Stress as a Causative Factor of Essential Hypertension and its Influence on the Cardiovascular System

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THERE seems to be general agreement that the cause of essential hypertension, as explained by the mosaic theory after Page,¹ consists of various factors, renal, cardiovascular, internal secretory, etc. The neurogenic factor is included among these and it appears to be important especially in the pathogenesis of essential hypertension. Therefore, cold stress tests were scheduled for patients with essential hypertension and their cardiovascular responses were investigated.

MATERIALS AND METHODS

Three hundred and fifty four hypertensive patients were hemodynamically analysed; using cardiac dynamics with *Blumberger-Holldack's* method,² and vascular dynamics with *Wezler's*³ method. They were classified⁴ into the following four types; high cardiac output type (M Type), high total peripheral resistance type (W Type), high volume elasticity coefficient type (E' Type) and their combined type. According to their age the patients were divided into a juvenile group (< 30 yrs.), a middle-aged group (31–60 yrs.), and an old-aged group (61 yrs.–). The cold pressor test was carried out with 10 cases of normal control and 37 cases of essential hypertension. According to the method of *Hines and Brown*,^{5,6} the following cases were evaluated as the hyperreactive type; 1. elevation of systolic blood pressure by the test was above normal

range (0– +22 mmHg) and the highest value of systolic pressure reached more than 145 mmHg; 2. elevation of diastolic blood pressure was more than 15 mmHg and the highest value of diastolic pressure reached over 95 mmHg. Other cases evaluated normoreactive type. Blood was drawn from the cubital vein of the patients before giving cold stress and just before withdrawal of the stress during 1 minute, then serum catecholamines were measured by *Weil-Mahlherb's*⁷ method, and cardiovascular responses were simultaneously recorded.

RESULTS

1. Hemodynamical analysis of hypertensive patients.

The results obtained from cardiovascular analysis of the 354 essential hypertensive cases were divided into three groups, according to their ages. We observed many cases of increased cardiac output (M Type) in the juvenile group (40%), while increased total peripheral resistance (W Type) and W + E' Type appeared in the middle-aged group, and increased volume elasticity coefficient (E' Type) and W + E' Type in the old-aged group. Thus, there are many patients with high cardiac output in the juvenile group but it is not known whether their vascular resistance is similar to normal control or not. Therefore, hemodynamically, we compared the interrelationship of cardiac output (CO) and total peripheral resistance (TPR) between the patients with juvenile hypertension and the control showing the same cardiac output. At the beginning, we studied the relationship between cardiac output and total peripheral resistance in normal persons younger than 30 years. In this

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Fig.1. The influence of cold stress upon the relationship between CO and TPR. In juvenile hypertension, the values of TPR which were within normal limits or slightly higher than those in control before cold stress test, increased remarkably after the test. In middle-aged hypertension, the values of TPR which were at higher level than that of control before cold stress test increased slightly after the test, but the grade of increment was rather slight extent comparing with that of juvenile hypertension.

study, 63 cases of the normal young adults exhibited the tendency of increased cardiac output accompanied by decreased total peripheral resistance. Then, we investigated the relationship between CO and TPR in juvenile hypertension. In the juvenile hypertensives, compared with the control group having the same CO, there were definite increases in TPR, even in the benign group, and this tendency was more remarkable in the groups with lower cardiac output and much clearer in the hypertensive state than in normotensive state, and in the group with severe hypertension the increase in TPR was the most prominent. In general, the opinion was that there were many cases with increased cardiac output (M Type) in juvenile hypertension and indeed, our observations verified this and in addition a few cases of W type, E' type and W + E' type were exposed. Nevertheless, compared with the results obtained from the normal control having the same cardiac output, as mentioned above, a definite increase in TPR was observed in Juvenile hypertension. Moreover, not only in the group having low cardiac output but the group showing high cardiac output, the vascular system of the patients with juvenile hypertension seem to have some

intrinsic vascular resistance promoting nature.

2. Cardiovascular responses of hypertensive patients under cold stress.

It is generally accepted that, in juvenile hypertension or in the initial stage of essential hypertension, the neurogenic factor⁸ is, among various factors, greatly concerned with the hypertensive state, and that the blood pressure rises remarkably under stressful conditions. Consequently, we prepared to investigate the hemodynamic response to cold stress. Using the method of Hines and Brown, the results of the cold pressor test on the hypertensive patients of various age groups showed that 81% of 11 patients in the juvenile group were hyperreactive whereas in 20 cases of the middle-aged group only 45% were hyperreactive, while 6 cases in the old age group and 10 cases in the normal control were all normoreactive. On the other hand, in the hyperreactive cases, the diastolic pressure elevated noticeably and this tendency was most distinct in labile and mild hypertensive cases rather than in fixed and severe cases.

Under cold stress conditions, many cases with the increased serum catecholamines, especially norepinephrine were noted, but there was little difference between the catecholamine content of

Fig. 2. Hemodynamical changes after cold stress test in hyperreactive cases in systolic pressure, diastolic pressure, and both respectively. After the cold stress test, the value of Pd/ICT increased in all juvenile groups, but decreased in middle-aged groups.

hyperreactive cases and that of normoreactive cases. As a result, we concluded that there is no relationship between the blood pressure elevation under cold stress and the concentration of serum catecholamines. Therefore, we investigated the hemodynamical changes in 18 cases of hyperreactive responses under cold stress.

Their cardiovascular status before cold stress was within normal range except for a high TPR displayed by one juvenile case and two in the middle-aged group. As for increased cardiac output there were five cases noted; two juvenile and three middle-aged cases. Results on all other cases remained in normal range.

Fig. 1 represents the relationship between the CO and TPR, in the above mentioned cases, while under cold stress. In juvenile group, the TPR value was within normal limits or slightly increased before cold stress as compared to the control group, but it showed a remarkable increase after cold stress test. But in middle-aged group, the value of TPR which was at a little higher level than juvenile group before cold stress, increased to some extent. The increment in TPR after the cold stress test in the middle-aged group was no greater than that in the juvenile group.

Fig. 2 shows the patients hemodynamical

changes in systolic pressure, diastolic pressure and in both respectively after cold stress. After the cold stress test, a definite increase in total peripheral resistance, systolic pressure and diastolic pressure was noticed as expected, but there was little change in pulse rate. The changes in cardiac output were similar in both the juvenile and middle-aged groups.

The value of Pd/ICT in the juvenile group increased after cold stress test, suggesting that the cardiac contractility was increased. On the contrary, in the middle-aged group, the value of Pd/ICT decreased after cold stress. The value of ET/PEP in the juvenile group did not show any tendency. This fact seemed to have resulted from the influence of the TPR, since the ET/PEP value has a tendency of lowering when TPR rises. On the other hand, in middle-aged group, there was no case with increased ET/PEP value after cold stress.

When we review the relationship between the changes of cardiac output or total peripheral resistance and those of Pd/ICT or ET/PEP after cold stress, the value of TPR increased in all 9 cases in the juvenile group, and Pd/ICT also increased in 4 juvenile cases in which the cardiac output showed no change or increase, indicating that the cardiac contraction was increased.

Moreover in the other five juvenile cases, in which there was some decrease in cardiac output, there was an increase or no change in Pd/ICT. From these results we presumed that the inotropic action increased after cold stress in this group. On the other hand, in the middle-aged group, there was only one case that showed an increase in Pd/ICT, the other 3 cases showed no change, and in 5 cases a decrease. Thus, under cold stress, the increase in TPR, decrease in CO and Pd/ICT was remarkable in the middle-aged group.

In regard to ET/PEP, in the juvenile group, there was an increase in half the cases and decrease in the other half. When we consider that ET/PEP is apt to have lower values as the TPR increases, such a result suggests an increase of cardiac contraction. In the middle-aged group there were many cases which exhibited an increase in TPR and decrease in cardiac output and all the cases showed no change or decrease in the value of ET/PEP.

DISCUSSION

The relation between pathogenesis of essential hypertension and increased vascular reactivity has long been discussed and it seem to have been accepted that the responsiveness to the vasoactive substance is increased in patients with essential hypertension.⁹ But there remains an uncertainty as to whether such an increase in responsiveness is a cause of hypertension or an effect of the hypertension.

On the other hand, we can consider the neurogenic factor as one of the causative factors which plays a great role in the development of essential hypertension. Therefore, in order to investigate the role of stress as a neurogenic factor in the development of hypertension, we performed our cold stress experiment. We inferred that some differences might be found between the cardiovascular responses in the early stage of hypertension and fixed hypertension, so the responsiveness to the cold stress test was investigated by using three age groups.

It is generally accepted, in hemodynamical analysis, that there are many cases in the group with juvenile hypertension which show M type with increased cardiac output or hyperkinetic circulation as mentioned by *Sannerstedt*.¹⁰ While our observation suggested that the vascular tone increased in the juvenile group so that the TPR can be compared with that of the control having the same CO. Under cold stress, there was

a great increase in TPR in this group. Moreover, the cardiac response to cold stress was so distinct in the juvenile group that cardiac contraction must have definitely increased, that is, many cases were seen in which the CO increased to a great extent in spite of the increase in TPR. Thus, it is characteristic of juvenile hypertension or initial stage essential hypertension that the patients respond greatly to stress in both cardiac and vascular reactions and such reactivity under stress is supposed to be a significant factor in the development of essential hypertension. After such responses are repeated for many years, organic changes in the cardiovascular system will gradually increase and an advanced stage of essential hypertension will be established, therefore, creating a less distinct cardiovascular reactivity than in the initial stage.

SUMMARY

Cardiovascular responses to cold stress were investigated in hypertensive patients. There were few differences in the changes under cold stress of the serum catecholamine concentration between the juvenile group and middle-aged group. In the juvenile group, a remarkable increase in TPR was observed under cold stress, suggesting that the vascular reactivity is increased and at the same time the cardiac response to inotropic action was increased under cold stress. On the contrary, in the middle-aged group, there was less increase in TPR under cold stress and no increase in inotropic action was observed. From such results, hyperreactivity to stress in the cardiovascular system is thought to be an important factor in the pathogenesis of essential hypertension. Such cardiovascular responses are seen more easily in juvenile hypertension or initial stage of essential hypertension. In the hypertensive patients after middle-age, organic changes will develop by the repeated pressure load to the cardiovascular system caused by various stimulations and the reactivity of cardiovascular system to stress becomes less manifest.

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Discussion:

Chairman: YOSHIKI MASUYAMA, Wakayama Med. College

The author presented the hemodynamic pattern and the cardiovascular responses to cold pressor test in the juvenile, middle-aged and the old-age groups of essential hypertension by using the polygraphic method by Blumberger-Holldack and by Wezler.

Dr. EIICHI UCHIDA (Cardiovasc. Inst., Tokyo): Showed the different responses of cardiac output to cold pressor test: Cardiac output was not significantly increased by the cold pressor test, compared with the value before the test, in stages I and II of essential hypertension by WHO classification, measured by dye-dilution method. No significant difference was also found in the responses of cardiac output between borderline and established hypertension, though more increase in total peripheral resistance was shown in established hypertension. Cardiac output was increased by the hand-grip test in essential hypertension.

Dr. TSUYUSAKI: The hemodynamic analyses were performed only in "hyperreactive" patients to cold pressor test defined by Hines and Brown. Cardiac output was increased in the hyperreactive patients in systolic pressor response alone and in both systolic and diastolic pressor response, while it was decreased in the hyperreactives only in diastolic pressor response.

Dr. YOSHIHIRO KANEKO (Yokohama City

Univ.): Asked the reliability and the range of errors of the method for the repeated measurements of cardiac output.

Dr. TSUYUSAKI: The Wezler's method was used to measure cardiac output and it was reliable and repeatedly used in short intervals from his experience.

This seems very important in this kind of experiments.

Dr. UCHIDA: Asked again the reason why the pressor responses of the elder group were lower than the younger. The responses should be higher from the viewpoint that structural resistance might be increased in this age group as Folkow had pointed out. And he commented that the decreased neural sensitivity to the stimulus and cardiac factor might affect on these lower responses of the elder age group.

Dr. TSUYUSAKI: Agreed to the decreased vascular sensitivity in the elder patients, induced by the organic changes from the long-term pressure load.

Dr. YUKIO YAMORI (Kyoto Univ.): Commented on the decreased responses to the stress in the elder group from his experience on spontaneously hypertensive rats (SHR). He pointed out that not only the medial hypertrophy but the increase in collagen protein, acceleration of fibrosis, were also found following one month duration of hypertension in SHR. Therefore, the decrease in the responsiveness might be explained, because the structural components of the vascular wall, inhibiting the vascular contraction, are also increased though the wall/lumen ratio is decreased.

Dr. OSAMU IIMURA (Sapporo Med. College.): Pointed out the following problems: 1) It is very natural and not a specific matter that total peripheral resistance was always increased when the hypertensive patients were compared with the normal controls having the same cardiac output.

2) It should be careful to conclude that the increased cardiac reactivity might play a role in the development of hypertension from the presented result, in which the increased cardiac contractility was shown in hypertensive patients with high after-load.

3) In his clinical experiment, the peripheral vascular reactivity to infused noradrenaline was higher in the younger group of hypertensive patients than the elder similar grade hypertensives.

Dr. TSUYUSAKI: 1) This experiment was designed to observe the changes of peripheral

vascular resistance in juvenile hypertension, because it had been shown that high cardiac output was often found in the juvenile or initial stage of hypertension. Total peripheral resistance was higher even in the normotensive state of labile hypertension than normal controls.

2) The increase in Pd/ICT by the cold pressor test, accelerated cardiac contractility, was found

only in the hyperreactive juvenile group, but not in the middle-aged group.

It was shown that in the juvenile hypertension high cardiac output was often found and the cardiovascular reactivity to cold stress was also increased. However, the changes of cardiac output and total peripheral resistance to cold pressor test remain for the further investigation.