Impaired myocardial function in spontaneously hypertensive rats with heart failure

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CONRAD, CHESTER H., WESLEY W. BROOKS, KATHLEEN G. ROBINSON, AND OSCAR H. L. BING. *Impaired myocardial function in spontaneously hypertensive rats with heart failure.* Am. J. Physiol. 260 (Heart Circ. Physiol. 29): H136–H145, 1991.—We have observed that many spontaneously hypertensive rats (SHR) between the ages of 18 and 24 mo develop findings suggestive of heart failure, including pleural and pericardial effusions, left atrial thrombi, and right ventricular hypertrophy. Isolated left ventricular papillary muscle function was studied in these animals (SHR-F), in age-matched SHRs without evidence of heart failure (SHR-NF), and in nonhypertensive controls (WKY). Preparations from SHR-F showed depression of active tension development (3.58 ± 1.75 g/mm^2; means ± SD) compared with both SHR-NF (7.17 ± 0.94) and WKY (6.17 ± 1.00) ($P < 0.01$). Shortening velocity was also depressed in SHR-F (0.95 ± 0.38 lengths/s) compared with SHR-NF (1.60 ± 0.30; $P < 0.05$) and WKY groups (2.15 ± 0.48; $P < 0.01$). Depression of muscle function was not found before 18 mo of age. Thus the aging SHR is a model in which one can observe the transition from chronic stable left ventricular hypertrophy to overt heart failure. Furthermore, left ventricular papillary muscles from SHRs with heart failure show evidence of significant contractile dysfunction, suggesting that impairment of intrinsic myocardial function underlies the development of heart failure.

left ventricular hypertrophy; cardiac muscle function; isolated papillary muscles

MYOCARDIAL HYPERTROPHY is an adaptive response of the myocardium in which the heart increases its mass to accommodate an increased load. Although hypertrophy may be a functionally important compensatory response, it has been suggested that stable hypertrophy may progress to a decompensated state, with myocardial depression and cardiac pump dysfunction (21). There has been considerable study of myocardial function with pressure overload hypertrophy in the absence of heart failure; much less is known about the transition from chronic stable hypertrophy to heart failure.

The spontaneously hypertensive rat (SHR) is a well-established model of genetic hypertension (25). Studies of spontaneously hypertensive rats (SHR) have demonstrated evidence of hemodynamic impairment in older animals (23, 26, 29), and it has been suggested that the progression from stable hypertrophy with normal cardiac function to heart failure with impaired cardiac function in the SHR is similar, in many ways, to the clinical course of patients with hypertension (35). Although findings from studies of cardiac pump function suggest left ventricular decompensation, it is unclear whether this is a result of intrinsic muscle dysfunction. A number of studies have demonstrated evidence of reduced ability of the hypertrophied myocardium to generate tension (9, 20, 32, 38). Others, however, have shown normal (1, 2, 5, 12, 15, 17, 36) or increased (4, 6, 18) active tension development. These studies have been carried out in a variety of animal models of ventricular hypertrophy of varying duration. Thus the effects of hypertrophy on cardiac muscle function and the relation of possible changes in function to the development of heart failure are unclear.

In previous studies of isolated muscle function in the SHR from 6 to 18 mo of age, we have observed animals to remain in good health, with stable or increased isolated muscle function (3, 4). We have now observed that, following a period of stable muscle function up to 18 mo of age, many SHRs develop evidence of heart failure between 18 and 24 mo of age; the present study is designed to test the hypothesis that intrinsic muscle function is depressed in the aging SHR with heart failure.

METHODS

Male spontaneously hypertensive rats (SHR) and nonhypertensive Wistar-Kyoto controls (WKY) were purchased as retired breeders at 6–9 mo of age (Taconic, Germantown, NY) and boarded at the animal facility at the Boston Veterans Administration Medical Center until the time of study (up to 24 mo of age). Systolic arterial pressure was measured by the tail-cuff method (27). To characterize the effect of age on myocardial function in the SHR, we studied SHRs at 12, 18, and 24 mo of age, as well as WKYs at these ages. For this analysis, animals were selected solely on the basis of age. A number of older SHRs had findings suggestive of heart failure, as described below, but were nevertheless included in the age analysis.

Beginning at the age of 18 mo, animals were observed daily. We noted that a number of SHRs exhibited rapid and labored respiration; these animals were studied within 1–2 wk after the time when they were noted to have respiratory difficulties. We found that most of these animals had left atrial thrombi and right ventricular hypertrophy; several had pleural and/or pericardial ef-

fusions (see Table 1). For the present study, animals were selected as members of a group of SHRs with findings suggesting heart failure (SHR-F) on the basis of rapid or labored respiration seen on clinical inspection and left atrial thrombi found on pathological examination. Several SHRs, without overt respiratory difficulties, were found to have left atrial thrombi at the time of study; these were also included in the SHR-F group. Several SHRs were found to have right ventricular hypertrophy without left atrial thrombi; these were not included in the analysis. No WKYs were found to have respiratory difficulties, left atrial thrombi, or right ventricular hypertrophy. Several SHRs with rapid and labored respiration died before they could be studied, and at autopsy these rats had the pathological findings consistent with heart failure; that is, effusions, left atrial thrombi, and right ventricular hypertrophy. An age-matched group of SHRs without any of these findings was identified for purposes of comparison (SHR-NF) as was an age-matched group of WKY.

At the time of study, rats were killed, their hearts were quickly removed, and placed in oxygenated Krebs-Henseleit solution (19) at 28°C. Papillary muscles were dissected and mounted as described below. Atria were removed, and the right ventricle was dissected free from the left ventricle. Tissues were gently blotted and weighed. Samples of left ventricle, right ventricle, lung, and liver were taken and dried at 60°C for 24 h; water content and dry left and right ventricular weights were calculated from these data. Left and right ventricular wet weight normalized by body weight (LV/BW and RV/BW, respectively) and dry weight by tibial length (LV/TL and RV/TL) (40) were used as indexes of ventricular hypertrophy.

The left ventricular anterior and posterior papillary muscles were dissected free, mounted between two spring clips, and placed vertically in a 100-ml acrylic chamber containing Krebs-Henseleit solution at 28°C and oxygenated with a mixture of 95% O_2-5% CO_2 (pH 7.38). The thinner, more uniform preparation was chosen for study. The muscles were stimulated at a rate of 12 contractions/min by parallel platinum electrodes delivering 5-ms pulses at a voltage 10% above threshold. The spring clip on the upper end of the muscle was attached to a low-inertia DC pen motor (G100-PD, General Scanning, Watertown MA), and the lower clip to a semiconductor strain gauge tension transducer (DSC-3, Kistler-Morse, Redmond, WA). A digital computer with an analog-to-digital interface allowed control of either tension or length of the preparation. Tension and length data were sampled at a rate of 1 kHz and stored on disk for later analysis.

After the muscles were mounted, they were equilibrated by contracting isotonically at a light load (on the

TABLE 1. *Clinical, pathological, and isolated muscle parameters for individual WKY, SHR-NF, and SHR-F animals*

	Experiment No.	Age, mo	Labored Respiration	Effusions	Left Atrial Thrombus	Fibrosis (gross)	LV/TL, g/cm	RV/TL, g/cm	AT, g/mm^2	CSA, mm^2
WKY										
	247	19					0.045	0.014	7.47	0.96
	372	22					0.054	0.014	4.34	1.31
	375	22					0.048	0.014	6.70	1.04
	376	22					0.051	0.014	5.23	1.05
	377	22					0.056	0.016	6.68	1.00
	378	22					0.054	0.015	7.40	0.68
	379	23					0.049	0.012	5.74	1.24
	381	24					0.059	0.015	5.37	1.16
	386	24					0.056	0.015	5.71	1.32
	401	21					0.056	0.016	7.10	1.18
SHR-NF										
	354	20				+	0.070	0.014	6.75	1.03
	355	20					0.077	0.012	5.36	1.02
	362	24				+	0.077	0.012	6.95	1.07
	365	24				+	0.077	0.014	7.82	0.73
	367	24				+	0.069	0.013	7.32	1.25
	371	22					0.074	0.016	7.00	1.07
	382	24					0.071	0.011	7.54	1.43
	408	24					0.070	0.013	8.86	0.94
	410	24					0.080	0.012	6.93	1.08
SHR-F										
	251	19	+	+	+		0.067	0.023	2.70	0.98
	353	20	+		+	+	0.075	0.027	2.39	1.27
	357	22	+	+	+	+	0.060	0.018	2.05	1.45
	358	22			+	+	0.078	0.015	4.98	0.86
	363	18	+		+		0.056	0.013	7.14	0.87
	368	22	+		+	+	0.072	0.025	2.23	0.76
	405	23			+	+	0.070	0.024	3.14	1.39
	407	23	+		+	+	0.073	0.022	4.03	1.32

LV/TL, left ventricular weight (dry)/tibial length; RV/TL, right ventricular weight (dry)/tibial length; AT, active tension; CSA, papillary muscle cross-sectional area.

TABLE 2. *Heart weight, body weight, age and blood pressure data*

	n	BP, mmHg	LV (wet), g	RV (wet), g	BW, g	LV (wet)/BW, mg/g	RV (wet)/BW, mg/g	TL, cm	LV (dry)/TL, g/cm	RV (dry)/TL, g/cm
A. 12-, 18-, and 24-mo WKY and SHR groups										
WKY										
12 mo	10	123±6	1.08±0.12	0.32±0.04	577±47	1.87±0.14	0.55±0.04	4.43±0.08	0.054±0.006	0.014±0.002
18 mo	10	138±7	0.93±0.17	0.28±0.06	453±65	2.06±0.12	0.61±0.12	4.14±0.15	0.048±0.007	0.013±0.002
24 mo	12	129±5	1.05±0.08	0.30±0.03	564±70	1.87±0.16	0.53±0.04	4.38±0.12	0.052±0.004	0.014±0.001
SHR										
12 mo	11	230±10	1.21±0.08[d]	0.26±0.02	406±22[d]	2.98±0.16[d]	0.63±0.06[d]	4.00±0.05[d]	0.067±0.004[d]	0.013±0.001
18 mo	9	179±7	1.30±0.15	0.29±0.08	356±42[d]	3.67±0.38[d]	0.81±0.24[c]	3.96±0.02[d]	0.069±0.007[d]	0.014±0.004
24 mo	12	199±11	1.45±0.10[d]	0.34±0.09	397±17[d]	3.66±0.27[d]	0.86±0.25[d]	4.06±0.06[d]	0.075±0.005[d]	0.017±0.005
B. 18–24-mo WKY, SHR-NF, and SHR-F groups										
WKY	10	125±5	1.02±0.07	0.30±0.02	563±74	1.84±0.17	0.54±0.06	4.26±0.17	0.053±0.004	0.015±0.001
SHR-NF	9	200±12	1.40±0.10	0.26±0.02	400±22	3.49±0.21	0.65±0.07	4.02±0.10	0.074±0.004	0.013±0.002
SHR-F	8	191±11	1.33±0.13	0.42±0.09	369±50	3.65±0.35	1.14±0.17	3.99±0.07	0.069±0.007	0.021±0.005

Values are means ± SD; *n*, no. of rats. BP, systolic blood pressure; LV, left ventricular weight; RV, right ventricular weight; BW, body weight; TL, tibial length. [a] $P < 0.05$, [b] $P < 0.01$ (age effect); [c] $P < 0.05$, [d] $P < 0.01$ (SHR vs. WKY); [e] $P < 0.05$, [f] $P < 0.01$ (group effect).

TABLE 3. *Heart, lung, and liver water content*

	n	LV Water, g water/g dry tissue wt	RV Water, g water/g dry tissue wt	Lung Water, g water/g dry tissue wt	Liver Water, g water/g dry tissue wt
		A. 12-, 18-, and 24-mo WKY and SHR groups			
WKY					
12 mo	10	3.54±0.07	3.96±0.16	4.46±0.27	2.22±0.09
18 mo	10	3.63±0.14	3.91±0.23	4.63±0.90	2.17±0.42
24 mo	12	3.62±0.10	3.98±0.19	4.95±0.77	2.21±0.10
SHR					
12 mo	11	3.48±0.07	3.78±0.11	4.48±0.41	2.20±0.06
18 mo	9	3.76±0.16	4.00±0.27	5.01±0.54	2.49±0.41
24 mo	12	3.77±0.14[d]	3.94±0.20	5.10±0.93	2.29±0.20
		B. 18–24-mo WKY, SHR-NF, and SHR-F groups			
WKY	10	3.55±0.09	3.88±0.15	4.53±0.55	2.10±0.21
SHR-NF	9	3.70±0.15	3.95±0.25	4.78±0.41	2.23±0.20
SHR-F	8	3.88±0.10	4.09±0.20	4.57±0.39	2.65±0.28

Values are means ± SD; *n*, no. of rats. LV, left ventricle; RV, right ventricle. See Table 2 for symbols.

TABLE 4. *Isolated muscle parameters*

	n	RT, g/mm²	AT, g/mm²	+dT/d*t*, g·mm⁻²·s⁻¹	EMD, ms	TPT, ms	$RT_{1/2}$, ms	$V_{0.5}$, lengths/s	CSA, mm²
				A. 12-, 18-, and 24-mo WKY and SHR groups					
WKY									
12 mo	10	0.89±0.25	6.23±1.12	74.5±12.8	27±3	145±11	193±16	2.18±0.42	1.22±0.21
18 mo	10	0.75±0.47	6.80±1.55	79.0±16.9	31±3	145±10	202±28	2.29±0.44	0.96±0.24
24 mo	12	0.87±0.20	6.79±1.12	74.7±14.6	32±4	157±11	211±16	2.03±0.23	1.17±0.18
SHR									
12 mo	11	1.05±0.25[c]	7.79±1.17	90.6±19.0[c]	34±1[d]	150±13[d]	205±20	2.16±0.32	1.20±0.17
18 mo	9	1.10±0.55[c]	6.75±3.23	69.0±39.6	39±5[d]	170±14[d]	201±36	1.66±0.63[c]	1.12±0.26
24 mo	12	1.22±0.57[c]	5.90±2.06	52.7±22.5[d]	37±7[d]	182±10[d]	195±29	1.46±0.43[d]	1.19±0.23
				B. 18–24-mo WKY, SHR-NF, and SHR-F groups					
WKY	10	0.62±0.23	6.17±1.00	68.8±14.7	32±5	157±14	218±30	2.15±0.48	1.09±0.19
SHR-NF	9	1.34±0.64	7.17±0.94	65.5±15.6	32±4	174±14	208±19	1.60±0.30	1.07±0.19
SHR-F	8	1.41±0.62	3.58±1.75	31.8±16.2	48±10	180±11	161±29	0.95±0.38	1.11±0.27

Values are means ± SD; *n*, no. of rats. RT, resting tension; AT, active tension; EMD, electromechanical delay time; +dT/d*t*, peak positive derivative of tension; TPT, time from onset of contraction to peak tension; $RT_{1/2}$, time from peak tension to 50% relaxation; $V_{0.5}$, shortening velocity, determined from quick releases to 0.5 g/mm² at 100 ms (normalized by muscle length at L_{max}); CSA, muscle cross-sectional area. See Table 2 for symbols.

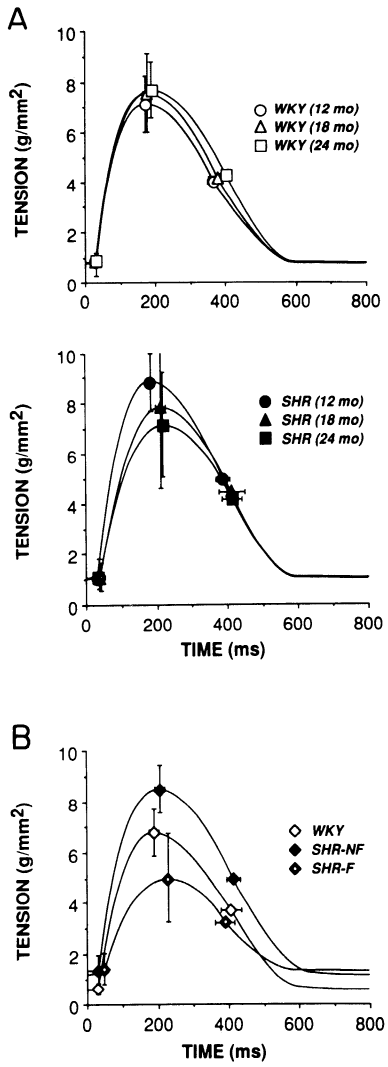

FIG. 1. Schematic representations of isometric contractions (tension vs. time) based on mean data for resting tension (RT), time to peak tension (TPT), active tension (AT), and time from peak tension to 50% relaxation ($RT_{1/2}$) (see Table 4). For each curve, left-most point represents RT at L_{max} at time of the onset of tension development (EMD). Next point to right represents peak total tension (RT + AT) at time of peak tension (EMD + TPT), and third point represents time of 50% fall in AT. Data are means ± SD. *A*: mean data for WKY and SHR groups as a function of age (12, 18, and 24 mo). *B*: mean data for 18–24 mo SHRs with heart failure (SHR-F) compared with age-matched WKYs and nonfailing SHRs (SHR-NF).

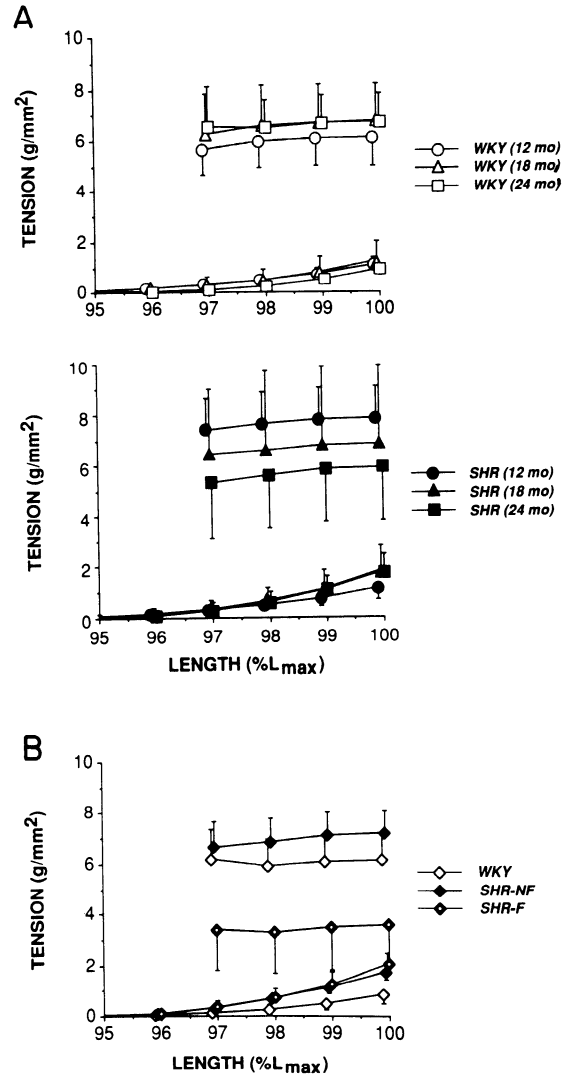

FIG. 2. Active tension (*top curves*) and resting tension (*bottom curves*) vs. length (%L_{max}). Data are means ± SD. *A*: WKY and SHR groups at 12, 18, and 24 mo. *B*: WKY, SHR-NF, SHR-F groups (18–24 mo).

order of 0.4 g/mm^2) for a period of 30 min. After this period, muscles were gradually stretched to the peak of the active tension vs. length curve (L_{max}, defined as the muscle length resulting in peak active tension) and equilibrated for an additional 15 min while performing physiologically sequenced contractions (33) with a preload equal to 50% of the preload at L_{max} and an afterload of 25% of isometric active tension at L_{max}. After this, five determinations of L_{max} were made. Once a stable L_{max} was determined, the muscle contracted isometrically at L_{max} for 5 min, and the resultant isometric contraction parameters were determined, which included resting tension (RT, g/mm^2), active tension (AT, g/mm^2, defined as peak isometric tension minus resting tension), peak rate of isometric tension development (peak +dT/d*t*, g·mm^{-2}·s^{-1}), electromechanical delay (EMD, ms, defined as the time from stimulation to the onset of tension development), time-to-peak tension (TPT, ms, defined as the time from the onset of tension development to the time of peak tension), and time from peak tension to 50% relaxation ($RT_{1/2}$, ms).

Force-velocity curves (shortening velocity vs. load) were determined from shortening velocity measurements following "quick releases" to loads ranging from 0.5 g to peak isometric tension performed 100 ms after stimulation. Release transients settled by 10 ms after release, and shortening velocity was measured using a digital smoothing and differentiating filter centered at 17 ms after the beginning of the release (31).

At the conclusion of the experiment, the muscles were removed from the clips, blotted, and weighed. Cross-sectional area was determined from muscle weight and length assuming a uniform cross-section and a specific gravity of 1.05. Muscles with cross-sectional area <0.5 or >1.5 mm^2 were excluded from analysis; there was no significant difference in cross-sectional area between groups.

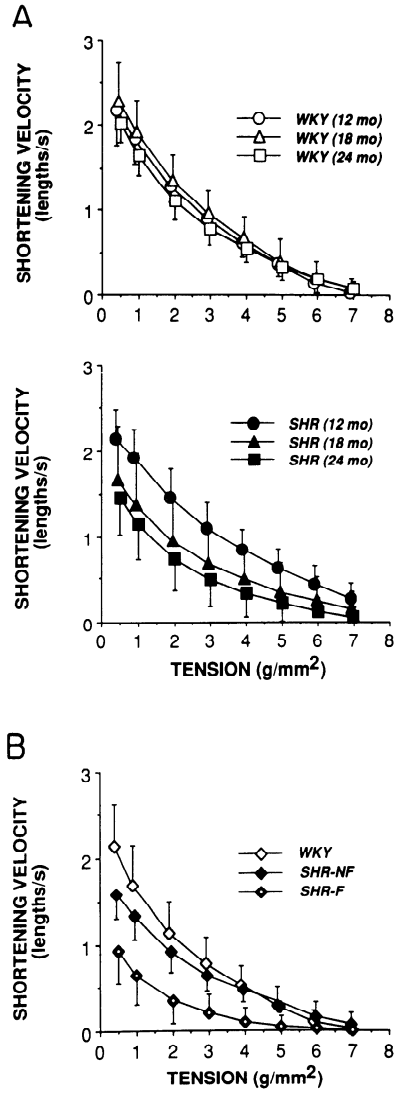

FIG. 3. Force-velocity curves (shortening velocity vs. load) for quick releases at 100 ms. Data are means ± SD. *A*: WKY and SHR groups at 12, 18, and 24 mo. *B*: WKY, SHR-NF, SHR-F groups (18–24 mo).

To determine the effect of aging on contractile function in the SHR and WKY, a group of each strain was studied at 12, 18, and 24 (±1) mo of age (SHR-12, n = 11; SHR-18, n = 9; SHR-24, n = 12; WKY-12, n = 10; WKY-18, n = 10; and WKY-24, n = 12). A two-way analysis of variance with replications (unequal cell size) (39) was used to test for strain and age effects, and the Newman-Keuls multiple sample comparison test (30) was used to localize differences where appropriate.

Data from 18- to 24-mo-old SHRs with heart failure (SHR-F; n = 8) were compared with that from age-matched nonfailing SHRs (SHR-NF; n = 9) and to WKYs (n = 10) using a one-way analysis of variance with replications and the Newman-Keuls multiple-sample comparison test. There was no significant difference in age between these three groups (SHR-F 21.1 ± 1.9 mo; SHR-NF 22.9 ± 1.8 mo; WKY 22.1 ± 1.4 mo). It should be noted that there is some overlap between the groups in the age analysis and those in the WKY vs. SHR-NF vs. SHR-F analysis. Two animals in the SHR-F group were 18 ± 1 mo of age at the time of study and were therefore included in the 18-mo-old group in the age analysis; similarly, two were 24 ± 1 mo of age and included in the 24-mo SHR group. Four other SHRs included in the SHR-F group (with ages between 20 and 22 mo) did not meet the age criteria for inclusion in either the 18 mo (17–19 mo) or 24 mo (23–25 mo) groups and were therefore not included in the age analysis. Data are expressed as means ± SD.

RESULTS

Clinical and pathological data. Clinical and pathological features of the 18–24 mo SHR-F, SHR-NF, and WKY groups are outlined in Table 1. Six SHRs between 18 and 24 mo of age were noted to have rapid labored respiration. All of these animals, as well as two not noted to have respiratory difficulties, were found to have left atrial thrombi at the time of study. In this group of eight animals (SHR-F), two had pleural and/or pericardial effusions. Six had evidence of right ventricular hypertrophy, as evidenced by increased right ventricular weight normalized by tibial length (RV/TL ≥ 0.018 g/cm) (Table 1). RV/TL ranged from 0.012 to 0.016 in WKYs and SHR-NF; RV/TL ≥ 0.018 was therefore chosen as a conservative criterion for right ventricular hypertrophy. Six animals had grossly visible endocardial fibrosis. Fibrosis was also observed in four of nine SHRs without evidence of heart failure. No WKYs exhibited any of these clinical or pathological features.

Systolic blood pressure, measured on the day before the rats were killed, was elevated in the SHR group compared with the WKY group at 12, 18, and 24 mo (P < 0.01) (Table 2*A*) and in both SHR-NF and SHR-F compared with WKY (P < 0.01) (Table 2*B*). SHRs appeared healthy and active up to the age of 18 mo, although their body weight was less than WKYs at all ages (P < 0.01). Raw and normalized ventricular weights for the 12- vs. 18- vs. 24-mo-age comparison are presented in Table 2*A* and for the WKY vs. SHR-NF vs. SHR-F comparison in Table 2*B*. Left ventricular weight was greater in SHRs than WKYs at all ages (P < 0.01), despite smaller body weight (P < 0.01). In addition, left ventricular weight was greater in the 24-mo than 12- and 18-mo SHRs (P < 0.01 and P < 0.05, respectively). Left ventricular hypertrophy was present in SHRs at all ages relative to WKYs as manifested by greater LV/BW (P < 0.01) and LV/TL (P < 0.01). Right ventricular weight was greater in SHRs than WKYs when normalized by body weight (P < 0.05), but there was no overall effect of strain or age on right ventricular weight normalized by tibial length (RV/TL) by two-way analysis of variance.

Left ventricular hypertrophy was found in both SHR-F and SHR-NF groups compared with the WKY group as manifested both by LV/BW (P < 0.01) and LV/TL (P < 0.01) (Table 2*B*). Right ventricular hypertrophy was present in SHR-F compared with SHR-NF and WKY groups both by RV/BW (P < 0.01) and RV/TL (P < 0.01).

Heart, lung, and liver water content data for the 12- vs. 18- vs. 24-mo comparison are presented in Table 3*A* and for the WKY vs. SHR-NF vs. SHR-F analysis in

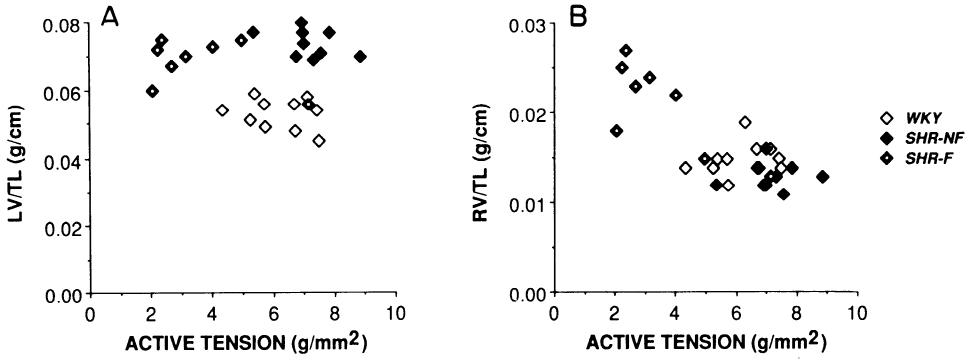

FIG. 4. Individual values for left ventricular weight normalized by tibial length (LV/TL; *A*) and right ventricular weight normalized by tibial length (RV/TL; *B*) plotted vs. isolated left ventricular papillary muscle active tension for 18- to 24-mo-old WKY, SHR-NF and SHR-F groups. Data are means ± SD. There is comparable left ventricular hypertrophy in SHR-NF and SHR-F groups. RV/TL is greater in SHR-F group than in SHR-NF and WKY groups. Active tension is depressed in muscle preparations from SHR-F, indicating that impaired left ventricular muscle function is associated with right ventricular hypertrophy (see text for discussion).

Table 3*B*. In the age analysis (Table 3*A*), left ventricular water content (expressed as g water/g dry wt) was increased in 18- and 24-mo-old SHRs compared with 12-mo-old SHRs ($P < 0.01$) and in 24-mo-old SHRs compared with WKYs ($P < 0.01$). There was no significant effect of strain or age on right ventricular water content. Lung water was slightly increased in both SHRs and WKYs at 24 mo compared with 12 mo ($P < 0.05$). Liver water was unchanged with strain or age. In the WKY vs. SHR-NF vs. SHR-F analysis (Table 3*B*), left ventricular water content was increased in the SHR-F group ($P <$ 0.01 vs. SHR-NF, WKY); there was no difference in right ventricular water content. Lung water content was not significantly different in the three groups, whereas liver water was increased in the SHR-F group compared with the SHR-NF and WKY groups ($P < 0.01$).

Isometric contraction parameters. Mean data for isometric contraction parameters for the 12- vs. 18- vs. 24-mo age comparison are presented in Table 4*A* and for the WKY vs. SHR-NF vs. SHR-F comparison in Table 4*B*. Schematic contractions based on these data are presented in Fig. 1; RT and AT as a function of length are presented in Fig. 2. There was no significant difference in cross-sectional area among any of the groups studied.

In the 12-, 18-, and 24-mo-old SHR and WKY groups (Table 4*A*), RT at L_{max} was greater in SHRs compared with WKYs at all three ages ($P < 0.05$); there was no significant age effect. There were no significant differences in AT with either strain or age. The peak rate of isometric tension development (peak +dT/d*t*) was greater in the SHR than in the WKY group at 12 mo of age ($P < 0.01$) but less at 24 mo ($P < 0.01$). TPT increased with age in both groups [at 24 mo in the WKY group ($P < 0.05$) and at 18 and 24 mo in the SHR group ($P < 0.01$)] and was greater in the SHR compared with the WKY group at both 18 and 24 mo ($P < 0.01$). EMD was greater in SHRs compared with WKYs at all ages ($P < 0.01$); there was no significant age effect. There was no significant difference in $RT_{1/2}$ with either strain or age.

When comparing the SHR-F group to age-matched (18–24 mo) nonfailing SHRs (SHR-NF) and WKYs (Table 4*B*), RT was greater in SHRs compared with WKYs ($P < 0.01$). AT was reduced in SHR-F compared with both SHR-NF and WKY (3.58 ± 1.75 vs. 7.17 ± 0.94 and 6.17 ± 1.00; $P < 0.01$) as was +dT/d*t* (31.8 ± 16.2 vs. 65.5 ± 15.6 and 68.8 ± 14.7; $P < 0.01$). EMD was increased in SHR-F compared with SHR-NF and WKY ($P < 0.01$), whereas TPT was increased in both SHR-NF and SHR-F compared with WKY ($P < 0.01$). $RT_{1/2}$ was reduced in the SHR-F compared with both SHR-NF and WKY ($P < 0.01$). These changes can be seen in the schematized isometric contractions presented in Fig. 1*B*.

Shortening velocity vs. load relations. Shortening velocity vs. load ("force-velocity") relationships are shown in Fig. 3; mean data for shortening velocity ($V_{0.5}$; quick releases to 0.5 g/mm^2 at 100 ms) are presented in Tables 4*A* (12- vs. 18- vs. 24-mo age analysis) and 4*B* (WKY vs. SHR-NF vs. SHR-F comparison). As shown in Fig. 3*A*, there was no evident change in shortening velocity with age in the WKY, whereas shortening velocity was reduced in the SHR at 18 and 24 mo compared with 12 mo ($P < 0.05$ and $P < 0.01$, respectively). In the WKY vs. SHR-NF vs. SHR-F analysis (Fig. 3*B* and Table 4*B*), there was a modest but significant reduction in shortening velocity in the SHR-NF (at light loads) compared with WKY (1.60 ± 0.30 vs. 2.15 ± 0.48 lengths/s; $P <$ 0.01) and a greater reduction in SHR-F (0.95 ± 0.38; P < 0.01 vs. SHR-NF, WKY).

DISCUSSION

It has been hypothesized that chronic pressure overload results in a state of chronic stable (compensatory) hypertrophy, followed by decompensation, with the development of overt heart failure (21). In previous studies of isolated muscle function in the SHR, a long period of stable or increased muscle function has been observed (3, 4, 8). In the present study, we find clinical and pathological evidence of heart failure, associated with impaired left ventricular papillary muscle function, in many SHRs between 18 and 24 mo of age.

It is interesting to note that the degree of left ventricular hypertrophy does not correlate with the impairment of left ventricular papillary muscle function. Right ventricular hypertrophy, on the other hand, is associated with depressed left ventricular muscle performance (Fig.

4). This association is consistent with the concept that left ventricular dysfunction results in elevated left-sided filling pressures, with secondary pulmonary hypertension and right ventricular hypertrophy. This possibility is supported by the observation that right ventricular hypertrophy is also seen in rats with large left ventricular infarctions induced by coronary artery ligation (1). It should be pointed out that biventricular hypertrophy has been reported in some WKY rats (28); thus right ventricular hypertrophy may occur in the absence of left heart failure. In the present study, right ventricular hypertrophy was not found in any age-matched WKYs. One must also consider the possibility that right ventricular hypertrophy might result from primary pulmonary pathology. Therefore, the finding of right ventricular hypertrophy should be accompanied by other findings consistent with left ventricular dysfunction to provide convincing evidence that impaired left ventricular function is the cause of right ventricular hypertrophy. Endocardial fibrosis was observed in both the SHR-NF and SHR-F groups, indicating that this finding is not specific for heart failure. While it is possible to have left ventricular failure in the absence of atrial thrombi or atrial thrombi in the absence of failure, the association of left atrial thrombi with poor left ventricular papillary muscle function in the SHR-F group suggests that left atrial thrombi are related to disease of the left ventricle.

Lung water, while increased slightly with age (24 mo) in both WKYs and SHRs, was not significantly different in the SHR-F compared with SHR-NF and WKY groups. While this might suggest that left ventricular filling pressures are not elevated in the SHR-F, Erdmann et al. (11) have shown the lung to be protected against extravascular fluid accumulation induced by hydrostatic pressure elevation. They conclude that the major factors responsible appear to be increases in lymph flow and interstitial protein washout. This observation may explain why there is no evident increase in lung water in the SHR-F. Liver water is increased in the SHR-F, suggestive of elevated right-sided filling pressures.

In the present study, we have observed clinical and pathological features suggestive of heart failure in the SHR. Cooper and Tomanek (8) studied SHRs at 1 and 2 yr of age and found no evidence of heart failure or impaired muscle function. While their findings in 12-mo-old animals are similar to ours, it is unclear why heart failure or impaired papillary muscle tension development was not seen in any of their 2-yr-old animals. There may be differences in the specific strain of SHRs studied (tail-cuff blood pressure, for example, was somewhat lower in their animals than in the present study). Others have studied hemodynamics and cardiac pump function in comparable animals, finding normal function in mature animals with stable hypertrophy and evidence of reduced function in older animals (16, 23, 26, 29). Pfeffer et al. (29) studied male Wistar, WKY, and SHR rats from 11 to 83 wk of age, using a volume infusion method. Peak stroke volume and cardiac index (normalized by left ventricular weight) were noted to be decreased in the 82-wk-old SHR compared with the controls. A later study (26) of 13- to 90-wk-old rats found function to be preserved in the Wistar and WKY at all ages and the SHR up to 52 wk, but a reduction in peak stroke volume and cardiac output in the 90-wk-old SHRs was noted and associated with an increase in left ventricular fibrosis and right ventricular hypertrophy. Mirsky et al. (23) studied female SHR and control animals (Wistar, WKY) at 6, 12, 18, and 24 mo of age using the same volume infusion method. They found a reduction in baseline and peak cardiac index in the 24-mo-old SHRs compared with controls, as well as a downward shift in the ejection fraction vs. afterload relation in 18- and 24-mo-old SHRs. Thus evidence of impaired cardiac function in intact animal studies parallels our clinical and pathological observations consistent with a transition to heart failure in the aging SHR.

Several studies have examined isolated muscle function in other models of heart failure. Right heart failure with depression of isolated muscle function has been observed in the cat with pulmonary artery banding (13, 32, 38), and Williams et al. (38) have demonstrated depression of right ventricular muscle function (at 72 wk) after a period of stable function (52 wk) in this model. Although the duration of right ventricular pressure overload relative to total life span is relatively short in these feline studies compared with the duration of left ventricular pressure overload in the SHR, the findings are consistent with those of the present study. The present study indicates that myocardial depression can be demonstrated in left heart failure following long-term left ventricular pressure overload due to hypertension. Yin et al. (41) have suggested that senescence may contribute to the alterations in myocardial function observed in the aging SHR beyond those changes attributable to hypertrophy alone.

We did not observe evidence of progressive left ventricular hypertrophy, based on the left ventricular weight-to-tibial length ratio, with aging in the WKY group in the present study, whereas alterations were noted in the time course of contraction. Although myocyte hypertrophy may be present with aging (34), these findings are consistent with the concept that senescence may cause functional alterations. Thus it is possible that factors related to aging, superimposed on chronic pressure overload, may contribute to the development of impaired myocardial function in the aging SHR.

The reduction in tension development in the failing SHR might be caused by one or more of a number of possible factors, related to a reduction in number of viable cells or to an alteration in cellular function. Engelmann et al. (10) studied SHR and WKY at 1 to 24 mo of age using morphometric techniques. They found the fractional area occupied by myocytes and interstitial space to be comparable in 1-mo-old SHRs and WKYs. At 12 mo, the SHR group had a greater percentage of myocytes and a smaller percentage of interstitial space, whereas this pattern was reversed at 24 mo. These data are consistent with our previous findings that contractile unit density and active tension is greater in SHRs compared with WKYs up to 18 mo of age (4) and those of the present study, in which active tension was found to be reduced in SHRs with evidence of failure. Myocardial ultrastructural changes have been reported in the aging SHR (34) that may relate to cellular dysfunction with

chronic pressure overload. Thus reduced ability of the myocardium to develop tension might result from abnormalities in function occurring at the level of the cell. Furthermore, coronary vascular pathology (14) and reductions in capillary density (per unit area) (10, 34) have been demonstrated in the aging SHR, although these changes may be partly due to the presence of fibrosis. Wexler et al. (37) found evidence of myocardial infarction, with fibrosis, ventricular aneurysm formation, and mural thrombi in SHRs studied up to 28 mo of age, suggesting progressive coronary vascular pathology with age and sustained hypertension. Although it is difficult to establish a causal relationship between vascular changes and pathological or functional abnormalities, it is possible that vascular changes might result in ischemia, cell loss, and fibrosis.

The present study implies a reduction in tension development per unit myocardium rather than per myocyte or contractile unit. A reduction in the density of contractile units, with or without an intrinsic defect in the contractile units, could explain the results noted here; further studies would be necessary to clarify the issue of whether or not there is a defect in function at the level of the myocyte or the contractile filaments themselves.

Shortening velocity, as determined by the quick-release method, did not change appreciably over the range of ages studied in the WKY, whereas the older SHRs showed a decrease in shortening velocity. In contrast to active tension development (where SHR-NF were not different from WKY at 24 mo), shortening velocity was reduced in the SHR-NF compared with the WKY group, and a further decrease was seen in SHR-F. While factors such as cell loss might affect shortening velocity as well as tension development, the apparent dissociation between shortening velocity and active tension might be due to factors such as changes in myosin isozyme composition (5, 7, 20, 22), which may alter shortening velocity without causing a reduction in active tension development. It has been shown that the proportion of V3 myosin is increased in the aging SHR (7, 22), and this may contribute to the observed reduction in shortening velocity. The functional significance of depression of shortening velocity vs. depression of active tension development is uncertain; whereas both may result in abnormalities of cardiac pump function, it appears that depression of tension development is only seen in the group of animals with heart failure. It is possible that depression of shortening velocity (with preserved tension development) does contribute to the pump dysfunction without overt heart failure noted in the aging SHR (23, 26, 29) but that overt heart failure results when tension development is depressed.

Several other features of the isometric contraction in the SHR-F are of interest. Resting tension at L_{max} was noted to be greater in SHRs compared with WKYs overall, without any significant difference between SHR-NF and SHR-F. While resting tension at L_{max} is subject to considerable experimental uncertainty, and can serve only as an index of myocardial passive properties; this finding is consistent with previous studies suggesting increased passive stiffness in chronic hypertrophy (23, 24) and suggests an alteration in myocardial passive properties in the SHR.

Electromechanical delay time and time to peak tension might both be considered indexes of the contractile activation time. Electromechanical delay was greater in SHRs than WKYs at all ages and was greatest in the SHR-F. Time-to-peak tension was greater in both the SHR-NF and SHR-F groups compared with age-matched WKYs, suggesting a prolongation of activation in the SHR. These changes in both electromechanical delay time and time-to-peak tension suggest alterations in excitation-contraction coupling, which are progressive with age, and more marked with hypertrophy and heart failure.

Thus the aging SHR is a model of chronic stable hypertrophy with late transition to left ventricular failure. The development of myocardial failure is associated with clearly demonstrable impairment of intrinsic muscle function. This model lends itself to studies of the mechanisms, treatment, and prevention of a pathological process of major clinical importance.

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