

Experimental Hypertension by Long-Term Cold Stress and Changes of Cardiovascular System

Masachika ISEKI

*Department of Pathology, Atomic Disease Institute,
Nagasaki University School of Medicine
Nagasaki, Japan*

Received for publication, May 15, 1985

Stress-induced hypertension was produced in rats by exposure to 4 ± 1 °C temperature from one month of age for one hour everyday over several months. Subsequently, significant changes of the cardiovascular system were observed in cold-stress rats. The present experiment used Sprague-Dawley rats (SD rats) and Wistar rats (W rats). There were a few differences between the two. In SD rats, angionecrosis of the coronary artery, fibromuscular sclerosis of the myocardial artery and PN-like lesion in the heart, kidneys and mesentery were observed. In W rats myocardial cell degeneration, fibrosis and mononuclear cell infiltration were detected and when compared to non-stress rats there was significant medial thickening of the myocardial artery under $100\mu\text{m}$ in stressed rats. The implications of exposure to cold in the analysis of cardiovascular pathology accompanied by stress-induced hypertension are discussed.

INTRODUCTION

The relationship between stress and hypertension is well known¹⁾. Since FARRIS *et al.*²⁾ reported that experimental hypertension was produced in rats by air blasting, reports of experimental hypertension induced by various kinds of stress have been presented¹⁾⁻¹³⁾. Pathological investigation of stress-induced hypertension was reported by HENRY *et al.*⁶⁾, LAWLER *et al.*⁷⁾, MARWOOD *et al.*⁸⁾, and so on though the numbers of those reports are few. We have reported that hypertension was produced in rats by using certain long-term stress e.g. "stick-poking harassment" and morphological changes were investigated⁹⁾⁻¹³⁾. In the present experiment, hypertension was produced in rats by exposure to 4 ± 1 °C temperature daily over several months and the changes of the cardiovascular system were investigated.

A part of this study was presented at the winter annual meeting of the Japan Atherosclerosis Society, Jan. 18, 1985.

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MATERIAL AND METHOD

In a preliminary experiment, 3 male and 3 female Sprague-Dawley rats were used and after one month of age were transferred to a cold room at 4 ± 1 °C for one hour everyday. The cold room was illuminated during the cold stress. During the experimental period, the systolic blood pressure and the weights of the rats were measured every other week. Eleven to twenty months after starting the cold stress, the rats were sacrificed by decapitation and sections for light microscopic investigation were prepared by the usual method and examined.

The present experiment was divided into two groups [experiment(1) and experiment (2)].

Experiment(1): Sprague-Dawley rats were used. After one month of age, the rats were exposed to cold in the same manner as in the preliminary experiment. During the experimental period, the systolic blood pressure and the weights of the rats were measured every other week. The rats in which the systolic blood pressure elevated to 170 to 180 mmHg breded, and were allowed to breed until the ninth generation using the same methods. The rats which elevated to a maximum blood pressure of 200mmHg and those that seemed unable to survive the cold stress were sacrificed by decapitation.

Experiment(2): Male Wistar rats were used. They were divided into two groups [the cold stress group (n=4) and the control group (n=5)]. The cold stress group rats were exposed to cold in the same method as in the preliminary experiment after one month of age. The control group rats were housed at 24 ± 2 °C temperature. During the experimental period, the systolic blood pressure and the weights of both groups of rats were measured every other week, and then 10 months later they were sacrificed by decapitation.

Except during exposure to cold, the rats of experiment(1) and (2) were individually housed at 24 ± 2 °C. Food and tap water were provided *ad libitum*. The systolic blood pressure was measured by the tail-cuff method (RAT automatic blood pressure recorder USM-105-R type). One week before completion of the experiments handling was carried out for 5 minutes everyday and then the rats were sacrificed by decapitation. After dissociating plasma from the collected blood, Na, K, Cl, BUN (blood urea nitrogen), cholesterol, free fatty acids, and β -lipoprotein were measured. The weights of organs were measured and the organ-to-body weight ratio was calculated. The organs were immersed in 10% buffered formaldehyde and embedded in paraffin using a SAKURA automatic tissue processor as usual. For light microscopy sections of the cardiovascular system were stained with Hematoxylin-Eosin (HE) stain, Elastica Van Gieson (EVG) stain, Weigert (W) stain and Mallory Azan (MA) stain.

In experiment(2), when sacrificed, the left adrenal gland was taken out immediately and the catecholamine contents were measured (by the high performance liquid chromatographic electrochemical method). Moreover, in experiment(2) the thickness of media was measured in myocardial arteries. The elastica interna of the section was irregularly curved

and so it was stretched to round regularly. The extension of section of myocardial arteries with EVG stain was projected and the thickness of media was measured by using image analyzing system (DAIANA-1). The media/radius ratio was calculated. Statistical processing was done by the Student's t-test.

RESULT

Preliminary experiment: Hypertension over 160mmHg was produced in all six rats. The mean value of the maximum systolic blood pressure was 179 ± 4.6 mmHg (means \pm S.E.). For pathological findings, subendothelial angionecrosis of the coronary artery was observed in one male rat of six rats (Fig. 1).

Experiment(1): Hypertension of over 160mmHg was produced one to eight months after starting the exposure to cold. It was expected that the period needed for elevating the blood pressure after starting the cold stress would be shortened by producing succeeding generations, but positive proof could not be obtained. Pathological changes of the cardiovascular system were observed in one male rat of the seventh and ninth generations.

The seventh generation rat which was 13 months of age indicated 164mmHg blood pressure 2 months after starting and then maintained hypertension and the maximum blood pressure was 200mmHg. For macroscopic findings, concentric hypertrophy and fibrosis in the heart (Fig. 2), swelling of the kidneys the surface of which were rough and granular (Fig. 3), and the rosary-like appearance of the mesenteric vessels (Fig. 4) were observed. By light microscopic investigation, a PN-like lesion (fibrinoid necrosis of the arteries and infiltration of neutrophils and lymphocytes and proliferation of fibroblast) was

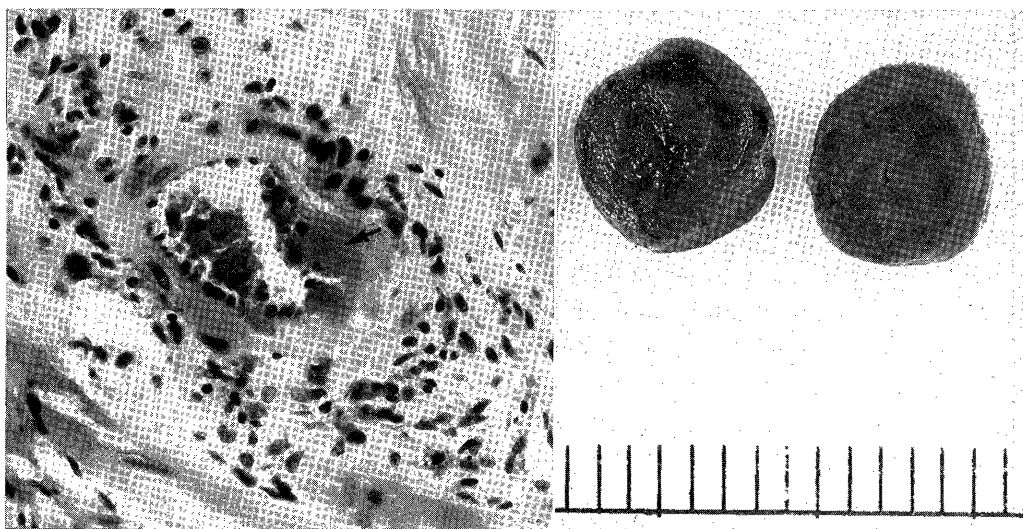


Fig. 1. Subendothelial angionecrosis (arrowed). [HE stain $\times 300$]

Fig. 2. Myocardial fibrosis and concentric hypertrophy of the heart.

observed in the heart, mesentery and kidneys (Fig. 5).

The blood pressure of the ninth generation rat which was 10 months of age had risen over 160mmHg, 4 months after starting and then maintained the hypertension. The maximum systolic blood pressure was 170mmHg. Light microscopically, fibromuscular sclerosis was observed in a myocardial artery of the left ventricle (Fig. 6).

Experiment(2): There was no significant differences in body weight gain between the two groups (Fig. 7). The blood pressure of the cold stress group had increased 3 months after starting the exposure to cold, and after that it was significantly higher than

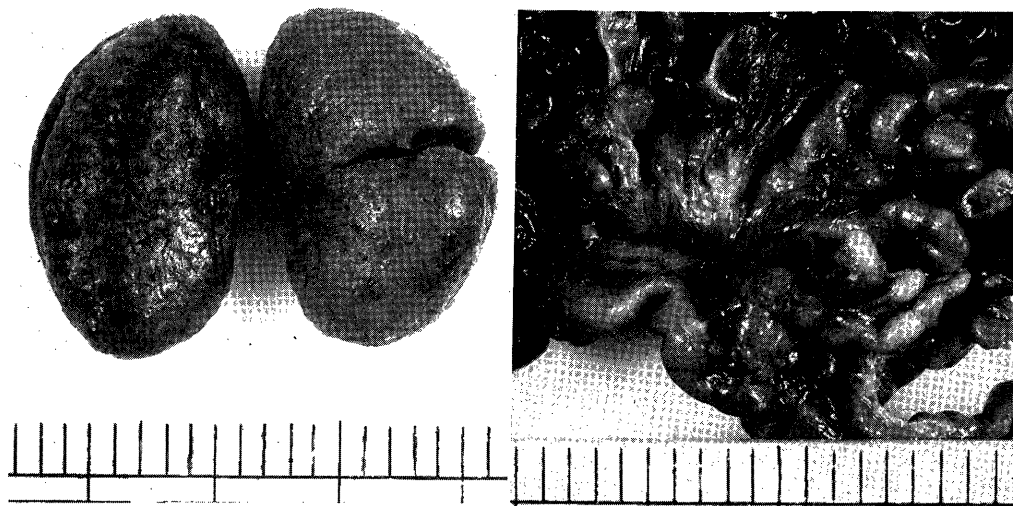


Fig. 3. Swellings of kidneys.

Fig. 4. A rosary-like appearance of mesenteric vessels.

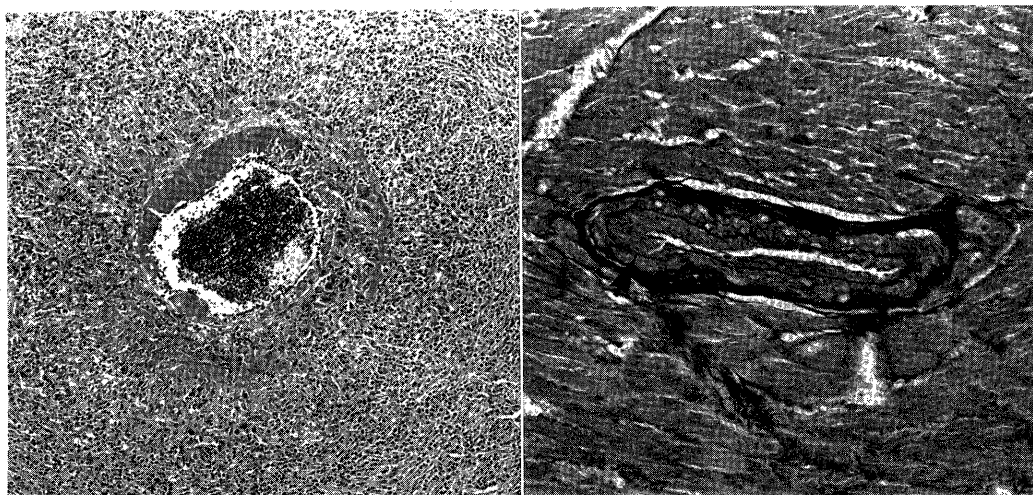
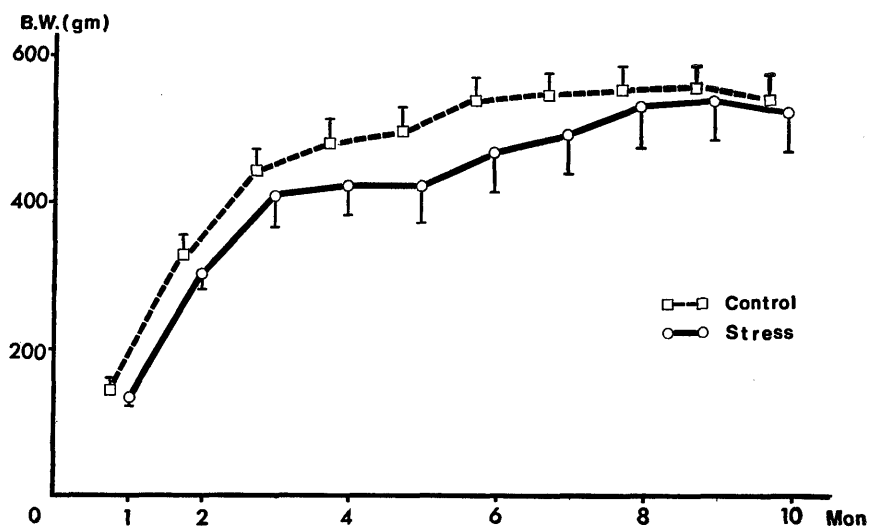


Fig. 5. PN-like lesion of the mesenteric artery.

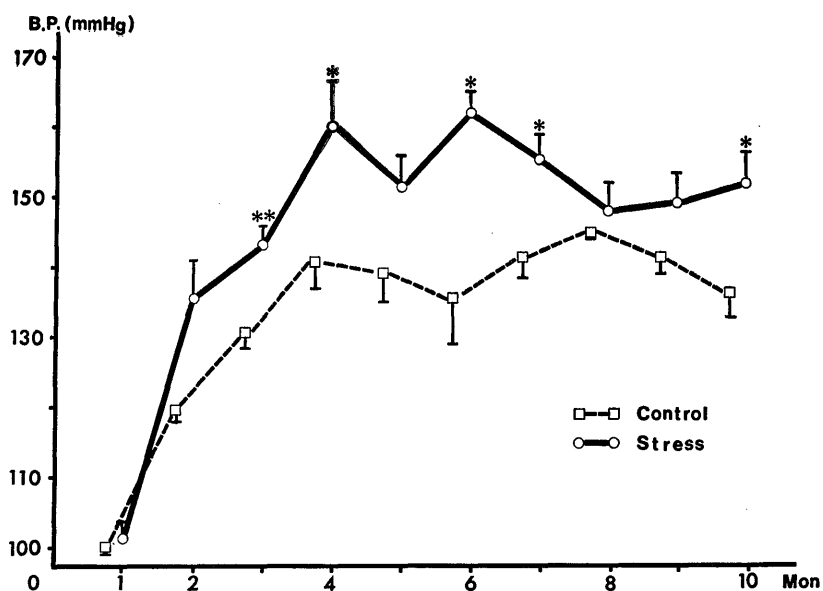
Fig. 6. Fibromuscular sclerosis of the myocardial artery (arrow: elastica interna). [EVG stain $\times 50$]

the control group almost every month (Fig. 8). There were no significant differences between the two groups in organ-to-body weight ratio of each organ and in serum electrolyte and serum lipid (Table 1, 2). Compared to the catecholamine content in the



Mean \pm S.E.

Fig. 7. Body weight comparing experimental groups [experiment(2)].



Mean \pm S.E. * $p < 0.05$, ** $p < 0.01$

Fig. 8. Blood pressure in cold stress group [experiment(2)].

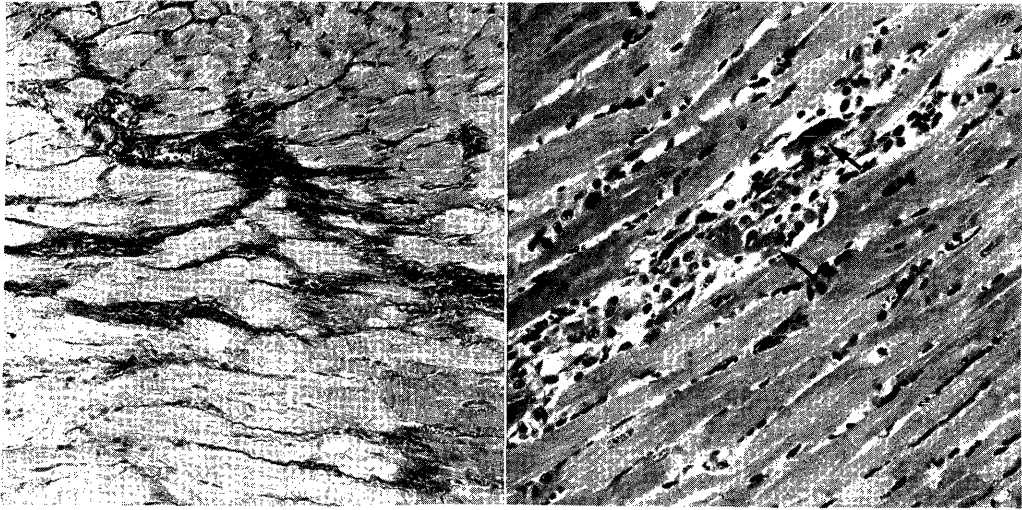


Fig. 9. Myocardial fibrosis. [EVG stain $\times 50$]

Fig. 10. Myocardial cell degeneration (arrowed) and mononuclear cell infiltration. [HE stain $\times 275$]

Table 1. Comparison of organ-to-body weight ratio

| Experimental group | Heart* | Kidneys* | Liver* | Lungs* | Adrenal glands** |
|--------------------|-----------------|-----------------|-----------------|-----------------|------------------|
| Control | 0.30 ± 0.01 | 0.72 ± 0.03 | 3.41 ± 0.01 | 0.60 ± 0.03 | 9.43 ± 0.97 |
| Stress | 0.28 ± 0.01 | 0.67 ± 0.03 | 3.16 ± 0.01 | 0.54 ± 0.03 | 8.30 ± 1.64 |

mean \pm S.E.

* (g%) ** (mg%)

Table 2. Comparison of serum lipid and serum electrolyte

| Experimental group | Na (mEq/l) | K (mEq/l) | Cl (mEq/l) | BUN (mg/dl) | T.chol (mg/dl) | FFA (mg/dl) | β -lipo (mg/dl) |
|--------------------|-----------------|---------------|-----------------|----------------|------------------|-----------------|-----------------------|
| Control | 144.3 ± 0.3 | 7.2 ± 0.1 | 105.5 ± 1.0 | 18.3 ± 0.4 | 99.6 ± 10.8 | 0.54 ± 0.04 | 188.4 ± 23.1 |
| Stress | 144.4 ± 1.1 | 6.9 ± 0.5 | 105.2 ± 1.0 | 18.9 ± 0.4 | 107.2 ± 15.9 | 0.52 ± 0.06 | 238.0 ± 56.0 |

mean \pm S.E.

BUN: blood urea nitrogen, T.chol.: total cholesterol, FFA: free fatty acids, β -lipo: β -lipoprotein

Table 3. Catecholamine contents in adrenal

| | norepinephrine (μ g) | epinephrine (μ g) |
|---------|---------------------------|------------------------|
| control | 5.25 ± 0.21 | 30.74 ± 2.32 |
| stress | $4.44 \pm 0.41^*$ | 29.10 ± 2.50 |

mean \pm S.E. * $p < 0.1$

Table 4. Pathological findings in heart

| Case | fibrosis* | cell infiltration** |
|------|-----------|---------------------|
| 1 | ++ | + |
| 2 | + | + |
| 3 | ++ | + |
| 4 | + | - |

*+ : mild, ++ : moderate

**- : absence, + : presence

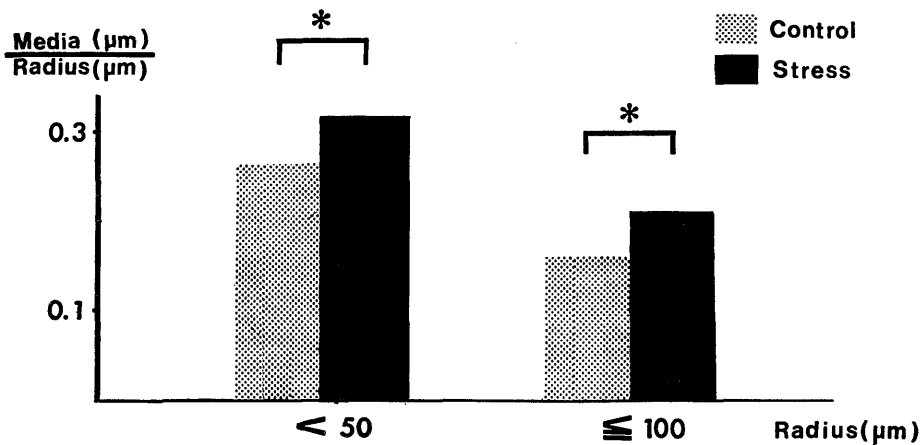
* $p < 0.05$

Fig. 11. Media/radius ratio in myocardial arteries [experiment(2)].

adrenal gland, norepinephrine was slightly decreased in the cold stress group but there was no significant difference (Table 3). No pathological changes were observed in the control rats. In all the cold stress group rats, myocardial fibrosis (scattered in the myocardium) and myocardial cell degeneration were observed light microscopically in the left ventricle and interventricular septum (Fig. 9, Table 4). Moreover, cell infiltration composed mainly of mononuclear cells was also seen in 3 out of 4 rats (Fig. 10). Comparing the media/radius ratio of myocardial arteries, both groups indicated 0.15 ± 0.01 (means \pm S.E.) in the radius 100 to 200 μm arteries, and no difference was found. However, in the radius to 50 μm arteries, the control group indicated 0.26 ± 0.01 and the cold stress group indicated 0.31 ± 0.01 . In the radius 50 to 100 μm arteries, the control group indicated 0.16 ± 0.01 and the cold stress group indicated 0.21 ± 0.01 . Thus the ratio of the cold stress group was more significantly increased than that of the control group in the radius under 100 μm arteries (Fig. 11).

DISCUSSION

There have been many reports that catecholamine is related to the cause of hypertension¹⁴⁾⁻¹⁶⁾. The system of reactivity to stress is considered to be the sympathetic nerve-adrenal medulla system and the pituitary-adrenal cortex system. *KVETNANSKY et al.*¹⁷⁾ reported that in rats subjected to repeated immobilization, adrenal medullary activity was increased and urinary excretion of epinephrine was greater than in unstressed or once-immobilized rats. *MATSUO et al.*¹⁸⁾ reported that there was a significant increase in epinephrine volume of the stress group rats (application of "stick-poking harassment" stress) by measurement of urine catecholamines than that of the control rats, and they supposed that stress-induced hypertension was caused by acceleration of adrenal medullary activity with acceleration of activity of catecholamine synthesis enzyme. *CHIUEH et al.*¹⁹⁾, *MCCARTY et al.*²⁰⁾, and *POPPER et al.*²¹⁾ reported that by application of stress such as exposure to cold, immobilization and electrical stimulus, activity of the sympathetic nerve-adrenal medulla system was increased and plasma catecholamines were increased. In the present experiment it was conjectured that activity of the sympathetic nerve-adrenal medulla system increased and also excretion of plasma catecholamine increased and it was assumed that these factors were related to the development of hypertension. It was also supposed that the peripheral resistance was raised by increased plasma level of norepinephrine and that this affected the development of hypertension.

A combination of factors is said to be more effective in the development of stress-induced hypertension than only one factor¹⁾. In the present experiment rats were transferred to a cold room which was illuminated during exposure. Therefore, it was considered that the change of living place and the exposure to cold in an illuminated room could affect the development of hypertension as psychogenic stress in rats which have a nocturnal habit.

*LEDUC*²²⁾ reported that adrenal epinephrine and norepinephrine of rats acclimated to cold increased significantly. *KVETNANSKY et al.*¹⁷⁾ reported that the adrenal epinephrine of rats subjected to one time-immobilization stress decreases, but that there was no decrease of adrenal epinephrine in rats subjected to repeated immobilizations though urinary excretion of epinephrine was still increased. It was suggested that the "adaptation" of the adrenal medulla to repeated stress in rats was caused by an enhanced ability to replace the released catecholamine. Although in the present experiment urinary catecholamines were not measured, from the report of *LEDUC*²²⁾, it was expected that urinary catecholamines would be increased.

In experiment(2), there were no significant differences in adrenal catecholamine contents between the two groups. This result was thought to be caused by "adaptation" to the cold stress.

There have been many reports about the production of experimental hypertension by various kinds of stress, but there are very few reports about stress-induced hypertension pathology⁶⁾⁻¹³⁾. The vascular changes in the present experiment(1) were as follows: a) angioneclerosis of the coronary artery: b) PN-like lesions in the heart, kidneys, and

mesentery; and c) fibromuscular sclerosis in the myocardial artery. LIMAS *et al.*²³⁾ supposed that not only the severity of hypertension but also its duration were significant determinants of vascular damage. The blood pressure of all the rats in which a) angioneclerosis, b) PN-like lesion, and c) fibromuscular sclerosis were observed, maintained levels of over 160mmHg for 7 to 11 months and it is suspected that over 160mmHg hypertension and its duration caused the vascular changes. GARDNER *et al.*²⁴⁾ supposed that the acceleration of vascular permeability might be the cause of fibrinoid necrosis in experimental hypertension. SHOWA²⁵⁾ reported that fibrinoid material was deposited in the intima and media of the arteries by repeated contraction of the mesenteric artery in the rat. It is considered that aging, hypertension and contraction of the arteries are significant factors in the PN-like lesion²⁵⁾²⁶⁾.

It is supposed that the changes of a) angioneclerosis and b) PN-like lesion were caused by cold stress-induced hypertension and repeated vascular contraction due to norepinephrine.

YAMORI²⁷⁾ supposed that maintained hypertension enhanced not only vascular collagen synthesis but also noncollagenous protein metabolism and thereby accelerated arteriosclerosis. In the rat with vascular change, i.e. fibromuscular sclerosis, hypertension of over 160mmHg was maintained for 7 months, and it was supposed that such lesions may be caused by cold stress-induced hypertension.

LAWLAR *et al.*⁷⁾ reported that severe hypertension was produced in borderline hypertension rats about 150mmHg by using wheel, noise, and electric stimulus, and that subsequently myocardial cell degeneration, fibrosis and inflammatory cell infiltration were observed. Similar lesions were observed in the present experiment(2). WALDENSTRÖM *et al.*²⁸⁾ reported that a sudden release of myocardial norepinephrine causes acute myocardial damage. UEDA *et al.*¹⁴⁾ reported that the myocardial norepinephrine increased significantly by electrical stimulation of the central gray stratum of the midbrain. It is conjectured that endogenous norepinephrine increases in the heart by exposure to cold and subsequently ischemia by vascular contraction and norepinephrine itself could cause the myocardial cell damage.

In the present experiment the thickness of the myocardial artery under 100 μ m increased significantly. LIMAS *et al.*²³⁾ reported that the thickness of the artery was in proportion to the duration of hypertension. Moreover, MARWOOD *et al.*⁸⁾ reported that sustained stress-induced hypertension was produced in Wistar rats by sound-withdrawal stimulation and that arterioles from the gastrocnemius muscle of rats had thicker walls and hence reduced lumen diameter. SUNAGA²⁹⁾ reported that endothelial damage-permeability acceleration, smooth muscle damage-edematous change and proliferation of collagen were observed by contraction effects of norepinephrine infused into the artery. JOHNSON *et al.*³⁰⁾ reported that hypertrophy of the arteries was induced by catecholamine infusion into rats.

In the present experiment, the systolic blood pressure of cold stress group rats was elevated to about 150mmHg, which was not so severe, but compared to the control group rats, the cold stress rats maintained a significantly higher blood pressure for 7 months.

It is suspected that higher blood pressure and endogenous norepinephrine could affect the medial thickening.

There was a few differences in pathology between experiment(1) and experiment(2). KUHN *et al.*³¹⁾ reported that there were endocrine differences between the Wistar and Sprague-Dawley rats exposed to cold. It is supposed that physiological sensitivity to cold stress might be different in different kinds of rats.

CONCLUSION

Changes of the cardiovascular system were observed in rats exposed to cold from one month of age. The results were as follows.

- I) In Sprague-Dawley rats ;
 - i) Over 160mmHg hypertension was produced and maintained by exposure to cold.
 - ii) Positive proof that the period needed for elevating the blood pressure after starting the cold stress was shortened by generation could not be obtained.
 - iii) It was conjectured that stress-induced hypertension causes the pathology in the from of a) angionecrosis of the coronary artery b) fibromuscular sclerosis of the myocardial artery and c) PN-like lesion in the heart, kidneys and mesentery.
- II) In Wistar rats ;
 - i) The blood pressure of cold stress group rats increased significantly compared to the control group.
 - ii) Myocardial cell degeneration, fibrosis and mononuclear cell infiltration were observed in cold stress rats.
 - iii) The thickness of the myocardial artery under 100 μ m increased significantly compared to the control group. It is suspected that endogenous norepinephrine could affect the medial thickening.
 - iv) There were no significant differences in adrenal catecholamine contents between the two groups. It was suggested that the "adaptation" of the adrenal medulla to repeated cold stress was caused by an enhanced ability to replace the released catecholamine.
- III) It is thought that the physiological sensitivity to cold stress might be different between the Wistar rats and the Sprague-Dawley rats.

ACKNOWLEDGEMENT

The author would like to express his gratitude to Professor I. NISHIMORI, Associate Professor I. SEKINE and Associate Professor M. KISHIKAWA for their valuable advices and encouragements. The author also thanks Dr. K. FUJINO for his valuable comments and his kind provision of rats, and the cooperative research students and skillful technical assistants in the Department of Pathology, Atomic Disease Institute, Nagasaki University School of Medicine.

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