SPONTANEOUSLY OCCURRING HYPERTROPHIC CARDIOMYOPATHY IN THE RAT

II. Distribution of, and Correlations between, Various Cardiac Abnormalities in the WKY/NCrj and Its Related Strains

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We performed gross-anatomic and histologic examinations quantitatively on 18 male and 30 female WKY/NCrj rats, and their 299 first generation offspring. The results were analyzed in comparison with those obtained from 3 other strains of rats. The offspring of the WKY rats showed various cardiac abnormalities quite similar to those in their parents. The cardiac abnormalities in the offspring of the WKY rats were: increased heart weight (in about 10%), left or right atrial hypertrophy (50%), disproportionate septal thickening (50%), small left ventricular cavity (40%), right ventricular hypertrophy (40%), abnormal fiber arrangement greater than 5% in either of the 3 ventricular walls (90%), myocardial fibrosis (70%), and abnormal location of arteries in the ventricular septum (30%). ECG findings of the WKY-F rats such as high QRS complexes and high T waves and axis deviation showed a high sensitivity and specificity in the diagnosis of marked cardiac hypertrophy. Another conspicuous histologic finding observed in the WKY hearts was that the continuity of the latitudinal fiber bundle of the ventricular septum with that of the left ventricular free wall, an important functioning unit for pressure generation in the left ventricle, was markedly disturbed in the area of junction between the 2 walls; the smaller the continuity, the greater the cardiac hypertrophy; the disadvantage of the discontinuity for the pressure generation may be related to the development of cardiac hypertrophy. Also examined were two strains of Wistar rats with the same origin as the WKY/NCrj. These rats also had gross-anatomic and histologic abnormalities of the heart quite similar to those in the 2 generations of WKY/NCrj rats, suggesting that a common factor related to the development of the abnormalities, probably a genetic predisposition, has been transmitted in these 3 strains.

Key words:

Discontinuity of muscle fibers between
ventricular walls
Abnormal location of mural arteries
Electrocardiogram

WE have reported that certain pathologic features similar to those of hypertrophic cardiomyopathy in humans are present in some of the hearts of rats of the WKY/NCrj strain and

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have suggested that the rat with these abnormalities may be a useful animal model in the study of the human disease.¹ The occurrence of the cardiac abnormalities in a specific strain strongly suggests that the abnormalities are genetically linked. Moreover, the WKY/NCrj is an inbred strain with a presumably similar genetic background. However, these cardiac abnormalities showed considerable individual variation, ranging from no difference from hearts of normal Wistar rats to quite obvious defects. Therefore, it is difficult at present to determine the extent of the abnormalities, which can be regarded as manifestations of a gene defect.

The present study was undertaken to clarify the distribution and varieties of the cardiac abnormalities in this strain and further to correlate the various abnormalities; a precise knowledge will be helpful in elucidating the pathogenesis and genetics of the abnormalities. We assessed quantitatively the gross-anatomic and histologic findings in as many WKY/NCrj rats of 2 generations as possible and compared them with those obtained from three strains of rats which were considered to have normal hearts. Several characteristic features observed in the WKY hearts, which have not yet been noted in the human disease, are also described. Furthermore, we present electrocardiographic findings which will be helpful in predicting the presence of cardiac hypertrophy while rats are alive. We show also findings in the hearts of 2 strains of Wistar rats of the same origin as the WKY/NCrj strain, which have been maintained in Japan.

MATERIALS AND METHODS

Materials: Eighteen male and 30 female rats of the WKY/NCrj strain (WKY-P), which were purchased directly, were mated at random. All of the 299 first generation offspring (WKY-F) and their parent rats were examined at 7–9 weeks and at 10–14 months of age, respectively. The rats were fed a stock chow diet (Nihon Clea) and tap water in an air-conditioned animal room (temperature, $23 \pm 2^\circ\text{C}$; humidity, $55 \pm 5\%$). The WKY-F rats were compared with 28 male and 20 female Wistar rats purchased from Shimizu Jikken Zairyo Inc. (Wistar-S), 30 male and 20 female Wistar rats from Nihon Ikagaku Inc. (Wistar-N), and 24 male and 21 female rats which are the first offspring of purchased SHR/NCrj rats; these rats matched the WKY-F in body weight. The male and female WKY-P were

compared with 11 male and 11 female adult Wistar rats of Shimizu Jikken Zairyo Inc. (Wistar-SA), which matched the WKY-P in body weight. Also examined were 3 male and 3 female Wistar rats of the strain maintained in the animal center of Kyoto University (Wistar-K), from which the WKY/NCrj originated, and 10 male and 10 female Wistar rats which diverged from the Wistar-K in 1981 and has been maintained in Shizuoka Dobutsu Kyokai (Wistar-SD).

Recording of blood pressure and procedures for gross-anatomic and microscopic examinations: With the rat under urethan anesthesia (100 mg/100g body wt), the carotid artery was cannulated. Blood pressure and heart rate were recorded by connecting the cannula to a strain gauge transducer with an inkless writing recorder (Nihon Kodan RM 6000). The heart beat was arrested at end diastole by infusing EDTA solution into the right atrium, and the heart was immediately fixed by perfusing the coronary artery with 10% formalin through the cannulated carotid artery under perfusion pressure maintained at 80 mmHg.^{1,2} Heart weight, wall thickness, transverse ventricular wall areas, left ventricular cavity size, and abnormal fiber arrangement were examined in the same way as described previously.¹ A difference in method from the previous study is that we determined the midventricular transverse areas of the left and right ventricular walls, with the left ventricular wall including the IVS and LVFW, and with the area of the left ventricular cavity including papillary muscles. The transverse area of papillary muscles was measured separately. Histologic examinations were done by use of one transverse tissue section at the midventricular level, because some serial tissue sections in the middle 1/3 of the base-apex axis showed quite similar histologic findings. The fixation of the heart at end diastole was considered to be successful when the heart became pale within a few seconds after the beginning of perfusion; about 10% of the hearts were unsuccessfully perfused and hence were excluded from the determination of absolute ventricular wall thickness and cavity size of the left ventricle.

Semiquantification of myocardial fibrosis: We described previously¹ three types of fibrosis characteristic of WKY hearts: anterior fibrosis, posterior fibrosis, and interstitial fibrosis. In this study, the fibrosis was designated as: grade 1, anterior epicardial thickening; grade 2, anterior epicardial thickening associated with interstitial

Fig.1. Transverse view of hearts at midventricular level. The anterior side of the heart is on the top. Scale represents 1 cm. A: normal heart of a male Wistar rat. B: from a male WKY rat with heart wt/body wt ratio of 4.67. Right ventricular hypertrophy is lacking. C: from a male WKY with heart wt/body wt ratio of 8.57. Biventricular hypertrophy is marked. D: from a female WKY rat with a ratio of 7.93. Right ventricular hypertrophy is predominant. E: from a male WKY with a ratio of 8.58. Left ventricle is dilated. F: from one of the 3 female Wistar rats of Kyoto University with heart wt/body wt ratio of 5.74. The left ventricular cavity is narrow in all hearts except A and E.

fibrosis beneath the epicardium; grade 3, wide distribution of grade 2 fibrosis, massive scars in the anterior subepicardium, obvious increase in interstitial fibrosis in areas other than the subepicardium, and/or posterior subepicardial fibrosis at the midventricular level; and grade 0, no fibrosis.

Quantitative assessment of location of arteries in the IVS: We have previously noted that arteries located on the left side of the IVS of hypertrophied WKY hearts were more numerous than in hearts of normal Wistar rats.¹ Selecting the five arteries with largest lumens, we measured the width of the IVS, T , at the level at which an artery was located, and the distance, L , from the right margin of the IVS to the center of each of the five arteries. An index which represents the leftwards deviation in location of arteries in the

IVS, i.e., the deviation index of arteries (DI), was determined from the equation; $DI = [\Sigma (CLA \times LT^{-1}) / \Sigma CLA] \times 100$, where CLA is the cross-sectional lumen area calculated as $(\text{the shortest lumen diameter})^2 \pi / 4$. This equation takes into account the size of arteries; the deviation of a large artery contributes to the DI more than that of a smaller artery.

Assessment of continuity of fiber bundles between LVFW and IVS: In normal hearts, the fiber bundles in the midwall layer of the IVS are oriented latitudinally, i.e., parallel to the transverse plane of the heart, and are smoothly continuous with those in the LVFW; they constitute jointly a circumferential unit of fiber bundles surrounding the left ventricle as a whole. The muscle fibers in the right ventricular free wall (RVFW), except for the longitudinal fibers in the

Fig.2. A: Area of anterior junction of the 3 ventricular walls of heart D in Fig.1. R and L = right and left ventricular free wall, respectively. S = interventricular septum. Original magnification, $\times 6.6$. B: A higher magnification of pannel A ($\times 25$). The shape of tissue clefts is helpful in identifying the site in A. The latitudinal fiber bundle of the S is not continuous to the L due to tissue clefts or muscle fiber disarrangement; it is rather continuous to the R. Clusters of red cells remain in the tissue clefts. C: Area of anterior junction of heart C in Fig.1. L = left ventricular side. Smoothly oriented latitudinal fiber fascicles are continuous to the subepicardial scar. Original magnification, $\times 25$. Clusters of red cells are noted in the clefts. D: Area of posterior junction obtained from the same tissue section as panel A. Original magnification, $\times 13.2$. Latitudinal fiber bundle is almost lacking in the S. The continuity of latitudinal fibers between the L and S was estimated to be zero in these hearts.

inner layer, are oriented continuously with the outer oblique or middle latitudinal fibers of the LVFW^{2,3}

A conspicuous histologic finding in the majority of WKY hearts was that the fiber bundles oriented latitudinally in the midwall layer were not smoothly continuous between the IVS and LVFW; the continuity of fiber fascicles was interrupted abruptly by large cleavages in the tissue section obviously not due to artifacts (Fig. 2-A, B), or disturbed by abnormal fiber arrangement (Fig.2-B); in some cases, latitudinal fiber fascicles in the IVS were continuous with the subepicardial scar (Fig.2-C) or latitudinal fibers were lacking in the IVS without fiber disarrangement, particularly in the vicinity of junctions (Fig.2-D). Deep clefts in the myocardial tissue in human HCM have been described by James and

Marshall⁴ This interruption of the continuity seemed to be more marked in WKY hearts when cardiac hypertrophy was severe.

We assessed quantitatively the extent to which the latitudinally oriented fibers were continuous between the IVS and LVFW. With an eye-piece micrometer, we measured the width of the LVFW at the thinnest two sites near the anterior and posterior junctions and the width of the fiber bundles which were smoothly continuous between the IVS and LVFW in the anterior and posterior junctional areas. We also measured the width of the fiber bundles which were smoothly continuous between the LVFW and RVFW in the anterior and posterior junctional areas. The magnitude of the continuity between the LVFW and IVS, C_{LS} , and that between the LVFW and RVFW, C_{LR} , were determined, respectively,

Fig.3. Limb lead electrocardiogram in Wistar-S and WKY rats with heart wt/body wt ratio of 7.64 and septum to free wall ratio of 1.32. Horizontal and vertical scales represent 1 second and 1 mV, respectively. S-T segment is lacking in both rats. P wave is much larger in the WKY than in Wistar rat. The axis of the QRS complex is markedly deviated towards the left in the WKY rat. The QRS shows a wide biphasic deflection in lead II, which was also one of the characteristic findings in WKY rats with marked cardiac hypertrophy. In this case, the width of the deflection was measured as the QRS voltage.

from the equation; C_{LS} or C_{LR} = (width of fiber bundles continuous in anterior and posterior junctional areas between LVFW and IVS, or between LVFW and RVFW) / (width of anterior LVFW + that of posterior LVFW). This method of estimating the continuity, however, must be considered to be semi-quantitative in the strict sense, because the margin of the latitudinal fiber bundles were not clear due to their gradual shifting into layers in which fibers are oriented longitudinally.

ECG recording: In 23 litters of the WKY-F rats, limb and precordial lead electrocardiograms (ECG) were recorded with an ordinary human ECG apparatus (Nihon Koden ECG 5403) prior to cannulation of the carotid artery and perfusion of the hearts. The speed of recording papers was set at 10 cm/second with a calibration of 1 mV at 4 cm. Small metallic clips were used as electrodes. The precordial lead recordings were

obtained from the ventral surface at the base of the xyphoid process and the right and left mid-points between the midsternal line and the 2 axillary lines on the same transverse plane in the supine position. The 3 precordial leads were designated in the order from right to left, Va, Vb, and Vc. We measured the axis of the QRS complex, the highest voltage of the QRS complexes and T waves in the limb leads, and QRS and T voltages in the Vc lead. The S-T segment was absent in the ECG of rats (Fig.3). The ECG findings were correlated with the anatomic features of the heart.

Statistical analysis: All data were expressed as mean $\pm$ SD. Differences between pairs of means for F-ratios at 5% or less were examined by Duncan's multiple comparison test or Student's t-test. In this case, the statistical significance of the difference in mean values between the WKYs and the other 3 strains was not

TABLE I HEART WEIGHT AND BLOOD PRESSURE

		WKY-F (M=149, F=150)	WKY-H (15, 10)	Wistar-S (28, 20)	Wistar-N (30, 20)	SHR (24, 21)	WKY-P (18, 30)	Wistar-SA (11, 11)
Body weight (g)	M	198±22	189±20	195±20	194±22	208±13	385±39	400±20
	F	140±12	138±14	133±8	151±19	139±5	260±23	254±12
Blood pressure (mmHg)	M	107±14*	104±11*	132±9	126±6	134±9	96±15**	134±10
	F	108±15*	118±14	122±13	127±10	129±9	100±15**	130±13
Heart rate (beats/min)	M	334±52*	331±58*	392±34	388±32	437±31	275±37**	386±33
	F	327±43*	327±44*	385±41	377±34	417±40	247±48**	374±35
Heart weight (g)	M	902±184	1302±202	954±75	896±87	961±74	1728±486	1850±120
	F	662±108	967±215	683±71	734±76	686±46	1231±356	1227±94
HW/BW ratio (mg/g)	M	4.58±0.90	6.90±0.98	4.90±0.39	4.63±0.37	4.63±0.27	4.50±1.12	4.63±0.30
	F	4.72±0.76	6.97±1.17	5.12±0.43	4.86±0.35	4.92±0.28	4.78±1.18	4.84±0.28
LAW/BW ratio (mg/g × 100)	M	10.1±3.2	17.7±1.2	7.2±1.3	7.6±1.4	8.5±1.2†	11.9±3.6	7.6±1.6
	F	10.5±2.8	17.4±1.8	7.6±1.3	8.0±1.4	9.1±1.3†	11.2±3.6	8.1±1.4
RAW/BW ratio (mg/g × 100)	M	9.8±2.9	18.5±1.9	6.9±1.2	7.2±1.3	8.2±1.6†	10.3±2.9	7.4±1.3
	F	8.8±2.4	15.1±2.8	7.1±1.2	7.3±1.5	8.5±1.2†	11.3±3.8	8.2±1.0

Data, mean ± SD. Abbreviations: WKY-F = offspring of WKY-P rats; WKY-H = WKY rats with heart weight/body weight ratio greater than 5.5 in WKY-F rats; Wistar-S = Wistar rats from Shimizu Jikken Zairyo Inc.; Wistar-N = rats from Nihon Ikagaku Inc.; WKY-P = parents of WKY-F; Wistar-SA = adult Wistar-S rats; M = male; F = female; HW = heart weight; BW = body weight; LAW and RAW = left and right atrial weight; Numbers in parentheses denote number of rats. No significant difference was found in mean weight ratios between Wistar-S, -N, and SHR. WKY-F and -P were not compared with Wistars and SHR, because the F-ratios were greater than 5% in most of pairs. * = $p < 0.01$, for comparison with Wistar-S, -N, and SHR. ** = $p < 0.01$, for comparison with Wistar-SA. †, $p < 0.01$, for comparison with Wistar-S and -N.

examined except for blood pressure, heart rate and electrocardiographic data, because the F-ratio was greater than 5% in the vast majority of the pairs. In order to judge various values of individual WKY hearts to be abnormal, we referred to the mean ± 2SDs of the values in the Wistar-S and Wistar-SA. Correlation coefficients between various cardiac abnormalities were calculated in WKY-F rats; they were considered to be statistically significant when their 95% confidence interval did not include zero, and they are presented as a 95% confidence interval in both males and females in parentheses in the text. The difference between the WKY-F and WKY-P in percentage of rats with a cardiac abnormality was tested by chi-square test. When the difference in mean values between 2 groups was compared between 2 regions of the heart, the interaction between the groups and regions under a 2-way analysis of variance with repeated measures was employed to test the statistical significance.

RESULTS

Gross anatomy

Heart weight and blood pressure (Tables I, III, VI): The mean heart weight/body weight ratio was similar in WKY-F, Wistar-S and -N, and SHR rats. However, the ratio in the WKY-F showed a wide range; 10% of the males and 7% of the females with a ratio greater than 5.5 were judged to have abnormally heavy hearts when compared with the mean + 2SDs in the Wistar-S. These rats with a heavy heart in the WKY-F were designated as WKY-H; their gross-anatomic, histologic and ECG data are presented separately in Tables. The ratio of the left or right atrial weight to the body weight ($100 \times \text{mg/g}$) was greater than 1.0 in more than half of the WKY-F and -P. It was significantly greater in the SHR than in Wistar-S and -N. In the WKY-F, there was a good correlation between the normalized right atrial weight and right ventricular transverse wall area ($0.63 \leq r \leq 0.79$, $0.58 \leq r \leq 0.76$, in the males and females, respectively), and also a significant cor-

TABLE II VENTRICULAR WALL THICKNESS AND TRANSVERSE WALL AREA

		WKY-F	WKY-H	Wistar-S	Wistar-N	SHR	WKY-P	Wistar-SA
<i>IVST</i>	<i>M</i>	2.72±0.40*	3.31±0.34*	2.36±0.17*	2.13±0.20	2.28±0.18*	3.50±0.53*	3.13±0.19*
(mm)	<i>F</i>	2.48±0.28*	2.64±0.34*	2.07±0.18	2.08±0.20	2.04±0.19*	2.98±0.50*	2.56±0.23*
<i>LVFWT</i>	<i>M</i>	2.38±0.26	2.66±0.24	2.50±0.14	2.19±0.18	2.45±0.12	2.85±0.31	3.35±0.26
(mm)	<i>F</i>	2.23±0.21	2.27±0.23	2.16±0.16	2.14±0.22	2.19±0.18	2.45±0.33	2.71±0.16
<i>IVST</i>	<i>M</i>	1.14±0.12	1.25±0.14	0.94±0.06	0.97±0.06	0.93±0.07	1.23±0.13	0.93±0.06
<i>LVFWT</i>	<i>F</i>	1.11±0.10	1.17±0.11	0.96±0.05	0.97±0.06	0.93±0.06	1.21±0.12	0.95±0.05
<i>LVWA</i>	<i>M</i>	1.80±0.20	2.29±0.25	1.89±0.12	1.80±0.16	1.89±0.14	1.71±0.32	1.75±0.08
<i>BW^{2/3}</i>	<i>F</i>	1.82±0.23	2.30±0.28	1.92±0.13	1.83±0.22	1.91±0.10	1.67±0.24	1.74±0.11
<i>RVWA</i>	<i>M</i>	0.41±0.11	0.65±0.14	0.34±0.03	0.35±0.03	0.32±0.03	0.37±0.12	0.33±0.03
<i>BW^{2/3}</i>	<i>F</i>	0.41±0.09	0.60±0.17	0.34±0.04	0.35±0.04	0.30±0.04	0.39±0.14	0.31±0.04
<i>RVWA</i>	<i>M</i>	0.23±0.04	0.28±0.04	0.18±0.02	0.19±0.03	0.17±0.02	0.22±0.05	0.19±0.02
<i>LVWA</i>	<i>F</i>	0.23±0.04	0.26±0.07	0.19±0.02	0.19±0.02	0.16±0.02	0.23±0.06	0.18±0.02
<i>PMA</i>	<i>M</i>	0.12±0.03	0.15±0.05	0.10±0.03	0.09±0.02	0.07±0.02	0.13±0.03	0.11±0.03
<i>BW^{2/3}</i>	<i>F</i>	0.12±0.02	0.12±0.03	0.11±0.02	0.10±0.02	0.07±0.01	0.12±0.02	0.12±0.02
<i>LVCA</i>	<i>M</i>	0.34±0.08	0.26±0.08	0.39±0.04	0.44±0.05	0.41±0.05	0.37±0.12	0.38±0.04
<i>LVWA</i>	<i>F</i>	0.33±0.08	0.35±0.13	0.41±0.05	0.43±0.06	0.43±0.05	0.36±0.14	0.39±0.03

Data, mean ± SD. Abbreviations: *IVST* and *LVFWT* = thickness of interventricular septum and left ventricular free wall, respectively; *LVWA* and *RVWA* = transverse wall area of left (*LVFW* + *IVS*) and right ventricle, respectively; *PMA* = transverse area of anterior and posterior papillary muscles. These areas (mm²) were normalized by body weight (g) raised to the power of 2/3. *LVCA* = left ventricular transverse cavity area. Other abbreviations and the rat number as in Table I. Rat numbers for *IVST*, *LVFWT*, and *LVCA/LVWA* are 10–20% lower than those in Table I, because coronary artery perfusion failed in some cases.

* = $p < 0.01$, for comparison between *IVST* and *LVFWT*.

relation between the left atrial weight and transverse area of the *IVS* plus *LVFW* (0.51~0.72, 0.48~0.70). The abnormally large heart weight/body weight ratio was present in about 20% of the *WKY-P*, a percentage not significantly different from that of the *WKY-F*. Blood pressure and heart rate were lower significantly in the *WKY-F* and *-P* than in the other strains.

Wall thickness and transverse areas of ventricular walls and cavity (Tables II, III, VI): The *IVS* of the *WKY-F* tended to be thicker than that of the other 3 strains; in about half of both males and females, it was at least 2.70 and 2.50 mm, respectively, and was judged to be abnormal; the *IVS* thickness correlated well with the heart weight/body weight ratio in both males and females (0.56~0.77, 0.47~0.69). The average *LVFW* thickness in the *WKY-F* was similar to that in the other three strains; however, a few rats of the *WKY-F* were judged to have an abnormally thick *LVFW*; the thickness correlated moderately with the heart weight/body weight ratio (0.39~0.63, 0.37~0.61). The ratio of the

IVS to *LVFW* thickness was greater than 1.3 in a small number of the *WKY-F*; however, it was greater than 1.1 with reference to the mean + 2SDs of the *Wistar-S* in about half of the *WKY-F*; the ratio did not show a high correlation with the heart weight/body weight ratio (0.22~0.51, 0.19~0.48). The thickness ratio was greater than 1.1 in 83% of the *WKY-P*, a percentage significantly greater than that of the *WKY-F*.

The mean transverse area of the *LVFW* plus *IVS* normalized by body weight raised to the power of 2/3 was not different between the *WKY-F* and the other three strains; in only a few *WKY-F* rats it was greater than 2.1. On the other hand, the mean normalized transverse wall area of the *RVFW* was obviously greater in the *WKY-F*; in about 40% it was more than 0.40; and it correlated well with the heart weight/body weight ratio (0.75~0.89, 0.67~0.82). The ratio in the area of the *RVFW* to the *LVFW* plus *IVS* was more than 0.22 in about half of the *WKY-F*; it also correlated moderately with the heart weight/body weight ratio (0.37~0.61, 0.30

TABLE III DISTRIBUTION OF GROSS-ANATOMIC INDEXES AND FIBROSIS IN WKY OFFSPRING

HW/BW (mg/g)			IVST/LVFWT			RVWA/LVWA			LVCA/LVWA			Fibrosis		
Grade	No.		Grade	No.		Grade	No.		Grade	No.		Grade	No.	
	M	F		M	F		M	F		M	F		M	F
≤3.75	3	1	≤0.95	2	7	≤0.18	13	9	≤0.20	5	1	0	9	5
≤4.00	24	13	≤1.00	20	12	≤0.20	25	23	≤0.25	16	14	1	38	43
≤4.25	35	17	≤1.05	14	21	≤0.22	31	40	≤0.30	24	27	2	81	88
≤4.50	36	27	≤1.10	29	30	≤0.24	36	33	≤0.35	35	35	3	21	14
≤4.75	23	42	≤1.15	25	32	≤0.26	20	23	≤0.40	28	21			
≤5.00	9	23	≤1.20	17	23	≤0.28	12	11	≤0.45	16	12			
≤5.25	3	12	≤1.25	19	12	≤0.30	5	4	≤0.50	3	3			
≤5.50	1	5	≤1.30	11	9	≤0.32	2	2	>0.50	6	7			
>5.50	15	10	>1.30	12	4	>0.32	5	5						

No. = number of rats in a grade. Other abbreviations and total rat numbers as in Table I and II.

TABLE IV PERCENTAGE AREA OF ABNORMAL FIBER ARRANGEMENT

		WKY-F	WKY-P	Wistar-S	Wistar-N	SHR	WKY-P	Wistar-SA
IVS	M	6.8 ± 3.8	12.2 ± 4.6	1.4 ± 1.3	1.5 ± 1.4	1.2 ± 1.2	5.2 ± 3.1	1.7 ± 1.3
	F	7.2 ± 4.1	8.8 ± 3.2	1.5 ± 1.0	1.6 ± 1.4	1.0 ± 0.8	4.1 ± 3.6	1.5 ± 1.1
LVFW	M	5.8 ± 3.7	7.9 ± 5.2	0.8 ± 0.6	1.2 ± 1.2	0.6 ± 0.7	4.6 ± 3.3	1.1 ± 0.9
	F	6.0 ± 3.5	6.6 ± 4.5	0.6 ± 0.8	0.8 ± 0.9	0.5 ± 0.7	3.9 ± 2.8	1.0 ± 0.8
IVS + LVFW	M	6.1 ± 3.1	9.2 ± 3.8	1.1 ± 1.0	1.3 ± 0.9	0.8 ± 0.6	4.7 ± 2.7	1.3 ± 0.7
	F	6.4 ± 3.1	7.2 ± 3.5	0.9 ± 1.0	0.9 ± 0.9	0.6 ± 0.5	4.0 ± 2.6	1.1 ± 0.8
RVFW	M	7.3 ± 4.1	5.9 ± 3.4	1.7 ± 1.1	1.7 ± 1.5	1.0 ± 1.1	5.1 ± 2.9	1.3 ± 0.8
	F	7.9 ± 4.0	6.5 ± 3.8	1.0 ± 1.2	2.1 ± 1.9	1.5 ± 1.7	5.3 ± 2.9	1.5 ± 1.2

Data, mean ± SD. Rat numbers as in Table I. Abbreviations: IVS = interventricular septum; LVFW = left ventricular free wall; RVFW = right ventricular free wall; others as in Tables I and II.

TABLE V LOCATION OF ARTERIES IN THE IVS AND CONTINUITY OF MUSCLE FIBER BUNDLE BETWEEN VENTRICULAR WALLS

		WKY-F	WKY-H	Wistar-S	Wistar-N	SHR	WKY-P	Wistar-SA
DI	M	25.8±10.2	36.0±10.8	21.6±5.1	21.7±4.8	18.7±4.2	33.2±9.3	22.3±4.1
	F	26.5± 9.8	35.0± 8.5	20.4±3.1	21.0±3.9	21.8±5.2	27.7±7.9	20.8±3.8
CLS (%)	M	16.7±6.7	3.3±3.3	23.3±3.2	22.3±4.3	21.4±3.0	11.8±5.1	20.9±2.5
	F	16.9±6.2	4.9±3.9	21.9±3.3	21.5±3.2	20.3±3.5	13.3±6.2	21.1±2.5
CLR (%)	M	16.9±3.2	13.4±3.7	21.1±3.4	19.2±3.8	19.5±2.1	15.9±4.4	21.9±2.9
	F	16.5±3.4	14.5±3.2	20.3±3.0	18.4±3.2	18.6±2.7	17.7±4.9	20.3±2.8

Data, mean ± SD. Abbreviations: DI = deviation index which represents leftward deviation of arteries (see text); CLS and CLR = extent to which the fiber bundle is continuous between interventricular septum and left ventricular free wall, and between interventricular septum and right ventricular free wall, respectively (see text). Rat numbers as in Table I.

~0.56). Furthermore, the difference in normalized transverse wall area between the WKY-H and

Wistar-S was significantly greater ($p < 0.05$) in the RVFW than in the LVFW plus IVS in both

TABLE VI PERCENTAGE OF RATS WITH CARDIAC ABNORMALITIES IN THE WKY

	WKY-F		WKY-P	
	M	F	M	F
HW/BW	10%	7%	17%	20%
LAW/BW	47	45	53	48
RAW/BW	50	39	46	44
IVST	49	48	56	52
LVFWT	7	4	0	0
$\frac{IVST}{LVFWT}$	56	53	83*	83*
	(8)	(3)	(28*)	(30*)
LVWA	7	6	28*	23*
RVWA	38	40	28	30
$\frac{RVWA}{LVWA}$	54	52	28*	27*
PMA	6	5	0	0
LVCA	34	35	23	33
LVWA	[4]	[6]	[6]	[6]
Disar.	62	64	44*	40*
Fibrosis	68	68	100*	83
DI	25	34	63*	40
CLS	45	45	61	57
CLR	44	40	50	47

Abbreviations: Disar. = disarrangement of fibers in the IVS; others as in Tables I, II, V. Individual values of each WKY rat were judged to be abnormal with reference to mean $\pm$ 2SDs in Wistar-S and -SA rats. Parentheses, percentage of rats with a value greater than 1.3. Square brackets, percentage of rats with a dilated left ventricle.

* = $p < 0.05$, significantly different from WKY-F.

males and females. These results indicate that the right ventricle usually hypertrophies more than the left, although septal hypertrophy predominated in the absence of right ventricular hypertrophy in some WKY hearts, as shown in Fig.1-B. The percentage of rats with an abnormally large left ventricular wall area was significantly greater in the WKY-P than in the WKY-F.

The normalized transverse area of papillary muscles correlated slightly with the heart weight/body weight ratio (0.21~0.49, 0.20~0.48); in only a small number of WKY-F it was more than 0.15.

The left ventricular transverse cavity area of the WKY-F, normalized for the left ventricular wall area, showed a wide range, with a slight negative correlation with the heart weight/body weight ratio (-0.21~-0.50 in males, -0.18~-0.47 in females) and with the percentage area of abnormal fiber arrangement in the LVFW plus IVS (-0.27~-0.55, -0.25~-0.53). In about one third of the WKY-F, the normalized cavity area was less than 0.30, whereas it was more than 0.50 in a few. The percentage of rats with a small or large left ventricular cavity size in WKY-P was similar to that in the WKY-F.

Histology

Abnormal fiber arrangement (Tables IV, VI): The area of abnormal fiber arrangement in the IVS was greater than 5% in about 60% of the WKY-F. The greater extent of fiber disarrange-

TABLE VII ELECTROCARDIOGRAM

		WKY (M=121, F=119)	WKY-H (11, 7)	Wistar-S (28, 20)	Wistar-N (30, 20)	SHR (24, 21)
Axis (degree)	M	32 $\pm$ 24	14 $\pm$ 69	53 $\pm$ 13	53 $\pm$ 18	50 $\pm$ 17
	F	35 $\pm$ 24	5 $\pm$ 50	51 $\pm$ 13	56 $\pm$ 22	53 $\pm$ 16
L-QRS (mV)	M	0.41 $\pm$ 0.08*	0.50 $\pm$ 0.16	0.33 $\pm$ 0.08	0.26 $\pm$ 0.05	0.25 $\pm$ 0.05
	F	0.41 $\pm$ 0.08*	0.48 $\pm$ 0.12	0.34 $\pm$ 0.08	0.27 $\pm$ 0.06	0.25 $\pm$ 0.04
L-T (mV)	M	0.19 $\pm$ 0.07	0.31 $\pm$ 0.12	0.18 $\pm$ 0.03	0.24 $\pm$ 0.05	0.20 $\pm$ 0.04
	F	0.19 $\pm$ 0.07	0.32 $\pm$ 0.14	0.16 $\pm$ 0.05	0.26 $\pm$ 0.05	0.22 $\pm$ 0.05
C-QRS (mV)	M	0.41 $\pm$ 0.11*	0.51 $\pm$ 0.11	0.29 $\pm$ 0.11	0.24 $\pm$ 0.10	0.20 $\pm$ 0.05
	F	0.40 $\pm$ 0.11*	0.50 $\pm$ 0.13	0.28 $\pm$ 0.12	0.23 $\pm$ 0.08	0.19 $\pm$ 0.06
C-T (mV)	M	0.19 $\pm$ 0.09	0.27 $\pm$ 0.11	0.09 $\pm$ 0.04	0.19 $\pm$ 0.09	0.14 $\pm$ 0.05
	F	0.18 $\pm$ 0.07	0.27 $\pm$ 0.13	0.10 $\pm$ 0.04	0.19 $\pm$ 0.08	0.17 $\pm$ 0.07

Data, mean $\pm$ SD. Abbreviations: L-QRS and L-T = voltages of the highest QRS complex and T wave in limb leads, respectively; C-QRS and C-T = voltages of QRS complex and T wave in Vc lead. Others as in Tables I and II. * = $p < 0.01$, for comparison with Wistar-S, -N, and SHR.

TABLE VIII SENSITIVITY AND SPECIFICITY OF ECG FINDINGS IN DETECTION OF MARKED CARDIAC HYPERTROPHY

	Sensitivity	Specificity
<i>Axis deviation</i>		
(≤ 0 or ≥ 90)	44% (16/36)	95% (311/326)
(≤ -30 or ≥ 110)	25% (9/36)	100% (325/326)
<i>QRS complex</i>		
(≥ 0.50 mV)	58% (21/36)	93% (306/326)
<i>T-wave</i>		
(≥ 0.25 mV)	86% (31/36)	93% (321/326)
(≥ 0.30 mV)	58% (21/36)	98% (321/326)
<i>T (≥ 0.25 mV) + QRS (≥ 0.50 mV)</i>	53% (19/36)	100% (325/326)

Sensitivity = true positive/(true positive + false negative). Specificity = true negative/(false positive + true negative). Heart wt/body wt ratio greater than 5.5 was termed cardiac hypertrophy.

ment in the IVS was not necessarily associated with that in the LVFW (0.12~0.41 in males, 0.15~0.44 in females) or in the RVFW (-0.04~0.28, -0.01~0.30). The magnitude of fiber disarrangement in the IVS correlated to a moderate extent with the heart weight/body weight ratio (0.35~0.59, 0.26~0.53) and with the IVS thickness (0.23~0.51, 0.20~0.48). There was also a moderate correlation between the percentage area of fiber disarrangement in the LVFW and LVFW thickness (0.27~0.54, 0.21~0.49), but no correlation between that in the RVFW and normalized transverse wall area of the RVFW (0.02, 0.01). In the WKY-P, the percentage of rats with fiber disarrangement in the IVS of an abnormal degree was significantly greater than in the WKY-F.

Myocardial fibrosis (Tables III, VI): The 3 characteristic types of fibrosis were present in the vast majority of WKY-F rats; grade 2-3 in about 70%, grade 1 in about one forth, and grade 0 in only 6% of males and 3% of females. The grade of fibrosis in the WKY-F was generally, but not always, greater in the hearts with marked cardiac hypertrophy. In the WKY-P, the grade 2-3 fibrosis was present in about 90%. Also in about 10% of the Wistar-S and SHR, anterior epicardial thickening was observed. In the Wistar-N rats, the grade 1 fibrosis was observed in about 1/3 and the grade 2 in about 10%.

Arteries in the IVS (Tables V, VI): The deviation index of the five largest arteries in the IVS tended to be higher in the WKY-F than in the other 3 strains; it was more than 30 in about one third of the WKY-F and showed a weak

correlation with the heart weight/body weight ratio (0.11~0.41, 0.06~0.37) and with the IVS thickness (0.05~0.36, 0.04~0.35). The percentage of rats with an abnormally large index tended to be greater in the WKY-P than in the WKY-F. Markedly hypertrophied WKY hearts did not necessarily contained arteries with a thick wall; obviously abnormal arterial wall thickening was seen in 14 of the 25 hearts of the WKY-H. The WKY heart without a marked hypertrophy never contained arteries with marked a wall thickening.

Continuity of fiber bundles between ventricular walls (Tables V, VI): The continuity index between the LVFW and IVS, C_{LS} , tended to be smaller in the WKY-F than in the other 3 strains, particularly in the WKY-H; in about half of the WKY-F, it was smaller than 15%; there was a high negative correlation between the C_{LS} and the heart weight/body weight ratio (-0.69~-0.82, -0.54~-0.73), and a moderate one between the C_{LS} and the IVS thickness (-0.43~-0.65, -0.40~-0.63); and also a significant negative one with the percent area of fiber disarrangement in the IVS (-0.35~-0.59, -0.30~-0.55). The percentage of rats with a decreased C_{LS} tended to be greater in the WKY-P than in the WKY-F. C_{LR} also tended to be smaller in the WKY-F than in the other 3 strains; there was a low negative correlation between the C_{LR} and normalized transverse area of the RVFW (-0.23~-0.51, -0.21~-0.49).

Electrocardiogram (Tables VII, VIII)

The axis of the QRS complex in the limb leads varied markedly from -120° to 100° in the

TABLE IX DATA FROM WISTAR RATS MAINTAINED IN KYOTO UNIVERSITY (WISTAR-K) AND SHIZUOKA DOBUTSU KYOKAI (WISTAR-SD)

		Wistar-K (M = 3, F = 3)	Wistar-SD (10, 10)
Body weight	M	358 ± 8	225 ± 3
	F	254 ± 5	169 ± 4
Blood pressure	M	122 ± 9	119 ± 10
	F	118 ± 10	120 ± 7
Heart weight	M	1549 ± 317	979 ± 124
	F	1177 ± 205	799 ± 55
Heart wt/body wt ratio	M	4.37 ± 0.95	4.68 ± 0.57
	F	4.83 ± 0.80	5.09 ± 0.51
$\frac{IVST}{LVFWT}$	M	1.23 ± 0.13	1.13 ± 0.10
	F	1.28 ± 0.42	1.15 ± 0.11
$\frac{RVWA}{BW^{2/3}}$	M	0.38 ± 0.09	0.41 ± 0.08
	F	0.45 ± 0.14	0.44 ± 0.09

Data, mean ± SD. Abbreviations as in Tables I and 2.

WKY-F. The mean voltage of the QRS complex was significantly greater in the WKY-F than in the other three strains in both the limb and Vc leads. The QRS voltages in the WKY-F correlated slightly with the heart weight/body weight ratio (0.21~0.51 in males, 0.20~0.50 in females) and with the normalized RVFW area (0.23~0.53, 0.17~0.49). The mean of the highest voltage of the T wave in limb leads and of the Vc T wave in the WKY-F were, respectively, not greater than the respective means in the other three strains. However, the T waves were obviously high in the WKY-H; there was a fairly good correlation between the T wave voltage in the limb leads and the heart weight/body weight ratio (0.56~0.76, 0.50~0.72), but no significant correlation between the Vc T wave voltage and the heart weight/body weight ratio (0.01, 0.11). The T wave voltage in the limb leads also correlated well with the normalized area of the RVFW (0.53~0.73, 0.46~0.68) and slightly with the IVS thickness (0.16~0.46, 0.13~0.43).

Using 362 male and female WKY rats, which included 122 male or female rats from other experimental series, we calculated the sensitivity and specificity of the ECG findings in determining the presence of marked cardiac hypertrophy from the following equations: sensitivity = percentage of rats with an ECG abnormality among those with a heart weight/body weight ratio greater than 5.5, specificity = percentage of rats without an ECG abnormality among those

with a heart weight/body weight ratio less than 5.5 (Table VIII). T waves higher than 0.25 mV or QRS complexes greater than 0.5 mV in the limb leads, axis deviation, or a combination of these findings showed a good sensitivity and specificity to the presence of marked cardiac hypertrophy. Furthermore, about 3/4 of rats with a false positive T wave (≥ 0.25 mV) or QRS complex (≥ 0.5 mV) had a significant right ventricular hypertrophy with a normalized transverse area of the RVFW greater than 0.4.

Results in Wistar-K and Wistar-SD Rats (Table IX)

The distribution of the heart weight/body weight ratio, IVS/LVFW thickness ratio, normalized transverse area of the RVFW in the Wistar-K and Wistar-SD rats was very similar to that in the WKY-F and -P rats. Various histologic findings were also similar. Fig.1-F shows the transverse view of the heart with typical gross-anatomic features in a female of the group of 6 Wistar-K rats.

DISCUSSION

We have shown that the gross-anatomic features of the heart are similar in WKY/NCrj, Wistar-K, and Wistar-SD rats. The Wistar-K rats had been maintained in the animal center of Kyoto University since 1951⁵. The Wistar-SD strain diverged from the Wistar-K strain in 1981.

The WKY/NCrj strain originated from the Wistar-K strain in 1971 and has been maintained by inbreeding for more than 30 generations in an environment free from specific pathogens (Commercial pamphlet from Charles River Japan Inc.). The relationship between the 3 strains strongly suggests that the determinant factors related to the development of cardiac abnormalities may have already existed in Wistar-K rats in 1971 and may have been transmitted in some unknown fashion. However, those abnormalities were never seen in the SHR/NCrj strain, which is also an inbred one originating from the Wistar-K before 1963⁵; the determinant factors may have developed after 1963 or the factors could not persist along with the development of hypertension.

The distribution of cardiac abnormalities in WKY-F rats was quite similar to that in the WKY-P rats, suggesting that the manifestation of abnormalities is due to a genetically inherited predisposition in the WKY/NCrj strain. Genetic transmission of HCM or asymmetric septal hypertrophy has been suggested in humans⁶⁻⁸ and in cats⁹ on the basis of its familial occurrence. If the determinant factors are genetically transmitted in the rat also, the gene disorder can be considered to have already existed prior to the beginning of inbreeding and to have spread widely in rats of the WKY strain, since, according to the theory of animal genetics, the maintenance of rats by inbreeding for more than 20 generations is enough to presume that the genes in the strain are homogeneous in one individual rat and similar in all the rats of that strain. In this connection, in reference to the mean $\pm$ 2SDs of normal strains, 97% of male and 96% of female WKY-F rats, and 100% of male and 97% female WKY-P rats had one or more abnormal values among the results in the present examination; this may reflect a widely spread genetic predisposition to the expression of cardiac abnormalities in the WKY/NCrj strain. However, the continuous distribution of cardiac abnormalities in WKY-F rats in wide ranges (Table III) suggests that the gene disorder may not be expressed as a definite entity as far as the pathologic features examined are concerned. Furthermore, we know little as yet about the mechanisms which could explain the development of, and correlations between, the various features, and hence it remains unclear what pathologic feature of the heart is most closely related to, or the primary manifestation of, the disordered gene.

Heart weight: The heart weight/body weight ratio was increased in relatively few of WKY-F and -P rats with reference to that of the other three strains. When we take into account the theoretical assumption of animal genetics that the disordered gene must have become widely spread in the WKY/NCrj strain, the incidence of an abnormally heavy heart does not seem to be high enough for it to be the primary phenotype of the genetic disorder. Furthermore, the WKY parents with a heavy heart did not necessarily produce offspring with a high incidence of a marked cardiac hypertrophy and vice versa, suggesting a complicated mechanism involved in the development of cardiac hypertrophy. And it seems to be difficult to make a definite criterion for the judgement of abnormality concerning the heart weight in rats with HCM. In this respect, human autopsies also have shown that the heart weight in HCM ranges widely from normal to very high (210–1250g in adults).^{10,11}

Left ventricular wall thickness: The IVS was considered to be abnormally thick in 40–50% of WKY-F and -P rats, whereas the LVFW was thick only in less than 10%. In only a small number of WKY-F and -P rats, the IVS/LVFW thickness ratio was greater than 1.3, one of the criteria for human HCM.¹² However, in more than 50% of WKY-F and 80% of WKY-P rats, the IVS/LVFW ratio was greater than 1.1, an abnormal value with reference to the mean $\pm$ 2SDs in the 3 normal strains; thus an IVS/LVFW ratio greater than 1.1 may be useful as a temporary standard of disproportionate septal thickening in rats. In this connection, several reports have suggested that an IVS/LVFW ratio smaller than 1.3 does not exclude the diagnosis of HCM in humans.^{8,13-15} Moreover, the mean IVS/LVFW ratio in cats with HCM was less than 1.1.^{16,17} Liu et al.¹⁸ suggested that an IVS/LVFW ratio greater than 1.1 may be an appropriate diagnostic criterion for disproportionate septal thickening in dogs. The greater percentage of rats with a disproportionate septal thickening in the WKY-P suggests its age-related progression.

Papillary muscle: It has been reported in humans, cats and dogs that papillary muscle involvement of HCM produces large muscle masses with a bullet-like shape.^{10,16} The normalized transverse area of papillary muscles was judged to be abnormally large in a few WKY-F rats also.

Left ventricular cavity size: In the vast majority of WKY hearts, the left ventricular

cavity was small or normal, as in human HCM^{10,11} and in the HCM of cats and dogs.¹⁶ However, in a few WKY-F and -P rats, the left ventricle was obviously dilated. In this regard, in 11 of 47 humans with HCM, the left ventricle was judged to be dilated.¹⁰ The present study did not provide any explanation of the factors which determine left ventricular dilatation in the WKY rats.

Right ventricular hypertrophy: The right ventricle was hypertrophied in about half of the WKY-F and -P rats. A study of SHR/ and WKY/NCrj rats by Haneda et al.¹⁹ also showed that the right ventricle was heavier in the WKY than in the SHR, although the total heart weight was greater in the SHR. The presence of right ventricular hypertrophy in human HCM has been noted already^{10,11}; however, no exact quantitative study has yet been done on the right ventricular hypertrophy. In cats with HCM, the mean right ventricular weight was 1.58 times greater than in normal cats, whereas the left ventricular weight was 1.47 times as great.⁹ The predominant right ventricular hypertrophy in WKY rats makes it necessary to consider the possibility that pulmonary valve dysfunctions might be the cause; a more careful examination of the valves by dissection microscopy revealed a thickening of the cusps, although the fusion of the cusps were not severe and it remains uncertain whether they are accompanied by functional disorders. Subvalvular stenosis of the right ventricle due to protrusion of the hypertrophied IVS^{11,20} may be related to the right ventricular hypertrophy in rats also. Ultimate elucidation of this problem will require right-sided hemodynamic studies.

Abnormal fiber arrangement: Muscle fiber disarrangement in the IVS in human HCM seems to be located in the midst of the latitudinally oriented fiber bundle in the midwall layer.²¹ This is not the case with HCM in rats; the latitudinal fibers in the median region of the IVS were almost always oriented smoothly, and the fiber disarrangement was most severe in or near the area of junctions. Abnormal fiber arrangement in more than 5% of the IVS was present in more than 60% of the WKY-F; such disarrangement in any of the three ventricular walls occurred in more than 90%. The high incidence of significant fiber disarrangement in WKY rats suggests that it is closely related to the probable wide distribution of the abnormal gene. Aging does not seem to be a factor promoting abnormal fiber arrangement in WKY or normal Wistar rats

as in humans.²¹ The correlation of fiber disarrangement with wall thickness or with normalized transverse wall area is considered to be not high enough, particularly in the RVFW, to indicate that the fiber disarrangement is directly related to cardiac hypertrophy. The absence of a significant correlation between the degrees of fiber disarrangement and cardiac hypertrophy has been reported in human HCM also.²²

Myocardial fibrosis: As far as we know, only one case report of human HCM²³ has described extensive fibrosis similar to the anterior and posterior fibrosis in the rat. Significant interstitial and anterior subepicardial fibrosis is usually present in and adjacent to areas of severe fiber disarrangement. This association of these 2 abnormalities suggests their close relationship, as in human HCM.²⁴ Fibrosis of these types seemed to occur more frequently in WKY-P than in WKY-F rats; furthermore, focal or microscopic scarring was often observed in the WKY-P myocardium, which was similar to that in adult SHR/NCrj rats.¹ This suggests an age-related progression of fibrosis in WKY hearts.

Leftward deviation of arteries in the IVS: In about 1/3 of WKY-F and -P rats, the location of relatively large arteries was noticeably deviated to the left. In normal hearts, a gradient of transmural pressure develops through the IVS, with the highest pressure on the left-sided sub-endocardium.²⁵ The intramural pressure is considered to be a factor of impeding coronary flow. Thus, if the right-sided development of relatively large arteries in normal hearts, as shown in the present study, occurs in accord with the transmural pressure gradients, the leftward deviation of IVS arteries in WKY hearts suggests the presence of a mechanism which interferes the normal development of the transmural pressure gradient.

Continuity of fiber bundles between LVFW and IVS or RVFW: The continuity of the latitudinal fiber bundle of the IVS with that of the LVFW (C_{LS}) was substantially decreased in about half of WKY-F and -P rats. It has been suggested that the circumferentially oriented fiber bundle through the IVS and LVFW contributes predominantly to the pressure development in the left ventricle.^{2,26} Therefore the discontinuity is considered to be disadvantageous for the generation of pressure in the left ventricle. In this connection, we have reported that, in the IVS of WKY hearts with marked hypertrophy, the hypertrophy of the myocytes is significantly

greater in the longitudinal fibers in the right and left layers than in the latitudinal fibers in the midwall layer in contrast to the predominant hypertrophy in the latitudinal fibers under pressure overloads^{2,27}; this may represent a compensatory response of the longitudinal fibers in the IVS for the disadvantage due to the uncoupling of the latitudinal fiber bundle of the IVS with that of the LVFW. The significant inverse correlation of the C_{LS} with the IVS thickness in WKY-F rats, together with the marked decrease in the C_{LS} in WKY-H rats, seems to support in part this speculation.

The continuity of the latitudinal fiber bundle of the RVFW with that of the LVFW also tended to be disturbed in WKY hearts, particularly in the anterior junctional area. It has been suggested that the latitudinal fiber bundles in the RVFW and LVFW constitute a co-operating functional unit for the generation of pressure in the right and left ventricles through their continuity^{2,28,29}. Therefore the discontinuity of the latitudinal fiber bundle of the RVFW with that of the LVFW is considered to be disadvantageous for pressure generation in the right ventricle, which may be related in part to the right ventricular hypertrophy. In this connection, in the rat heart with HCM, the myocyte hypertrophy in the RVFW was most marked in the longitudinal fibers of the inner layer in contrast to the predominant hypertrophy in the middle and outer layers under pressure overload^{2,27}.

Abnormal fiber arrangement and myocardial fibrosis were most marked in the junctional area where the continuity was disturbed, and there was a moderate inverse correlation between the degree of fiber disarrangement and the C_{LS} , suggesting a close relationship between these abnormalities. It is difficult at present, however, to explain the mechanism underlying the correlations between these abnormalities.

ECG: High voltage QRS complexes and T waves were unique in WKY/NCrj rats, particularly in those with marked cardiac hypertrophy. Although it is uncertain what these findings represent in the various abnormalities of WKY hearts, the high sensitivity and specificity of these findings to marked cardiac hypertrophy indicate that they are useful in predicting the presence of marked cardiac hypertrophy while the rats are alive. The selection of parental rats by ECG patterns might facilitate the breeding of a strain with a higher incidence of marked cardiac hypertrophy, which may serve as a better

animal model for human HCM; however, it may be doubtful whether a further enhancement of the incidence of marked cardiac hypertrophy is possible, since the strain is an established inbred one which has persisted for more than 30 generations, and the gene defect was very probably present before inbreeding was started. In either case, we must still search for the pathogenesis or mechanism of development of the abnormalities and genetic basis, to which issues the selection of parental rats by the ECG findings will contribute considerably.

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