Ischemic Heart Disease and Catecholamines*

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Raab has repeatedly pointed out an importance of cardiotoxic effect of catecholamines in the causation of degenerative heart disease. And it was reported that administration of large dose of adrenaline often precipitates anginal attack in the patients with coronary heart disease. However, a precise mechanism with which catecholamines induces cardiac hypoxia in patients was poorly understood.

Previous invesagation from our laboratory revealed a physiological dose of noradrenaline or adrenaline caused electrocardiographic changes with or without cardiac pain in the presence of coronary atherosclerosis. These results suggest that catecholamines released by sympathetic-adrenomedullary activity could be a trigger of anginal attack.

The present investigation extended further our previous studies and clarified a possibility that the stress factors produced cardiac ischemia mediated by the release of endogenous catecholamines.

Materials and Methods

Materials: The study was performed on 74 patients with ischemic heart disease (age; 35 to 72 years), 16 patients with essential hypertension (age; 31 to 61 years), and 51 normal subjects (age; 35 to 69 years).

Measurement of plasma catecholamines: Plasma noradrenaline and adrenaline levels during spontaneous anginal attack (12 cases), before and during the infusion of noradrenaline (10 cases) or adrenaline (10 cases) and immediately after Master's double two step test (7 patients and 6 normal subjects) were determined fluorometrically by the method of Weil-Malherbe and Bone.

Catecholamines and angiotensin-II infusion test: After about thirty minutes of rest in recumbent position, 1-noradrenaline bitartrate at a constant rate of 0.2 µg/kg/min., 1-adrenaline-bitartrate of 0.1 µg/kg/min. or val²-angiotensin II-asp. β-amide of 0.015 µg/kg/min. was infused intravenously for 15 minutes with constant perfusion pump.

Electrocardiograms and hemodynamic measurements: Throughout Master's exercise test or the infusion test, electrocardiograms were continuously recorded and blood pressure was measured frequently using spygmanometer or continuous blood pressure monitor at intervals of one or two minutes. The ischemic changes of these electrocardiograms were evaluated according to Master's criteria (1961). Moreover, heart rates were estimated from these electrocardiograms and then cardiac effort index (heart rate × mean blood pressure) were calculated.

Since it had been observed in our laboratory that there is a positive correlation between the basal blood pressure and pressure-rise responded to administered noradrenaline, the changes of cardiac effort index were compared

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between the controls and the patients whose basal mean blood pressure was almost matched together.

**Results**

**Plasma noradrenaline and adrenaline levels:** The plasma level of noradrenaline and adrenaline during spontaneous anginal attack in 12 patients was 0.951±0.232 and 0.305±0.059 µg/L, respectively. These were the same values which obtained after Master's exercise test in 7 patients (1.060±0.189 and 0.263±0.140) and in 6 normal subjects (0.976±0.188 and 0.226±0.026).

The changes in plasma catecholamine levels following the administration of catecholamines are graphically presented in Fig. 1. It is deservedly supposed that a higher plasma level would be required in the case of exogenous administration than endogenous release of catecholamines, in order to obtain the same effect on the heart muscle. In the present studies, therefore, the administrated dose of catecholamines was designed to maintain the plasma levels somewhat higher than those during spontaneous anginal attack or after exercise, i.e., 0.2 µg/kg/min. of noradrenaline and 0.1 µg/kg/min. of adrenaline.

**Evaluation of electrocardiographic changes during catecholamines infusion:** As shown in Table I, the majority of patients and the minority of control subjects exhibited ischemic changes on electrocardiogram following the administration of noradrenaline or adrenaline. The response of the patients to infused angiotensin-II and of the patients with essential hypertension to catecholamines were clearly different from that of coronary patients to

![Fig. 2. Changes in heart rate in the patients with ischemic heart disease following the administration of noradrenaline (0.2µg/kg/min.) and adrenaline (0.1µg/kg/min.) and Master's double two step exercise test as compared with those in normal subjects matched to patients in their basalmean blood pressure. (Solid and double circle shows the patients with and without ischemic response on electrocardiogram, respectively, evaluated according to Master's criteria, and open circle shows the normal subjects).](image)

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Table I

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Positive response on electrocardiogram according to Master's criteria</th>
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<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>Per cent</td>
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<tr>
<td><strong>Noradrenaline</strong></td>
<td></td>
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<tr>
<td>0.2 μg/kg/min</td>
<td>33</td>
<td>0</td>
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<tr>
<td>Normal subjects</td>
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<tr>
<td>Patients with IHD</td>
<td>46</td>
<td>71.9</td>
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<tr>
<td>Patients with HT</td>
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<td>0</td>
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<tr>
<td><strong>Adrenaline</strong></td>
<td>38</td>
<td>13.2</td>
</tr>
<tr>
<td>0.1 μg/kg/min</td>
<td>62</td>
<td>93.6</td>
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<tr>
<td>Normal subjects</td>
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<td></td>
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<tr>
<td>Patients with IHD</td>
<td>58</td>
<td></td>
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<tr>
<td>Patients with HT</td>
<td>7</td>
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<tr>
<td><strong>Angiotensin-II</strong></td>
<td>10</td>
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<tr>
<td>0.015 μg/kg/min</td>
<td>26</td>
<td>23.1</td>
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<tr>
<td>Normal subjects</td>
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<tr>
<td>Patients with IHD</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

Master's double exercise test
- Patients with IHD: 70
- Positive: 66
- Per cent: 94.3

IHD: Ischemic heart disease  HT: Essential hypertension

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Systolic blood pressure

Fig. 3. Changes in systolic and diastolic blood pressure in the patients with ischemic heart disease compared with those in normal subjects from the same investigation as Fig. 2.

Diastolic blood pressure

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catecholamines.

**Hemodynamic effects of catecholamines in the patients with ischemic heart disease**: The response of the heart rate and systolic and diastolic blood pressure to catecholamines are shown in Fig. 2 and 3. Following the administration of noradrenaline, systolic and diastolic pressure were elevated and heart rate was reduced in both patient and control group, and the systolic pressure-rise was significantly
greater in the former group. Adrenaline infusion produced a increase in heart rate and systolic pressure and a decrease in diastolic pressure. The change in systolic and diastolic pressure was significantly larger \( p < 0.05 \) and smaller \( p < 0.05 \) in coronary patients than normal subjects, respectively. Master's exercise test produced directionally similar changes with those following the adrenaline infusion, and these changes were greater in the patients.

Fig. 4 represented the changes of the cardiac effort index in the patients with ischemic heart disease (thick line) and in normal subjects (thin line) during infusion of catecholamines or angiotensin-II or immediately after Master's exercise test. These procedures increased the value of cardiac index in both patients and normal subjects. And the increase in patients was significantly greater than in normal subjects, i.e., noradrenaline, adrenaline, and exercise increased the index by \( 960 \pm 860, 1230 \pm 1030, \) and \( 2560 \pm 890 \) in the patients and by \( 220 \pm 810, 560 \pm 620, \) and \( 570 \pm 1080 \) in normal subjects, respectively. Angiotensin-II also produced a similar increase in this index, whereas the positive response in electrocardiogram following its administration was observed in only a few patients as shown in Table I.

In Fig. 5 the changes of cardiac effort index in the patients with ischemic heart disease were plotted. The increase of this index was greater in the patients who showed positive electrocardiographic findings than those with negative electrocardiogram.

**Discussion**

The causative mechanism underlying the myocardial hypoxia precipitating angina pectoris has been unknown. Raab\(^2\) presented observations that excess catecholamines liberating from sympatho-adrenomedullary system by stresses disturbs the oxygen economy of myocardium and intensifies the cardiac oxygen...
consumption, and resulting myocardial hypoxia produces anginal attack in the patients with coronary arteriosclerosis. It has been well known that physical and mental stress including the attack of ischemic heart disease augmented the release of endogenous catecholamines, and Gases et al.\textsuperscript{12} reported the increment of plasma catecholamines level after physical exercise was more remarkable in the patients with coronary heart disease. Similarly, Nestel et al.\textsuperscript{13} observed mental test produced greater output of urinary catecholamines and their metabolites in the coronary patients. Despite of these observations, it is not yet clear whether the increase of catecholamine release is a cause or a result of the anginal attack. As reported previously\textsuperscript{9}, small amounts of exogenous catecholamines produced anginal pain in some of the patients, but none of the normal subject. This small dose of catecholamines also caused ischemic changes in electrocardiogram in majority of patients, but not in normal subjects or hypertensive patients. Administered angiotensin-II, in contrast, did not show such a response in the patients with ischemic heart disease. The plasma level of catecholamines following the administration of this dose was almost comparable or somewhat higher than the level obtained during spontaneous anginal attack or immediately after Master’s two step test. Thus, although causative role of catecholamines for establishment of angina pectoris is still a matter of speculation, it is quite possible that catecholamines released from sympathetic-adrenomedullary system acts, in part at least, as a trigger to precipitate the attack of effort angina.

The evidences have been reported recently from some laboratories that an increase in cardiac work exists prior to the onset of anginal attack.\textsuperscript{14–17} It is reasonable to presume that the augmentation of cardiac work, which is an important determinant of myocardial oxygen consumption, relates in anginal attack. In this investigation, the changes of heart rate and blood pressure were observed, and the changes of cardiac effort index were estimated before and following the administration of catecholamines or angiotensin-II and after Master’s exercise test. The heart rate was decreased by noradrenaline and increased by adrenaline in the similar degree in both patients and normal subjects. Master’s exercise test, in contrast, produced significantly higher increase of heart rate in the patients. For the blood pressure, both noradrenaline and adrenaline infusion resulted in more remarkable increase in the patients and Master’s exercise showed similar tendency. One of the most impressive findings was that the increase of cardiac effort index by noradrenaline or adrenaline as by exercise was significantly greater in the patients with ischemic heart disease than that in normal subjects. Moreover, it was found that the patients with more remarkable increase of cardiac effort index showed high incidence of positive electrocardiographic findings. It is of interest that though approximately equal increase in the index was produced by angiotensin-II, ischemic changes in electrocardiogram were much less frequently observed.

These findings suggest that catecholamine released by physical or mental stress may cause marked augmentation of the cardiac work by the way of elevation of blood pressure. In addition, hypermetabolic effect of catecholamines causes a disturbance of oxygen balance in the myocardium in the presence of coronary sclerosis.

**Summary**

In order to evaluate a role of sympathetic-adrenomedullary system in the causative mechanism of the anginal attack, the electrocardiographic and hemodynamic changes following the administration of physiological dose of catecholamines were observed in 74 patients with ischemic heart disease, in 51 normal subjects and 16 patients with essential hypertension.

Following the administration of 0.2 \( \mu g/kg/min \) of noradrenaline and 0.1 \( \mu g/kg/min \) of adrenaline the ischemic changes in electrocardiogram evaluated according to Master’s criteria were found in 46 out of 64, 58 out of 62 patients, none of 33 and 5 out of 38 normal subjects, none of 10 and 7 out of 14 hypertensive patients, respectively. On the other hand,
angiotensin-II (0.015 μg/kg/min.) showed positive electrocardiogram in only 6 out of 26 patients.

Noradrenaline and adrenaline produced a decrease and an increase of heart rate, respectively, neither of which showed any difference between patients and normal subjects. Noradrenaline increased both systolic and diastolic pressure and adrenaline increased systolic pressure and reduced diastolic pressure. These changes were significantly greater in the patients with ischemic heart disease as compared with those in normal subjects. Moreover, catecholamines and Master's exercise test produced significantly greater increase of cardiac effort index in the patient group. And the patients who showed greater increase of this index was associated with the higher incidence of positive electrocardiogram and the tendency was more remarkable in adrenaline than noradrenaline.

Following the infusion of angiotensin-II the ischemic change on electrocardiogram was rarely observed despite of marked elevation of the cardiac effort index.

Based on these findings, the importance of the sympatho-adrenomedullary system in the precipitation of anginal attack was discussed.

Acknowledgement

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REFERENCES