STROKE-PRONE SHR (SHRSP) AS MODELS FOR CLINICAL AND EPIDEMIOLOGICAL STUDIES ON HYPERTENSION-RELATED CARDIAC DISEASES IN HUMANS

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R ecent epidemiological studies on cardiovascular diseases indicate that hypertension is a major risk factor not only for cerebral stroke but also for ischemic heart diseases such as myocardial infarction and angina pectoris. Essential hypertension has become prevalent to the extent that cerebral accidents and ischemic heart diseases are the major causes of death both in Japan and in Western countries, respectively. In making comparisons between these conditions in Japan and Sweden, the age-adjusted death rates are 165.9 for cerebral stroke and 39.0 for ischemic heart diseases in Japan, while in Sweden the rates are 58.1 for cerebral accidents and 195.2 for ischemic heart diseases, respectively, as calculated in terms of 100 thousands persons.

In Japan, the incidence or death rate of cerebro-cardiovascular diseases is geographically and occupationally related. For example, in rural areas such as Akita Prefecture, where the traditional livelihood and dietary habits have changed little, the prevalence and incidence of hypertension and cerebral stroke are the highest in all Japan. However, it must be noted that in these patients the serum total cholesterol levels were lower and obesity indices smaller than those living in urbanized areas such as Osaka City. There the incidence of stroke is far lower, while the incidence of ischemic heart disease is 4 times higher than in Akita. These epidemiological results suggest the etiological difference between the cerebral stroke and the ischemic heart diseases.

In an attempt to determine the relationship between cerebral stroke and ischemic heart diseases, studies were done using spontaneously hypertensive rats (SHR) and stroke-prone SHR (SHRSP) as models. SHRSP with severe hypertension and a high incidence of stroke showed lower serum total cholesterol levels and smaller body weight. Moreover, a high-fat-cholesterol diet rather prevented cerebral stroke in SHRSP. In these respects SHR may be regarded as the appropriate model for prevalent types of the hypertensive in Japan.

MATERIALS AND METHODS

Experiment 1

Vectorcardiographical and pathological studies were done on hearts of 4 groups of male normotensive Wistar-Kyoto rats (WK), from which spontaneously hypertensive rats (SHR) had been derived, SHR, and stroke-prone SHR (SHRSP). In adult SHRSP with a blood pressure of over 200 mmHg, cerebral stroke developed spontaneously in over 80% of all the animals. Classification of the 4 groups is given in Table I.

Vectorcardiography for small animals such as rats was carried out according to the Takayasu
TABLE I  AGE, BODY WEIGHT AND HEART WEIGHT IN 4 EXPERIMENTAL GROUPS

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Animals</th>
<th>Age (days)</th>
<th>Body Weight (g)</th>
<th>Heart Weight (g)</th>
<th>Heart Weight per g Body Weight ( \times 10^3 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>adult WK</td>
<td>10</td>
<td>143 ± 5</td>
<td>349 ± 20</td>
<td>1.16 ± 0.08</td>
<td>3.31 ± 0.11</td>
</tr>
<tr>
<td>adult SHR</td>
<td>10</td>
<td>154 ± 2*</td>
<td>292 ± 7**</td>
<td>1.31 ± 0.09*</td>
<td>4.51 ± 0.10**</td>
</tr>
<tr>
<td>old WK</td>
<td>10</td>
<td>375 ± 15***</td>
<td>400 ± 14**</td>
<td>1.40 ± 0.05*</td>
<td>3.50 ± 0.18**</td>
</tr>
<tr>
<td>old SHRSP</td>
<td>10</td>
<td>415 ± 21++</td>
<td>275 ± 18***</td>
<td>1.97 ± 0.14***</td>
<td>7.42 ± 0.44***</td>
</tr>
</tbody>
</table>

WK: Wistar-Kyoto rats, SHR: Spontaneously Hypertensive Rats, and SHRSP: Stroke-prone SHR.
Values represent mean ± SE. Statistically significant difference from adult WK (*: 0.01 < p < 0.05,
**: p < 0.01), from old WK (***: p < 0.01), and from adult SHR (++: p < 0.01).

Fig.1. Coronary angiogram of the rat.
R.C.A.: Right coronary artery, L.C.A.: Left coronary artery,
A.D.B.: Anterior descending branch, C.B.: Circumflex branch,
S.B.: “Large septal branch” specific in the rat.

lead system\[^{18,19}\] Six electrodes consisting of 2 small ones (placed at the head and the tail) and 4 large ones (placed at the front and back, right and left sides of the chest) were used, and orthogonal 3 axes — X, Y, Z — configurated 3 planes, frontal, left sagittal and horizontal planes. Vectorcardiogram (VCG) was recorded by a memory vectorcardiography, MVC-40 (Nihon Kohden). To obtain a close, secure attachment of the electrode plate, the hair of the rat was neatly cut and a
Rats were anesthetized with ether inhalation, and allowed to breathe freely by means of a cannula inserted into the trachea through a trachotomy incision. By means of thoracotomy through the third or fourth intercostal space, (using a rib retractor), the pericardium was opened with care and the anterior descending branch of the left coronary artery was ligated by passing a fine needle suture (ELP) around it at the height of the lower rim of the left atrium (Fig. 1). Thoracotomy alone was done in cases of sham operation.

VCG was followed up in each rat from 1 hour after the operation until the rat was sacrificed a few days later. The heart was then histopathologically examined.

Experiment IV

About 200 SHRSP were autopsied after a natural death, and the vascular and tissue lesions in the brain, the heart and the kidney were microscopically examined following staining with hematoxylin-eosine.

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**TABLE III QRS AND P DURATIONS, AND PQ INTERVAL**

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Animals</th>
<th>QRS Duration (msec)</th>
<th>P Duration (msec)</th>
<th>PQ Interval (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>adult WK</td>
<td>10</td>
<td>18 ± 0</td>
<td>19 ± 1</td>
<td>48 ± 1</td>
</tr>
<tr>
<td>adult SHR</td>
<td>10</td>
<td>21 ± 0**</td>
<td>22 ± 1**</td>
<td>50 ± 2</td>
</tr>
<tr>
<td>old WK</td>
<td>10</td>
<td>19 ± 1*</td>
<td>20 ± 1</td>
<td>50 ± 2</td>
</tr>
<tr>
<td>old SHRSP</td>
<td>10</td>
<td>26 ± 1**+++</td>
<td>24 ± 1***+++</td>
<td>55 ± 2***</td>
</tr>
</tbody>
</table>

WK, SHR and SHRSP: Refer to Table I.
Values represent mean ± SE.
Statistically significant difference from adult WK (*: p<0.05, **: p<0.01) and from old WK (++: p<0.01).

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Experiment II

Five each of 2-month-old male WK and SHRSP were vectorcardiographically followed up until 1 year of age, the objective being the observation of the changing process of the QRS vector.

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Experiment III

The surgical treatments - the ligature of the coronary artery for inducing myocardial infarction and the sham operation were respectively given to 2 groups of five 6-month-old male WK, in a clean but not aseptic manner.20

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thin cotton mat wet with saline solution was placed between the skin and the plate. The rats were anesthetized with pentobarbital (40 mg/kg, i.p.) and placed in a prone position. The animals were inside 4 transparent plastic walls and had large electrode plates around the trunk during the recording of VCG.

After the VCG, the rats were sacrificed and the heart weight were measured. Then, the heart was microscopically observed following staining with hematoxylin-eosin (H-E).

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RESULTS

Experiment I

The hearts of adult (5-month-old) male WK and SHR, and old (over 1-year-old) WK and SHRSP, 10 of each, were studied vectorcardiographically and pathologically. The results are summarized in Table I–III, and a typical VCG of each group is shown in Figs. 2–5. The heart weight, particularly the body weight-adjusted heart weight was significantly increased in adult SHR and old SHRSP as compared to adult and old WK, respectively (Table I).

As for vectorcardiographical findings, the so-called LVH (Left Ventricular Hypertrophy) pattern of SHR — left superior (posterior) orientation of major QRS portion usually with ST-T changes — was noted in all adult SHR and in 8/10 of the old SHRSP, respectively. Magnitude of maximum (max.) QRS vector in the frontal plane tended to be greater in adult SHR and old SHRSP than adult and old WK, respectively, although there was no statistically significant difference. The configurations of QRS vectors in old SHRSP showed irregularity or deformity with deviation, in which the left superior orientation of major QRS vector was not necessarily clearly observed as in adult SHR (Fig. 5). Such a deformity with deviation of QRS vector in old SHRSP corresponded well to the pathological findings of the infarction-like myocardial fibrosis as shown in Figs. 6 and 7. QRS and P durations, and PQ interval were also measured. Both of QRS and P durations

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were significantly prolonged in adult and old SHRSP, as compared to adult and old WK, respectively. The PQ interval was longest in old SHRSP (Table III).

Experiment II

The changing process of the QRS vector in SHRSP is shown in Fig. 8, and here the VCG at the age of 5 months had characteristically changed 4 months later. The latter VCG indicated the deformity and deviation of QRS vector with predominantly prolonged QRS duration, compared
Fig. 7. Ventricular map — Localization of myocardial fibrosis in old SHRSP. The same material as shown in Figs. 5 and 6.

Fig. 8. Changing process of the QRS vector shown in the same material of SHRSP. (Cal. 1mV.)
(a) At the age of 5 months.
(b) At the age of 9 months.

Fig. 9. VCG of the artificial acute myocardial infarction in the rat. (Cal. 1mV.)
(a) Preoperation.
(b) At 90 min. after operation.
(c) At 48 hours after operation.

with the former VCG.

Experiment III
In all the WK in which the coronary artery had been ligated showed deformity and deviation of QRS vector and ST-T elevation in scalar electrocardiogram (ECG) even 90 min. after the operation (Fig. 9). Such was never seen in the sham-operated WK (Fig. 10). These vectorcardiographical findings in the coronary-ligated WK well corresponded to the pathological findings of the heart, massive myocardial necrosis with slight fibrosis as shown in Figs. 11 and 12.
Experiment IV

Incidences of the organ lesions — cerebral stroke, nephrosclerosis and myocardial fibrosis — in SHRSP were obtained in 200 autopsy cases following a natural death (Figs. 13 and 14). The results are summarized as follows: (1) Such organ lesions were age and sex dependent, (2) Cerebral stroke was rarely seen alone and was usually accompanied by myocardial fibrosis and/or nephrosclerosis, (3) Coexistence of these 3 types of organ lesions increased with age, while the incidences in which these 3 organs remained simultaneously intact became less, nearly 0% at last at about 1 year of the age (Fig. 14). (4) According to increase in the incidence for myocardial fibrosis, the incidences of organic changes of the coronary artery — wall thickening and thrombosis increased. Thrombosis of the coronary artery was observed from 5 months of the age until the incidence reached over 20% at about 1 year of age. This thrombosis was usually observed in the bifurcated smaller branches (Fig. 6).

DISCUSSION

Characteristic vectorcardiographical and pathological findings of the heart were obtained from adult SHR and old SHRSP and compared

Fig.10. VCG of the rat sham-operated against the artificial acute myocardial infarction. (Cal. 1mV.)
(a) Preoperation.
(b) At 90min. after operation.

Fig.11. Histological findings of the artificial acute myocardial infarction in the rat. Forty-eight hours after the operation. Myocardial necrosis is accompanied by inflammatory cell infiltration. The same material as shown in Fig.9.
with adult and old WK, respectively. Particularly in old SHRSP, deformity and deviation of QRS vector corresponded well to degeneration or fibrosis of the myocardium, in which the wall thickening with narrowed lumen or the thrombosis of the coronary artery was also observed. The former organic change of the coronary artery was noted even in the prehypertensive state in SHR as well as cardiac hypertrophy indicated by the slight increase of the heart weight or the vectorcardiographical LVH pattern.

The distinguished prolongation of QRS duration in old SHRSP may be reflected by the aggravated left ventricular hypertrophy or the dilated left ventricular cavity. Prolongation of P duration in adult SHR and old SHRSP suggests a dysfunction of the left atrium due to the volume or pressure overload to the left atrium and that there is tendency toward heart failure in adult SHR with severe hypertension. This may be also supported by the fact that the left atrial thrombosis is often observed, in addition to liver enlargement, pleural effusion, general edema etc. (Figs. 15 and 16), in the status of heart failure in old SHR.

From the results of Experiment III, deformity and deviation of QRS and ST-T vectors in VCG, or deep Q wave and predominant ST-T elevation in the scalar ECGs of X, Y and Z were ascertained to correspond to myocardial organic changes, necrosis or fibrosis. These vectorcardiographical and pathological features in the artificial myocardial infarction of the rat also corresponded to those of acute myocardial infarction in humans.

In Experiment II, the infarction-like myocardial fibrosis in SHRSP could be clearly detected vectorcardiographically when the rats were about 1 year of the age. This myocardial lesion was known to develop progressively with ageing, but

### TABLE IV

**CHARACTERISTICS OF ELECTRO- AND VECTORCARDIOGRAPHIC PATTERNS OF SHR, COMPARED WITH THOSE OF LEFT VENTRICULAR HYPERTROPHY AND MYOCARDIAL INFARCTION IN HUMANS**

<table>
<thead>
<tr>
<th>Left Ventricular Hypertrophy in Humans</th>
<th>Corresponding Findings in SHR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ECG</strong></td>
<td></td>
</tr>
<tr>
<td>Left axis deviation</td>
<td>Predominantly observed</td>
</tr>
<tr>
<td>High R in left chest leads</td>
<td>Often observed in left chest leads and extremity leads</td>
</tr>
<tr>
<td>ST-T changes (ST depression, T inversion)</td>
<td>Usually observed</td>
</tr>
<tr>
<td><strong>VCG</strong></td>
<td></td>
</tr>
<tr>
<td>Increased spatial QRS vector</td>
<td>Often observed</td>
</tr>
<tr>
<td>Left (superior) posterior orientation of major QRS portion</td>
<td>Usually left superior (posterior) orientation is observed</td>
</tr>
<tr>
<td>Changes in ST-T vector</td>
<td>Usually observed</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Myocardial Infarction in Humans</th>
<th>Corresponding Findings in SHR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ECG</strong></td>
<td></td>
</tr>
<tr>
<td>Abnormal Q</td>
<td>Observed</td>
</tr>
<tr>
<td>ST-T changes</td>
<td>Observed</td>
</tr>
<tr>
<td><strong>VCG</strong></td>
<td></td>
</tr>
<tr>
<td>Lesion specific deviation and deformity of QRS vector</td>
<td>Characteristic deviation and deformity of QRS vector</td>
</tr>
<tr>
<td>Changes in ST-T vector</td>
<td>Observed</td>
</tr>
</tbody>
</table>

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rather gradually, compared with "sudden onset" of such acute myocardial infarction as presented in Experiment III. However, heart failure finally occurs in SHRSP as is shown in Figs. 15 and 16, even in cases where cerebral stroke does not occur.

Characteristic vectorcardiographical findings of SHR are summarized in Table IV and are compared with those of LVH and myocardial infarction in humans.

From Experiment IV, it was revealed that the organ lesions tended to accompany one another. In particular, cerebral stroke was rarely a sole manifestation, rather myocardial fibrosis and/or nephrosclerosis were accompanying disorders. These experimental results correspond to recent epidemiological reports that the electrocardiographical abnormality was one of the risk factors for cerebral stroke and to clinical studies in which electrocardiographical abnormalities were often
observed in patients with cerebral stroke. Therefore, electro- or vectorcardiogram is expected to be one of the parameters for determination of the prognosis of hypertension or one of the indices for predicting and preventing cerebral stroke as well as cardiac diseases.

As for the vascular changes in the organs, a specificity was noted. The arterial, particularly medial wall thickening or so-called "fibro-muscular arteriosclerosis" was the basic vascular change of SHR. Arterionecrosis, a typical vascular lesion seen in cases of severe hypertension in humans was manifested most often in the brain and then in the kidney in SHR. Interestingly, arterionecrosis was rarely observed in the coronary arteries.

The organ specificity of the vascular changes was also noted under the modified environment. That is, in 200 male SHRSP fed a high-fat-cholesterol (HFC) diet, containing 20% suet, 5% cholesterol and 2% cholic acid, for a short term (1–3 weeks), ring-like fat deposits were noted most clearly in the mesenteric artery and then in the cerebrobasal artery. Such was also noted in the intracerebral and intracranial arteries, however, only rarely in the coronary arteries, although a long term (over several months) HFC diet induced clear fat deposits in the coronary artery, microscopically detected under Sudan III staining (Fig. 17).

To determine the organ specificity, particularly of the heart, the degree of noradrenergic innervation was studied using fluorescence microscopy. Noradrenaline varicosities were most intense in the mesenteric artery and then in the cerebrobasal artery, however, were relatively few in the coronary arteries. On the basis of such experimental results, the answers for the above question may be summarized as follows: (1) difference in tissue surrounding the vessels, (2) difference in innervation of the vessels, and (3) difference of blood perfusion phase of the organ related to its function, that is, only in the pulsating heart are the coronary arteries mainly perfused in the diastolic phase. However, despite

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Fig. 14. Relationship among cerebral stroke, nephrosclerosis and myocardial fibrosis at the ages of 91–210 days, 211–330 days and 331–450 days in male SHRSP. The incidences in which these 3 types of organ lesions coexist increase with age (Brain-Heart-Kidney), while the incidences in which these 3 organs remain simultaneously intact decrease (No Particular Lesions).

Fig. 15. General edema due to congestive heart failure in SHR.

Fig. 16. Cardiac hypertrophy with thrombosis in the left atrium (arrow). Slight nephrosclerosis is noted, but the brain is intact.

Fig. 17. Fat deposit in the coronary artery in SHRSP fed a high-fat-cholesterol diet (Sudan III staining).

<table>
<thead>
<tr>
<th>TABLE V</th>
<th>AGEING PROCESS OF THE HEART IN SHR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Months)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Morphological Findings</strong></td>
<td></td>
</tr>
<tr>
<td>LVH</td>
<td>+?</td>
</tr>
<tr>
<td>Hyperplasia of cor. artery</td>
<td>+</td>
</tr>
<tr>
<td>Thrombosis of cor. artery</td>
<td>−</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>−</td>
</tr>
<tr>
<td><strong>VCG Findings</strong></td>
<td></td>
</tr>
<tr>
<td>Left axis dev.</td>
<td>+</td>
</tr>
<tr>
<td>ST-T changes</td>
<td>+?</td>
</tr>
<tr>
<td>Deformity and dev. of QRS loop</td>
<td>−</td>
</tr>
<tr>
<td>X-P CTR enlargement</td>
<td>/</td>
</tr>
<tr>
<td>Heart Failure (General Edema)</td>
<td>−</td>
</tr>
</tbody>
</table>

LVH: Left ventricular hypertrophy, VCG: Vectorcardiogram, CTR: Cardiothoracic ratio

such different features of the heart, thrombosis was often observed in the coronary arteries as well as in the cerebral arteries, particularly in old SHRSP (Fig. 6). Thus, disorders of the fibrinolytic and coagulation systems may occur in SHR.38–40

The ageing process of the heart in SHR is summarized in Table V. In these studies, a functional and morphological analysis was made of the importance of genetic hypertension and ageing in the case of myocardial lesions or "myocardial infarction" in SHR, as related to the lesions of the brain and the kidney. It has been also clarified that hypertension without hyperlipidemia can evoke "myocardial infarction", and such is considered to correspond to some types of myocardial infarction in humans. Thus, in the rural inhabitants of Akita Prefecture, myocardial infarction and scar with or without the obvious thrombosis of the coronary artery were noted in the autopsied materials from patients who were hypertensive but not hypercholesterolemic.2–4

From the results of these experimental and human pathological studies, and the comparative epidemiological studies, it is speculated that there are probably etiological differences in ischemic heart diseases between Japan and Western countries, as well as in case of cerebral stroke as mentioned in INTRODUCTION.

That is, as for hypertension and hyperlipidemia, the two major risk factors for cardiovascular diseases1–6 relatively speaking the former may affect the Japanese and the latter those in Western countries. The difference of the disease at the first-rank death rate, namely cerebral stroke in Japan and ischemic heart diseases in Western countries, respectively, may also support this idea.7

Recent advances in therapeutic medicine have established effective operative techniques for cardiovascular disorders, for example, the aorto-coronary bypass operation for myocardial infarction or angina pectoris.41 However, in the postoperative process, problems such as sclerosis or thrombosis of the grafted saphenous vein42 and the remaining available coronary arteries may occur. That is, even with surgical repair, "preventive" treatments for coronary arteriosclerosis, including the control of hypertension and dietary regulation are essential. Thus primary prevention and appropriate therapy must work hand in hand, particularly in dealing with the disorders of the circulatory system.

SUMMARY

Spontaneously hypertensive rats (SHR) and stroke-prone SHR (SHRSP) were vectorcardiographically and pathologically studied for myocardial lesions with left ventricular hypertrophy, and findings were compared with those in normotensive Wistar-Kyoto rats (WK).

Characteristic vectorcardiogram (VCG) in adult SHR was left superior (posterior) deviation of major QRS portion usually with ST-T changes, which corresponded to the pathological findings such as increased weight of the heart and the left ventricle. In old SHRSP, VCG showed deformity and deviation of QRS loop with prolonged P and QRS durations, and ST-T changes which corresponded to the pathological findings of myocardial degeneration or fibrosis with aggravated left ventricular hypertrophy.

Such myocardial lesions were vectorcardiographically followed up in the ageing process and compared with findings in cases of induced, acute myocardial infarction.

Vascular or tissue lesions of the brain, the kidney and the heart were clarified to be organ specific and to be related. Vector-or electrocardiogram are parameters for predicting cerebral stroke and/or ischemic heart diseases in humans.

Primary prevention and appropriate therapy should be concomitantly considered.

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