PATHOPHYSIOLOGICAL SIGNIFICANCE OF SYMPATHETIC ACTIVITY IN CARDIOVASCULAR DISEASES

Kiyotaka Kimura

The autonomic nervous system, especially its sympathetic activity, is one of the most important regulatory mechanisms of hemodynamics. In recent years, the modification of the sympathetic activities in cardiovascular diseases, such as valvular disease, essential hypertension and coronary heart disease are demonstrated, owing to the development in the measuring methods of catecholamines (shortened as CA in the following), of their precursors and metabolites, and of activities of the CA-metabolism-related enzymes, as well as to the development in the studies in their metabolic antagonists and on the receptor blocking agents on sympathetic nerve endings. And their pathophysiological significance is also getting to be made clear.

In the case of congestive heart failure, caused by valvular disease or hypertension, the sympathetic activity is augmented, doing a good contribution for the improvement of diseased states. In this case, the sympathetic hyperactivity is shown as an increase of CA levels in blood and urine and a decrease in myocardial stores of noradrenaline. In the case of essential hypertension, as its clinical findings and the hemodynamics resemble the changes caused by the CA-administration, and as many of the antihypertensive drugs now on use have such a mode of action as depress the action of CA on the cardiovascular system or as depress the transmission at a certain site of the central to peripheral sympathetic nervous system, it can be said almost certain that CA play some role in the pathogenesis of hypertension, the primary relationship between them being still left uncertified. The CA metabolism, cardiovascular responsiveness to CA in essential hypertension are on numerous investigation.

In the case of coronary heart disease, the roles of CA in the pathogenesis on coronary arteriosclerosis are being examined from a viewpoint of the energy metabolism. An anginal attack can also be induced by the administration of isoproteanol. The inducing factor of an anginal attack can, in many cases, also related to be a CA releasing factor. It is considered well possible that the increased CA-secretion may give rise to myocardial ischemia by causing the cardiovascular hyperdynamics and then the activation of the myocardial metabolism which results in an increase in the myocardial oxygen consumption. Up to the present, however, the precise mechanism is still uncertain.

Thus, on the above-mentioned cardiovascular diseases, the changes in sympathetic activity are demonstrated, and each of the changes is also getting to be proved pathophysiological important. Such sympathetic hyperactivity will be inevitably caused by emotional or physical stress in our daily life. So, we have had the following experiments with a view to examining the changes in sympathetic activity induced by drugs or by physical exercise, and then making the pathophysiological significance of the sympathetic activity in these diseases clear.

Materials and Methods

Materials: The following cases were selected out for the study from the patients admitted to the Department of Internal Medicine, Division I, School of Medicine, Kobe University; the pati-
ents with valvular disease, essential hypertension, and coronary heart disease, the latter group was documented by previous episode of acute myocardial infarction or angina pectoris, every case in all the groups being estimated Class I and Class II according to the functional classification of the cardiac disease, by New York Heart Association.

Methods: (I) On the selected 5 cases of valvular disease, 9 cases of essential hypertension and 8 cases of coronary heart disease, the following drug tests and exercise test were carried out:

Each examined person needed to rest for an hour in recumbent position, to urinate, and to rest again for an hour. Then, the tests were taken as follows.

Blood pressure, pulse rate and electrocardiogram (shortened as ECG in the following) were monitored continuously, before and after the tests, and each value of the maximum changes was taken as the response value to the drug or exercise test. And urinary excretion of CA in one hour, before and after the test, was measured through THI method, as a modified method of Euler-Flodin method. Five healthy persons, nearly age-matched, were used to serve as a control.

1. Pilocarpine test: 1% pilocarpine (showtened as P in the following) was administered intramuscularly at the rate of 130 mcg/Kg.

2. Noradrenaline test: 1000 mcg of noradrenaline (shortened as NA in the following) was dissolved in 250 ml of Ringer's solution and the intravenous drop infusion of it was done for 30 minutes at the rate of 0.15 mcg/Kg/min.

3. Exercise test: The examined person was made to climb down stairs from the ninth floor to the second floor and then up vice versa; it took him 3 minutes.

Methods: (II) β-Blocker test: To examine the influences of a β-blocker on the sympathicotony and on the hemodynamic responses induced by the exercise, the following tests were carried out upon the newly selected 9 cases of valvular disease, 9 cases of essential hypertension and 12 cases of coronary heart disease. Five healthy persons, nearly age-matched, were used to serve as a control. Ko 1366 (by Boehringer), O-[2-Hydroxy-3-(tertiary butylamino)-propoxy]-benzonitrile hydrochloride, was used as a β-blocker. An exercise on the bicycle ergometer (25 Watt,
Sympathetic Activity in Cardiovascular Disease

Fig. 3.

Fig. 4.

40 r.p.m., for 5 minutes) was taken, blood pressure, pulse rate, cardiac output and excreted CA in each urine secreted in one hour being measured before and after it. After one-hour's rest, the β-blocker, Köl366 was injected intravenously at the rate of 50 mcg/10 kg, and 10 minutes later, a similar exercise was taken, each hemodynamic index and the urinary excretion of CA being measured by the same method as stated above.

Cardiac output was measured by dye-dilution method, using diagnostan green. Total peripheral resistance (dyne sec. cm⁻⁵) was obtained as - mean blood pressure (mmHg) × 80/cardiac output (L/min); and cardiac effort index¹⁰ (shortened as CEI in the following) as - heart rate X mean blood pressure. Ischemic changes on ECG were estimated by Master's Criteria¹¹

RESULTS

(I) Pilocarpine test (Figs. 1 and 2): Pulse rate revealed significant increase in every group, and there was no difference in the modes of increase in the four groups. Blood pressure was elevated slightly but insignificantly in a control, and a significant increase was shown in both systolic and diastolic blood pressure on the hypertension group, and in only systolic blood pressure on the coronary-heart-disease group, almost no change being shown on the valvular-disease group. On the urinary excretion of CA, adrenaline (shortened as Ad in the following) was increased significantly in the valvular-disease group, and slightly but insignificantly in the hypertension and coronary-heart-disease groups. NA was increased significantly in every group, and it was valued a little larger in the valvular-disease, coronary-heart-disease and hypertension groups, than that in a normal control. In these and the following figures, a solid line means one showing significant difference, and an interrupted line means one showing no significant difference.

Noradrenaline test (Figs. 3 and 4): Pulse rate was decreased slightly, but by no significant difference, in every group. Both the systolic and diastolic blood pressure levels were elevated in the hypertension and coronary-heart-disease groups, but changed only slightly in a normal control and the valvular-disease groups. On the urinary excretion of CA, the amount of NA increased naturally, but no significant difference was demonstrated, its per-cent increase being

*Japanese Circulation Journal Vol. 38, March 1974*
about 2–2.5% of the administered dose of NA in each group.

Exercise test (Figs. 5 and 6): Pulse rate was increased significantly in every group. Both the systolic and diastolic blood pressure levels were increased significantly in the hypertension and valvular-disease groups, only the systolic level was increased significantly in the coronary-heart-disease group, and each level was increased slightly but insignificantly in a normal control. As to the urinary excretion of CA, it was increased slightly but insignificantly in a normal control, significantly in the valvular-disease and coronary-heart-disease groups, and only slightly in the hypertension group by no significant difference from that in a normal control.

In respect of ECG, ischemic depression was demonstrated by 2 in 8 cases on the P test, by 3 in 8 cases on the NA test and 4 in 8 cases on the exercise test in the coronary-heart-disease group, but no such changes on ECG was demonstrated on all the tests in the other three groups. As to CEI, it was elevated remarkably on every test in the hypertension and coronary-heart-disease groups.

(II) β-Blocker test:

Normal control: In the case of Fig. 7, both systolic and diastolic blood pressure levels were elevated 15 to 20 mmHg and pulse rate was increased 12/min, on the exercise. Stroke volume was increased about 20 ml/beat. In these hemodynamic changes due to the exercise, an increase in blood pressure and pulse rate was shown to tend to be suppressed by the β-blocker pretreatment, that of stroke volume, however, was not suppressed, being increased 18 ml/beat. During the rest before the exercise, the β-blocker showed almost no influence on blood pressure and pulse rate, but decreased stroke volume slightly, 4 ml/beat. As to the urinary excretion of CA, Ad was increased slightly, and NA increased significantly, after the exercise, a further increase being shown after the β-blocker administration.

Valvular disease: In the case shown in Fig. 8, blood pressure changed remarkably, estimated 44 mmHg increase in systolic blood pressure. Pulse rate was also increased remarkably, 54/min. Stroke volume was slightly decreased. In these hemodynamic changes due to the exercise, an increase in blood pressure was suppressed re-

*Japanese Circulation Journal Vol. 38, March 1974*
Sympathetic Activity in Cardiovascular Disease

Coronary heart disease: In the case shown in Fig. 10, the systolic and diastolic blood pressure levels were increased 40 mmHg and 21 mmHg respectively, pulse rate increased 38/min, and stroke volume was decreased slightly. In these hemodynamic changes due to the exercise, the increase in blood pressure and pulse rate was shown to tend to be suppressed by the β-blocker pretreatment, although stroke volume was shown free from being influenced. During the rest before the exercise, the β-blocker was shown not to act upon blood pressure or pulse rate, but to decrease stroke volume by 9 ml/beat. As to the urinary excretion of CA, Ad was increased 0.3 mcg, and NA 0.2 mcg after the exercise, a further increase being shown after the β-blocker administration.

Explanations on a typical case in each disease have been done above, and, now, the changes in blood pressure, pulse rate, cardiac output, total peripheral resistance and the urinary excretion of CA will be shown summed up in the following:

(1) Blood pressure (Fig. 11): On the exercise, blood pressure was increased remarkably in the three groups of hypertension, coronary

heart disease and valvular disease, compared with in a control. By the β-blocker pretreatment, the increase in blood pressure was suppressed less remarkably in the hypertension group, but suppressed remarkably in the valvular-disease group. In the coronary-heart-disease group, it was shown to stand in the middle of the former two groups.

(2) Pulse rate (Fig.12): On the exercise, pulse rate was shown increased in all the four groups, most remarkably in the valvular-disease group, next in the coronary-heart-disease group, and by still smaller degree, than that in the former two, in the hypertension group, where any significant difference, from that in a control, was not noted. By the β-blocker pretreatment, the increase in pulse rate was suppressed less strongly in the valvular-disease group than that in a control, in the hypertension and coronary-heart-disease groups.

(3) The urinary excretion of CA (Figs. 13 and 14): In the valvular-disease group, the urinary excretion of both Ad and NA was increased significantly. In the hypertension and coronary-heart-disease groups, the urinary excretion of CA before the exercise was shown normal, after the exercise being shown slightly but insignificantly greater than that in a control. After the β-blocker pretreatment, the urinary excretion of CA was increased by the exercise in the valvular-disease, coronary-heart-disease and hypertension groups, especially greatly in the former two groups.

(4) Cardiac output (Fig. 15): During the rest, cardiac output was shown about 5.0 L/min equally in the four groups with no difference being noted, and the similar tendency was shown after the β-blocker administration. By the exercise, cardiac output was increased almost evenly in all groups except for the valvular disease group which showed slightly lesser increase in comparison with the other three groups. After the β-blocker pretreatment, the increase in cardiac output by the exercise was reduced in the valvular disease and coronary-heart-disease groups.

(5) Total peripheral resistance (Fig.16): During the rest, total peripheral resistance was shown higher by about 600 dyne sec. cm⁻² in the hypertension group, and by about 300 dyne sec. cm⁻² in both the coronary-heart-disease and valvular-disease groups than that in a control. By
the exercise, total peripheral resistance was shown to fall, but compared with that in a control, it was shown to remain still high in the three groups with underlying diseases. After the \( \beta \)-blocker administration, both total peripheral resistances before and after the exercise were estimated high in the three groups with underlying diseases, showing same tendency to them before the administration. By the exercise after the \( \beta \)-blocker administration, total peripheral resistance fell less greatly, than that in a control in the hypertension and coronary-heart-disease groups.

**DISCUSSION**

It seems clear from many previous reports, that the marked augmentation of the sympathetic activity was induced by an appearance of heart failure, especially by a severe one, being caused by various sorts of underlying factors, contributing to the maintenance of cardiac function in a resting or exercising patient.

In the present paper, it is studied; on what state the sympathetic activity stands when the cardiac function is slightly lowered; how the sympathetic activity responses to the emotional and physical stresses which can be expected in a daily life; and whether the effects of the changes in sympathetic activity on the hemodynamics differ or not in regard to the sort of underlying disease responsible for cardiac failure. With these purposes, the changes in hemodynamics were tried to be demonstrated, as well as the changes in sympathetic activity by the same occasion, which were detectable by measuring the urinary excretion of CA. And the following tests were carried out; first, a constant exercise was taken to induce a physiological elevation in the sympathetic activity, second, a constant amount of P was administered to increase endogenous CA in response, and as a third, a constant amount of NA was administered as exogenous CA. As P induces the excitement of the sympathetic nerve center in response, the excitability of this center and responsiveness of cardiovascular system to endogenous CA are able to be shown\(^{12}\) As NA acts directly on the cardiovascular system, the reactivity of the cardiovascular system can be
Fig. 13. The effects of β-blocker on exercise-induced changes in the urinary excretion of CA.

Fig. 15. The effects of β-blocker on exercise-induced changes in the urinary excretion of CA.

Fig. 14. The effects of β-blocker on exercise-induced changes in the urinary excretion of CA.

Fig. 16. The effects of β-blocker on exercise-induced changes in total peripheral resistance.

*Japanese Circulation Journal Vol. 38, March 1974*
easily observed. Furthermore, the effects of β-blocking agent on hemodynamic changes induced by the exercise can show how much extent the sympathetic activity exerts the influence on the cardiovascular functions. With these aimsings, valvular disease, hypertension and coronary heart disease were selected out, and the responses in the sympathetic activity and hemodynamics to various tests mentioned above were studied, the results being to be examined by each case of disease in the following.

In the case of valvular disease, though the studied cases were ones estimated Class I and Class II to according to the functional classification by NYHA, the amount of the urinary excretion was demonstrated greater than that in a control, and by this fact it will be indicated that the patients are already in the sympathicotonic state even at rest. The increase in urinary excretion of CA resulting from the induced excitement of the sympathetic nerve center by the P administration was significantly greater than that in a control. This fact will suggests, about the state of valvular disease, that the excitement in the sympathetic nerve center and the following sympathetic hyperactivity can easily be induced. The increase in the urinary excretion of CA by the exogenous NA administration in valvular disease did not differ from that in a control, and this suggests that the uptake of the circulating CA into tissues, and the metabolism of CA in tissues and blood, as well as other functions are not different from those in a control.

As to the hemodynamic responses produced by the NA administration, a decrease in pulse rate in valvular disease did not show significant difference from that in a control, but an increase in blood pressure, which showed no difference from that in a control, was characterized by being smaller than that in the hypertension and coronary-heart-disease groups.

It is recognized by Kroner that the reactivity of the peripheral vascular bed to NA is elevated in heart failure. And yet the increase in blood pressure due to NA in the valvular-disease group did not differ significantly from that in a control, but was shown significantly smaller than that in the hypertension and coronary-heart-disease groups. These facts will suggest that the reactivity of a failing heart to CA has not been elevated. Tomomatsu et al. pointed out the sympathetic hyperactivity demonstrated by the increase of CA levels in blood and urine and the decrease in myocardial stores of CA when heart failure occurred. In such a case, the reactivity of the peripheral sympathetic receptors is expected normal or rather depressed. These facts are clear contrast with the phenomena that hypersensitivity to CA are observed in the state of the markedly decreased contents of CA in tissues and blood after reserpine pretreatment. In a failing heart, the depressed adenyl cyclase activity causes a decrease in the production of 3', 5' cyclic AMP, that is, the second messenger of CA, and this leads to a reduction in the positive inotropic response to CA. Furthermore, the efficiency in converting the myocardial tension into useful circulating work is kept depressed by such geometric factors as ventricular size, shape, and thickness. It may also be expected that these biochemical and mechanical factors cause a decrease in the reactivity of a failing heart to NA.

As to changes on the exercise, the significant increase in the urinary excretion of CA suggests the increase in the activity of the sympathetic nerve center in heart failure. Similar reports were presented by Jiri and Chidsey et al. This shows good concurrence with the results in the P test stated above. And it might be taken as one of the mechanisms to maintain homeostasis against the depression of reactivity to NA in a failing heart. As to the changes in blood pressure, it may give a queer impression that blood pressure was elevated significantly by the exercise although the reactivity of the heart to NA was not shown increased in the valvular-disease group. It is said, however, that the NA secretion from the sympathetic nerve endings, responsible for the control of blood vessels, is increased in heart failure by the tyramine administration more greatly than in a normal case, and this causes a stronger response in elevating blood pressure. And the blood-pressure-elevating response to the exercise is also expected to be augmented through a similar mechanism.

As to the changes in cardiac output, the increase in cardiac output by the exercise was not so great as that in a control, although the cardiac output before the exercise was almost the same as that in a control. Here considering the significant increase in CA secretion, this result also suggests that cardiovascular response to CA is depressed in a failing heart. In regard to the mechanisms of depressing the response to CA in a failing heart during the exercise, it is also expected, as a third mechanism, that decrease in

*Japanese Circulation Journal Vol. 38, March 1974*
myocardial stores of NA in a failing heart causes the reduction in the sympathetic-nerve-center stimulated NA release from the myocardial sympathetic nerve endings\textsuperscript{19} in addition to the above-stated two mechanisms, that is, the reduction of the efficiency in converting myocardial tension into useful circulatory work, and the depression of the 3', 5' cyclic AMP production resulting from the reduced adenyl cyclase activity.

Almost the same marked increase in heart rate was shown by the exercise after the $\beta$-blocker pretreatment in valvular disease, as was shown before the administration (that is, an increase by the exercise was not suppressed by the $\beta$-blocker administration). Stroke volume was, on the other hand, not shown increased, and this will mean that the increase in cardiac output by the exercise in valvular disease depends upon the increase in heart rate rather than the increase in stroke volume, the latter being observed in a control. The increase in pulse rate was less suppressed by the $\beta$-blocker administration than in a control, and it will suggest the possibility of the decreased parasympathetic inhibition or of another pacing mechanism than that by the $\beta$-adrenergic system. This result, too, means that an increase in heart rate is necessary to maintain the cardiac function during the exercise. As to cardiac output, though a further increase in CA secretion by the exercise was induced by the $\beta$-blocker administration, the increase in cardiac output was reduced on the contrary. On the other hand, concerning the myocardial stores of CA, it is regarded by Ueba\textsuperscript{20} that myocardium of the failing heart fails to increase CA stores with $\beta$-blocking agent as great extent as the normal. It is indicated that CA is an important factor in maintaining the cardiac function.

The simplest way to determine whether CA plays a causative role in essential hypertension or not is to measure the urinary excretion of CA and the metabolites in hypertension and in a normal control, because the measurement of the urinary excretion of CA and the metabolites presents the most proper index to understand a whole sympathetic activity in vivo. According to the reports on this respect by other investigators, it is generally concluded that the sympathetic activity as a whole in vivo will not be elevated in hypertension\textsuperscript{21,22} for no significant difference in the amounts of the urinary excretions of Ad, NA and their metabolites during the rest is noted between hypertension and normal control. It was reported by Ikoma\textsuperscript{23} however, that the urinary excretion of CA was observed high in cases of labile hypertension showing no renal disturbances. But he also reported that, in the cases having long history of hypertension or strong disturbances in vessels, no significant difference in the amount of the urinary excretion of CA was able to be pointed out, in comparison with that in a control. The above-mentioned reports by many investigators were on the urinary excretion of CA and the metabolites during the rest. As to it, present study, as well as those by other investigators, gives no significant difference in it between in hypertension and in a control.

Our daily life, however, is filled with continuous physical and emotional stresses, and considerations on these common and frequent factors to stimulate the CA secretion will make it essentially necessary to examine the influences of such stresses upon hypertension. Further, the level of the sympathetic activity and the responses upon it cannot be regarded evenly equal in each site of the body even if the level of the sympathetic activity is observed normal.

In the hypertension group, the amount of the urinary excretion of CA on the P or exercise test was slightly greater than that in a control, but with no significant difference. Recently, many reports suggested that the sympathetic activity tends to be easily stimulated by physical or emotional stresses in labile slight hypertension\textsuperscript{24–28} Present report, referring to slight to moderate hypertension, also suggests the possibility of the phenomenon similar to these reports by other investigators. When I take in into consideration, however, that there is some difference in the hemodynamic responses to the exogenous NA administration between in present cases and in a normal control, it may be said significant elevation in blood pressure by the P or exercise test does not depend merely on the abnormally augmented activity of the sympathetic nervous system including the sympathetic nerve center. That is, because, blood pressure was remarkably elevated, though the exogenous-NA metabolism was able to be regarded as normal, according to the urinary excretion of CA before and after the NA administration. This fact suggests the increased vascular reactivity to CA in essential hypertension and coincides with Miyahara's report\textsuperscript{29} In this respect, it must be discussed whether the increased reactivity depends on a organic change in the vessel wall and/or on biochemical factors.

\textit{Japanese Circulation Journal Vol. 38, March 1974}
Folkow’s theory conflict with the present results that show the lowered reactivity to NA in coronary heart disease than that in hypertension, because he postulated increased wall-to-lumen ratio was responsible for the vascular hyperreactivity. Furthermore, many reports by other investigators show a normal reactivity to NA in renal and renovascular hypertension or Raynaud’s disease in every case of which the wall-to-lumen ratio is also increased, and these results suggest the necessity to consider biochemical factors as well as the organic change as the cause of an increase vascular reactivity in hypertension. Then, what are the so-called biochemical factors to elevate the vascular reactivity to NA —it is the main point of interest in the pathogenetical relationship between hypertension and CA. According to the increased urinary excretion of H1-NA, Gitlow et al. consider, as one of the biochemical factors, the disturbance in NA-reuptake, which causes an elevated vascular reactivity. There is, however, also some objection to their theory and good agreement is not yet established in this respect.

As to the results in hemodynamic changes by the exercise in hypertension, the increase in cardiac output was not so different from that in a control or in coronary heart disease, but the elevation in blood pressure was more remarkable not only than that in a control but also in coronary heart disease. The decrease in total peripheral resistance was, then, shown not so large as that in a control. On the β-blocker administration, the increase in pulse rate and cardiac output by the exercise was suppressed by the almost equal degree to that in a control, but almost no suppression was shown in the blood-pressure elevation, and the decrease in total peripheral resistance was smaller than that in a control. These results mean that, in the case of hypertension, cardiac inotropic and chronotropic responses are suppressed by a β-blocker, but α-receptors on peripheral vessels remain intact, or still at the hyperactivity. Nicotero also expects the possibility of hyperactivity of α-receptors in hypertension.

According to the demonstration of elevated blood pressure due to the β-blocker administration in spontaneously hypertensive rats (shortened as SHR in the following), Tabei et al. reported that the peripheral vascular factors are more deeply responsible for hypertensive mechanisms rather than the cardiac factors in SHR, the sensitivity of α-receptors being augmented relatively more high than that of β-receptors. Mori also recognized the augmented sensitivity of α-receptors in SHR. Recently, it is also reported that the cerebrovascular disturbances are observed in SHR as seen in clinical cases, and the CA metabolism in the organs of SHR is similar to that of heart failing rabbits, a similar pattern of CA metabolism being reported by Champlain also in hypertensive rats treated with DOCA-NaCl. The close relationship between the origination of hypertension and the sympathetic activity is expected.

In the coronary-heat-disease group, no significant difference, from that in a control, was shown in the amount of the urinary excretion of CA, suggesting that the sympathetic activity is nearly normal. Clinically, it is generally observed that emotional or physical stresses exist prior to the ischemic changes on ECG or the onset of the anginal attacks. So, to understand the sympathetic activity pathophysiologically in coronary heart disease, it is necessary to make observation both on responsiveness in the sympatho-adrenal system and on changes in the hemodynamics, which are expected to be induced by stress given on the object.

On observation on the responsiveness to the P and exercise tests, the increase in the amount of the urinary excretion of CA was shown greater than that in a control, and this will suggest that the responsiveness of the sympathetic nervous system to stress is more easily elevated in coronary heart disease than that in a control. This result coincides with the reports demonstrating elevated responsiveness of the sympatho-adrenal system to stress in coronary heart disease.

As to the hemodynamic responses, they were observed remarkably large in coronary heart disease, compared with them in a control, either to the P administration or to the NA administration at a dose equivalent to make the same NA concentration in blood as is shown during the anginal attack or to the exercise. These results also revealed that elevation of CEI, one of the indices for cardiac work, was significantly greater in coronary heart disease than that in a control and valvular disease, being nearly equal to that in hypertension. Considering the great influence of the amount of cardiac work on myocardial oxygen requirement, it indicates a significant increase in myocardial oxygen requirement in coronary heart disease compared with that in a control.
Hitherto, it is known that the increased index for cardiac work is relative to the onset of an anginal attack, regardless of the inducing condition or procedure. And recently, Wiener reported that an increase in cardiac work exists prior to the onset of an anginal attack. Each patient needs his own fixed level of an increase in cardiac work to induce an anginal attack, and an attack occurs when an increase in cardiac work has exceeded the critical level. Recently a similar observation was established on electrocardiographical changes, which exists prior to the anginal attack. In coronary heart disease, diseased coronary arteries will naturally set the critical level lower than that in a normal control or in hypertension, and this will explain the myocardial ischemia induced even by the physiological dose of NA or by the exercise in some cases of coronary heart disease, no such phenomenon being demonstrated in the cases of hypertension and valvular disease, needless to say in a normal control. These facts suggest that the physiological range of the amount of NA can cause the same disease state as a spontaneous attack or exercise-induced myocardial ischemia, and that there are important factors in the sympatho-adrenal system to cause myocardial ischemia in the daily life.

As to the changes in these responses after the β-blocker pretreatment, decreases in pulse rate and stroke volume were observed even when the exercise was not yet taken, and the increases both in blood pressure and pulse rate by the exercise were suppressed. These results will be explained by the increase in the sensitivity of receptors, which augment the effect of the β-blocker, even if the amount of the urinary excretion of CA as an index for the sympathetic activity is in a normal range during the rest. As its suppressing effect is remarkably great during the exercise, the β-blocker seems to be of clinical use in preventing an anginal attack.

**SUMMARY**

On cases with valvular disease, essential hypertension and coronary heart disease, each of which has a cardiac function estimated Class I and Class II according to the functional classification by NYHA, the reactivity of the sympathetic nerve center to the endogenous or exogenous stimulation, and the responses in the cardiovascular system to the induced sympathetic hyperactivity were studied, and the following results are obtained:

(A) Valvular disease

1. A sympathicotonic state was shown even during the rest, and the reactivity of the sympathetic nerve center to various stimuli was augmented.

2. The responsiveness of a failing heart to CA was normal or lowered. This leads to an increase in the CA secretion as a homeostatic mechanism.

3. Despite the increase in the CA secretion, cardiac output during the exercise was less greatly increased than that in a control. As to the β-blocker administration, the increase in the CA-secretion by the exercise was augmented but that in cardiac output was suppressed conversely by the β-blocker. These facts will mean that CA plays an important role in the regulatory mechanism in a failing heart, limits having been naturally set to its effects.

4. The suppressing effect of the β-blocker on the tachycardia caused by the exercise was not so great as that in a control, in hypertension, or in coronary heart disease. The changes in stroke volume by the exercise were slight, regardless of being pretreated by the β-blocker or not. In a failing heart, pulse rate plays an important role in maintaining the cardiac output. And it will be understood as a compensatory mechanism to maintain the cardiac output that the increase in heart rate by the exercise is not easily suppressed by the β-blocker. The heavy suppression of the increase in heart rate may, therefore, possibly induce aggravation of heart failure.

(B) Essential hypertension

1. The sympathetic activity during the rest was normal, and the responsiveness of the sympathetic nerve center to various stimuli was slightly but insignificantly higher than that in a control.

2. The reactivity of the peripheral vascular system to the exogenous or endogenous sympathetic stimulation was demonstrated greater than that in coronary heart disease as well as than that in a control.

3. The increase in blood pressure by the exercise was suppressed by the β-blocker not so greatly as that in a control or in the other disease groups.

4. The increase in stroke volume by the exercise was suppressed only slightly by the β-blocker.

From above, it indicates that the α-receptors in the peripheral vascular beds are on a hypersensitive state, and, furthermore, the sympatho-adrenal system may participate greatly in the pathogenesis of essential hypertension.

*Japanese Circulation Journal  Vol. 38, March 1974*
(C) Coronary heart disease

1. The reactivity of the sympatho-adrenal system to endogenous or exogenous stimuli was elevated.

2. Augmented hemodynamic responses to CA were demonstrated, and the oxygen-requirement as well as cardiac work was liable to be increased, and even an amount of NA within a physiological range can also cause a similar diseased state to exercise-induced myocardial ischemia.

3. The response of the cardiovascular system to the exercise was suppressed by the β-blocker.

These results suggest that the sympatho-adrenal system plays an important role in myocardial ischemia and that the β-blocker is of clinical use in preventing an anginal attack.

On cases of valvular disease, essential hypertension and coronary heart disease, the reactivity of the sympathetic nerve center, and the corresponding changes in the sympathetic activity, as well as the reactivity of the cardiovascular system, were studied. Each of them in one of the three underlying diseases was demonstrated to differ from those in other underlying diseases. Under these observations, as well as the observation on the changes caused by the β-blocker, the differences in pathophysiological significance of the sympatho-adrenal system were also demonstrated.

Acknowledgement

The author is grateful to Prof. T. Tomomatsu for his kind guidance and express many thanks to Drs. Y. Ueba, M. Oda, H. Kogame, T. Yao, Y. Ito, Y. Yamamoto, K. Mori, and H. Tanimoto.

REFERENCES


20. UEBA, Y.: to be published.


