml)</td>
<td>1.0</td>
<td>0.02</td>
<td>0.12</td>
<td>0.46</td>
<td>0.24</td>
<td>0.37</td>
<td>0.17</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma Renin Activity (ng/ml/hr)</td>
<td>9.7</td>
<td>1.3</td>
<td>1.5</td>
<td>11</td>
<td>6.6</td>
<td>6.0</td>
<td>2.0</td>
<td>NS</td>
</tr>
<tr>
<td>Body Temperature (°C)</td>
<td>34.8</td>
<td>35.7</td>
<td>35.1</td>
<td>34.7</td>
<td>34.6</td>
<td>35.0</td>
<td>0.20</td>
<td>NS</td>
</tr>
<tr>
<td>Bleeding Volume (ml)</td>
<td>287</td>
<td>259</td>
<td>253</td>
<td>217</td>
<td>108</td>
<td>225</td>
<td>31</td>
<td>NS</td>
</tr>
<tr>
<td>Intravenous Fluid Volume (ml)</td>
<td>1550</td>
<td>1350</td>
<td>1330</td>
<td>1350</td>
<td>1100</td>
<td>1340</td>
<td>71.4</td>
<td>NS</td>
</tr>
<tr>
<td>Stenosis Rate (%)</td>
<td>83.3</td>
<td>82.1</td>
<td>82.3</td>
<td>88.0</td>
<td>83.3</td>
<td>83.8</td>
<td>1.08</td>
<td>NS</td>
</tr>
</tbody>
</table>

The upper row represents the five dogs in the control group and the lower row represents the dogs in the model group. NS: not significant (P<0.05)
Figure 3. The change in mean aortic pressure in both groups measured at 30-min intervals. The increase in mean aortic pressure (MAoP) shown in peak 1 is significant (P<0.001 at 30, 60 min, P<0.05 at 90 min) and corresponds to the restoration of blood flow in the left coronary artery beyond the stenosis.
peaks in the model group. Peak 1, which is steep, represents the immediate increase in blood pressure after restoration of blood flow, and peak 2, which has a gentle slope, describes the slow increase in blood pressure. In the control group, the quick increase in blood pressure as shown by peak 1 in the model group was not observed, though the pattern did show a slower rise like that of peak 2.

When the mean aortic pressure showed a maximum, the change was a mean increase of $21.2 \pm 3.61$ mmHg (from 13 to 33 mmHg), $26.5 \pm 4.41$ % (from 14.4 to 36.8 %), in the model group and a mean increase of $8.6 \pm 3.32$ mmHg (from 1 to 18 mmHg), $10.7 \pm 4.54$ % (from 1.5 to 22 %), in the control group. The mean aortic pressure increased significantly ($P<0.05$) in the model group (Fig. 4). The mean time at which the mean aortic pressure showed a maximum was approximately "100 minutes" in the model group and "170 minutes" in the control group. In the model group, the dogs tended to show the larger mean aortic pressure a short period after restoration of blood flow, but the difference in the two groups was not significant.

When the mean aortic pressure showed a maximum, the systemic vascular resistance of the model group increased significantly compared with that of the control group (Fig. 5). However, neither the central venous pressure (Fig. 6) nor the cardiac output (Fig. 7) showed any significant difference in the two groups.

When the mean aortic pressure showed a maximum, the plasma noradrenaline level of the model group increased significantly ($P<0.01$) from 0.452 to 0.506 ng/ml and that of the control group
Figure 4. Changes in mean aortic pressure. When the mean aortic pressure showed a maximum in each group, the change was significant (P<0.05) only in the model group.
Figure 5. Changes in systemic vascular resistance. The systemic vascular resistance of the model group increased significantly (P<0.01) compared with that of the control group when the mean aortic pressure showed a maximum.
Figure 6. Changes in central venous pressure. No significant difference in central venous pressure was observed between the two groups.
Figure 7. Changes in cardiac output. No significant difference in cardiac output was observed between the two groups.
hardly changed (from 0.368 to 0.364 ng/ml). The difference in plasma adrenaline level was not significant, although it had also increased from 0.064 to 0.095 ng/ml in the model group and was almost stable (from 0.020 to 0.023 ng/ml) in the control group. The plasma renin activity increased from 4.08 to 4.95 ng/ml/h in the model group and from 6.02 to 7.70 ng/ml/h in the control group, but this change was not significant (Fig. 8).
Figure 8. Changes in adrenaline, noradrenaline, and plasma renin activity. Only the plasma noradrenaline level of the model group increased significantly (P<0.01).
Discussion

Coronary artery bypass graft surgery is difficult to perform on dogs from the point of view of operative manipulation, because the diameter of the left coronary artery is very small and the aortic wall is particularly weak, and because of expense and time, since it is necessary to employ an extracorporeal circulatory system for the animals. We therefore modified the surgery by inserting the catheter into the left coronary artery and forming a thrombotic stenosis around it. This method seemed optimal since stimulus to the area around the left coronary artery, which may cause a sympathetic drive, would be avoided when we reopened the chest.

We prepared various-sized catheters and chose one for each dog according to the expected increase in stenosis due to the thrombus forming around the catheter. Despite all our precautions, 14 of 33 dogs (42.2 %) in which we were able to implant the catheter died of heart failure, which may have been due to complete obstruction of the left coronary artery. Although we might have been able to keep more of the dogs alive if we had inserted a smaller catheter, it is currently uncertain how decrease of the stenosis would have affected the increase in blood pressure.

The only significant differences between the two experimental groups that we can recognize are blood pressure and systemic vascular resistance from a hemodynamic standpoint, and plasma noradrenaline level from a humoral standpoint. We did not see any significant difference in other important factors like
intravenous fluid volume, bleeding volume, anesthetic method, and temperature. A graph recording change in mean aortic pressure showed two peaks in the model group and only one in the control group. The single peak in the control group occurred at 160 min and was similar in time of appearance and gradient to peak 2 of the model group. This similarity led us to conclude that the peak represented a slower rise in mean aortic pressure resulting from a natural defense reaction to the increased stress from the thoracotomy, which had lasted up to 6 hours. The effect of increased stress was observed and recognized as Mayer's wave[20-21] in almost one third of the dogs even 4 hours after the beginning of the experiment.

Since it appeared only in the model group, peak 1 may be related to the restoration of blood flow in the left coronary artery and an increase in blood pressure due to an increase in systemic vascular resistance; when the mean aortic pressure showed a maximum, systemic vascular resistance also increased and there was no change in central venous pressure and cardiac output. The increase shown in peak 1, which is steep and different to peak 2, is significant (P<0.001) and seems to confirm similar findings in other clinical reports.

Some investigators have shown that there is a significant correlation between the increase in blood pressure and the alteration in plasma catecholamine levels[3,17]. We acknowledge that the plasma noradrenaline level increased significantly (P<0.01) when the mean aortic pressure showed a maximum in the model group. The plasma adrenaline level, on the
other hand, did not show a significant increase, though it did tend to show a higher value when the mean aortic pressure showed a maximum in the model group. This suggests that the increased level of plasma noradrenaline originates from the sympathetic nerve endings of the entire body and the corresponding increase in blood pressure shown in the model group is closely related to sympathetic overdrive. Some investigators reported the involvement of the renin-angiotensin system[3,13], but others were unable to document a definite correlation between plasma renin activity and this type of hypertension[17,22,23]. As it is known that increased activity of the sympathetic nervous system increases renin secretion mediated by way of beta 1-adrenergic receptors and cyclic AMP generated in the juxtaglomerular cells[24,25], these reports are not contradictory; nevertheless, further research will be necessary. In our model, we did not see a significant increase in plasma renin activity.

Although stimuli to the atria, ventricles, and great vessels elicit mainly depressor reflexes, a stimulus to the area around the left coronary artery causes pressor reflexes[26-29], which, as can be seen from the results of one report[30], may be quite long-lasting. As shown in Fig. 3, the difference in mean aortic pressure between the control group and the model group did not return to zero. Indeed, this condition was maintained for more than 6 hours in two of the dogs in the model group. Though some reports have indicated that even small levels of plasma renin activity can participate in the development and maintenance of increased blood pressure[31], we could not be certain that this
increase was due to the renin-angiotensin system, which may have been triggered by the sympathetic nerve reflex. Another study points out that operative manipulation during surgery may stimulate the receptors located around the left coronary artery[4]. In our experiment, therefore, we paid special attention to operative manipulation, particularly to the area around the left coronary artery so as not to provoke a stimulus when we reopened the chest. When we began measuring each of the above items, we confirmed that each one was stable and that the values did not differ from those we obtained before reopening the chest. As we also avoided measuring left ventricular end-diastolic pressure (LVEDP), because a reflex could have been elicited by the tip of the inserted catheter touching the endocardium, the only difference between the two groups is whether there was restoration of blood flow to the distal area beyond the stenosis. Therefore, though several other factors may cause this type of hypertension[12], we can attribute these significant differences, at least in part, to the restoration of blood flow, which in turn may be sufficient to elicit a sympathetic overdrive mediated by way of a pressor reflex from the left coronary artery.

Some studies have suggested that this type of hypertension may be related to preoperative propranolol therapy[22], difference in anesthetic method[4], pulsatile perfusion[32], and serotonin levels[14-16]. These ideas could be refuted by our experiments since we did not administer any propranolol, anesthesia was performed using only sodium pentobarbital, and
heparin concentration was kept constant by an infusion pump throughout the experiment, thus decreasing the likelihood of serotonin release from platelet aggregation. Although heparin concentration was kept constant and the thrombus was minimal, there is the possibility of reflexes resulting from myocardial ischemia secondary to shower emboli following the forcing of blood through a thrombosed catheter.

The hemodynamic and humoral characteristics shown in the model group are quite similar to those which are generally agreed upon in clinical reports. Furthermore, in our model, we can directly detect nerve impulses and conditions such as the existence of a stenosis and restoration of blood flow which are similar in human patients. Therefore, we believe this model is suitable for animal experiments on hypertension following coronary artery graft bypass surgery.
Acknowledgment

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