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Performance of Papillary Muscles from the Aging Spontaneously Hypertensive Rat: Temporal Changes in Isometric Contraction Parameters[1] (42551)

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Abstract. Myocardial mechanics in the male spontaneously hypertensive rat (SHR) and Wistar–Kyoto rat (WKY) at 18 months of age were studied. Left ventricular hypertrophy was documented in the SHR by an increase in left ventricle/body weight and left ventricle/tibial length ratios when compared to the WKY ($P < 0.001$). Isolated left ventricular papillary muscles were studied at 28°C while contracting 12 times/min at the apex of the length–tension curve. Active and passive length–tension relations were measured at relatively early (65 ± 3 min) and late (200 ± 5 min) times following sacrifice. No significant differences in passive length–tension relations between strains were observed. Between early and late measurements, a significant decrease in passive tension within the length spectrum 89–100% L_{max} occurred in both SHR and WKY, accompanied by a significant increase in passive stiffness ($P < 0.01$, SHR; $P < 0.001$, WKY). Isometric performance was measured at relatively early (81 ± 3 min) and later (190 ± 5 min) times following sacrifice. Strain differences in active muscle performance were of a greater electromechanical delay time (EMD) ($P < 0.05$, early; $P < 0.001$, late) and time-to-peak tension (TPT) ($P < 0.001$, late) in SHR compared to WKY. Between early and late measurements, decreases in EMD ($P < 0.01$, SHR; $P < 0.001$, WKY), TPT ($P < 0.001$; $P < 0.001$), the half-time of relaxation ($P < 0.001$; $P < 0.001$), and the resting tension ($P < 0.01$; $P < 0.001$) were observed, and the maximum rate of fall of tension increased ($P < 0.01$; $P < 0.01$). We conclude that studies must be precisely referenced from the time of sacrifice of the animal in order to accurately evaluate the effects of experimental hypertrophy on isolated muscle performance. No evidence for the depression of papillary muscle isometric performance was seen in the 18-month SHR when compared to the WKY, although prolonged EMD and TPT were observed.

The effects of hypertrophy on myocardial performance remain controversial. Isometric performance of preparations from hypertrophied hearts has been reported as normal (1–8), enhanced (3, 9–11), depressed (12, 13), and transiently depressed (14, 15). Possible reasons for the variability in findings include species and strain differences, ventricle choice, method for producing hypertrophy, time after load imposition, and variation in technique among laboratories (16). The present study utilized the 18-month-old spontaneously hypertensive rat (SHR), chosen from the available models of hypertrophy because it is considered to be a model of essential hypertension in man (17–20) and because hemodynamic performance in the SHR has been reported to be impaired in the SHR at 18 months of age (19, 21–23). Prior to 18 months, the SHR maintains a relatively prolonged period of apparently stable hypertrophy. In order to further elucidate fundamental pathophysiological events occurring in hypertrophied myocardium at the time of impaired hemodynamic function, the intrinsic properties of isolated left ventricular muscle preparations from 18-month SHRs were compared with those of age matched Wistar–Kyoto (WKY) rats.

In previous studies we have noted that the mechanical properties of isolated muscle preparations vary to some extent over the duration of an experiment. The temporal characteristics of the contraction and the passive properties of the preparation were among the factors which appeared to be affected. Since these parameters are also among those most

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consistently reported as altered in studies of cardiac hypertrophy, it is necessary to evaluate these changes in a particularly careful and systematic fashion.

Materials and Methods. Male spontaneously hypertensive rats (n = 15) and normotensive Wistar–Kyoto rats (n = 13) were studied at 18 months of age. All rats were housed under identical conditions, maintained on a 12-hr light/dark cycle, and had free access to food and water. Body weights (body wt) ranged from 340 to 554 g. Systolic arterial pressures were measured weekly (24) and at time of sacrifice averaged 176 ± 2 mm Hg in the SHR and 139 ± 3 in the WKY ($P < 0.001$).

Hearts from freshly decapitated rats were quickly removed and placed in oxygenated Krebs–Henseleit solution at 28°C (25). The composition of the solution in millimolarsper liter was as follows: 118.5 NaCl, 4.69 KCl, 1.25 CaCl, 1.16 $MgSO_4$, 1.18 KH_2PO_4, 5.50 glucose, and 25.88 $NaHCO_3$. The anterior papillary muscle of the left ventricle was dissected free, placed between two spring clips, mounted vertically in a 100-ml Plexiglas chamber containing Krebs–Henseleit solution at 28°C, and gassed with 95% O_2 and 5% CO_2, resulting in a pH of 7.3–7.4. The time between animal sacrifice and completion of the muscle mounting procedure was less than 5 min. The muscle was stimulated to contract at a frequency of 12/min by parallel platinum electrodes delivering 5-msec pulses at voltages 10% greater than the minimum necessary to produce a maximum mechanical response. The spring clip on the tendon end of the muscle was connected to the lever arm of a low inertia dc motor (General Scanning, Model G 100PD) above the chamber; the spring clip on the lower end of the muscle was attached to a semiconductor strain gauge transducer (Kistler-Morse Corp., Model DSC3) immersed in the bath. Damage to the ends of the preparation was assumed to be consistent throughout the experiments, and the resultant artifact introduced into the measurements was assumed to be comparable between strains. The muscle preparation and the muscle load control system have been described in detail elsewhere (26). Basically, the force or length of the preparation could be adjusted by means of an electronic servosystem (27) controlled by a digital computer (Data General Corp., Nova 2). Muscle contractions were recorded by an analog-to-digital converter which sampled muscle length and force at a rate of 1 kHz (28). Quantitation error was less than 5 μm for length and 20 mg for force. Contractions were examined on a CRT display screen and recorded on magnetic disk for future analysis.

Newly mounted muscles contracted isotonically against a light load of 0.4 g for 30 min during an equilibration period, followed by 15 min of physiologically sequenced contractions. At 65 ± 3 min following sacrifice, preparations were lengthened gradually to the peak of their length–tension curve (L_{max}) by means of an automatic computer routine which monitored the third isometric contraction following successive 1% increases in muscle length and halted when developed force declined from its previous value. The L_{max} routine was repeated five times, usually with excellent replication. Muscles then contracted isometrically at L_{max} for 5 min. At 81 ± 3 min following sacrifice, five isometric contractions at L_{max} were recorded for later analysis and average values for active tension (AT), resting tension (RT), maximum rate of rise of tension ($+dT/dt$), maximum rate of fall of tension ($-dT/dt$), and half-time of relaxation (RT1/2) were calculated. Electromechanical delay time (EMD) was determined by measuring the time interval from muscle stimulation to the time when muscle force crossed a threshold of 100 mg. The five isometric contractions were almost identical, with differences between measured parameters averaging less than 1%. Isometric and length–tension relations were repeated approximately 2 hr after the first set of measurements, at 190 ± 5 min, and 200 ± 5 min following sacrifices, respectively. The absolute lengths of the muscle preparations were measured after the early measurement sequence and prior to the late measurement sequence using a 40× Gaertner cathetometer. During these muscle length measurements, the servosystem was in isotonic mode with preload equal to the average passive tension at L_{max} recorded during the five early L_{max} routines.

At the end of each experiment, muscles were removed from the spring clips, blotted, and weighed. Cross-sectional area was calculated assuming cylindrical uniformity and a density of 1.00 g/cm^3. Preparations with cross-sectional areas greater than 1.5 mm^2 were not

TABLE I. ANIMAL, HEART, AND TIBIA DATA

	LV (g)	RV (g)	BW (g)	TL (dry) (cm)	CSA (mm^2)	LV/BW ($\times 10^3$)	RV/BW ($\times 10^3$)	LV(dry)/ TL(dry) (g/cm)	RV(dry)/ TL(dry) (g/cm)
SHR ($n = 15$)	1.42 ± 0.04	0.30 ± 0.02	404.93 ± 10.30	4.04 ± 0.04	1.13 ± 0.06	3.53 ± 0.10	0.74 ± 0.04	0.074 ± 0.002	0.014 ± 0.001
$P <$	0.0001	NS	0.01	0.05	NS	0.0001	0.05	0.0001	NS
WKY ($n = 13$)	0.87 ± 0.03	0.28 ± 0.01	455.00 ± 15.13	4.13 ± 0.02	1.06 ± 0.07	1.91 ± 0.04	0.62 ± 0.03	0.047 ± 0.001	0.014 ± 0.001

Note. LV = left ventricle; RV = right ventricle; BW = body weight; TL = tibial length; CSA = papillary muscle cross-sectional area. Means ± SEM.

included in the data base used for this study. Approximately 20% of the SHR papillary muscles which were isolated had cross-sectional areas greater than 1.5 mm^2 and were excluded from analysis. Thus, preparations of similar muscle cross-sectional areas were compared (see Table I). All force data compiled during the protocol were normalized by the cross-sectional area of the muscle and all length data were normalized by the muscle length.

Both tibias were removed and the atria and right ventricular free wall (RV) were dissected from the left ventricle (LV, including intraventricular septum), after which both ventricles were weighed. The ventricles and tibias were placed in a drying oven at 80°C, tissue samples were reweighed, and tibias were measured 24 hr later for calculation of dry LV/dry tibial length (TL) and dry RV/TL ratios (29, 30).

Body and ventricular weights, tibia and papillary muscle lengths, iosmetric performance, and length–tension data were evaluated statistically using paired (early vs late) and unpaired (SHR vs WKY) *t* tests. When data were of unequal variance as determined by the *F* test—occurring in 7% of the comparisons—the appropriate *t* test for unequal variance was employed. When data were nonnormal—occurring in 7% of the comparisons—either the nonparametric Wilcoxon signed rank test (for paired data) or the Wilcoxon Mann–Whitney ranked sum test (for unpaired data, preceded by the Ansari–Bradley test for equality of dispersion) was employed. Passive length–tension relations were assumed to be exponential with an asymptote at zero tension; tension = Ae^{BL}, where A and B are constants and L equals muscle length expressed as a percentage of L_{max}. To characterize B—the "passive stiffness index (length^{-1})"—the natural logarithms of all tension data were derived, and linear regression analyses were performed on all length–ln(passive tension) relations. Passive stiffness indices were compared using either a paired (early vs late) or unpaired (SHR vs WKY) *t* test (31). All values expressed are means ± SEM.

Results. *Body and ventricular weights and tibia length data (Table I).* WKY body weight was significantly greater than that of SHR ($P < 0.01$), yet the reverse relationship was true

for left ventricular weight ($P < 0.001$). With ventricular weight expressed relative to body weight, LV/BW was greater for SHR than for WKY ($P < 0.001$). RV/BW was similarly elevated in SHR ($P < 0.05$). Ventricular weight-to-tibial length ratios were also utilized to evaluate cardiac hypertrophy (29, 30), and LV/TL was elevated in the SHR compared to WKY ($P < 0.001$). SHR and WKY right ventricle weights and RV/TL were similar, as were left ventricular papillary muscle cross-sectional areas.

Isometric performance (Table II). Eight isometric performance parameters were measured. A significant prolongation of electromechanical delay time and time-to-peak tension was observed in the SHR compared to WKY: EMD was longer in SHR at both early and late measurements ($P < 0.05$; $P < 0.001$, respectively); TPT was longer in SHR at both measurements, also, but significantly so only at the late measurement time ($P < 0.001$).

Significant differences between early and late measurements for five parameters were seen in both SHR and WKY. EMD ($P < 0.01$, SHR; $P < 0.001$, WKY), TPT ($P < 0.001$, SHR; $P < 0.001$, WKY), the half-time of relaxation ($P < 0.001$, SHR; $P < 0.001$, WKY), and the resting tension ($P < 0.01$, SHR; $P < 0.001$, WKY) all decreased with time, while $-dT/dt$ increased ($P < 0.01$, SHR; $P < 0.01$, WKY). No significant time-dependent differences for active tension, total tension, or $+dT/dt$ were found.

Length–tension relations (Fig. 1). All muscle preparations were lengthened to L_{max} in 1% increments. At early and late measurements, the length of SHR muscle preparations averaged 7.040 ± 0.462 and 7.054 ± 0.469 mm, respectively (P = not significant), averaging a 0.13 ± 0.19% change in length. WKY preparations increased in length from 7.648 ± 0.473 to 7.729 ± 0.479 mm between early and late measurements ($P < 0.001$), averaging a 1.05 ± 0.19% change in length.

Although SHR passive and active tensions were elevated relative to WKY at both early and late measurements (Fig. 1, top panel), differences between strains were not statistically significant (except for one point).

Between early and late measurements, passive tension declined significantly over the entire length of the spectrum, 89–100% of L_{max}

TABLE II. ISOMETRIC CONTRACTION PARAMETERS MEASURED AT L_{max}

		EMD (msec)	TPT (msec)	RT1/2 (msec)	RT (g/mm^2)	AT (g/mm^2)	TT (g/mm^2)	$+dT/dt$ (g/mm^2/sec)	$-dT/dt$ (g/mm^2/sec)
SHR ($n = 15$)	Early	41.29 ± 2.92	180.69 ± 2.93	223.69 ± 8.42	1.79 ± 0.22	7.20 ± 0.58	9.00 ± 0.50	72.46 ± 6.72	26.36 ± 1.81
	$P <$	0.01	0.001	0.001	0.01	NS	NS	NS	0.01
	Late	35.41 ± 1.31	166.37 ± 2.63	211.36 ± 6.85	1.36 ± 0.19	7.21 ± 0.58	8.57 ± 0.54	76.27 ± 7.06	28.05 ± 2.23
WKY ($n = 13$)	Early	34.41 ± 1.38	172.84 ± 4.57	233.23 ± 10.22	1.25 ± 0.15	6.31 ± 0.64	7.53 ± 0.58	65.97 ± 7.20	21.97 ± 1.95
	$P <$	0.001	0.001	0.001	0.001	NS	NS	NS	0.01
	Late	29.05 ± 1.00	150.85 ± 2.76	199.72 ± 7.20	0.95 ± 0.13	6.48 ± 0.51	7.43 ± 0.50	72.23 ± 5.59	25.98 ± 1.68
SHR vs WKY	Early $P <$	0.05	NS	NS	NS	NS	NS	NS	NS
	Late $P <$	0.001	0.001	NS	NS	NS	NS	NS	NS

Note. Measured at 81 ± 3 min (early) and 190 ± 5 min (late) following sacrifice. EMD = electromechanical delay time; TPT = time-to-peak tension; RT1/2 = half-time of relaxation; RT = resting tension; AT = active tension; TT = total tension; $+dT/dt$ = maximum rate of rise of tension; $-dT/dt$ = maximum rate of fall of tension. Means ± SEM.

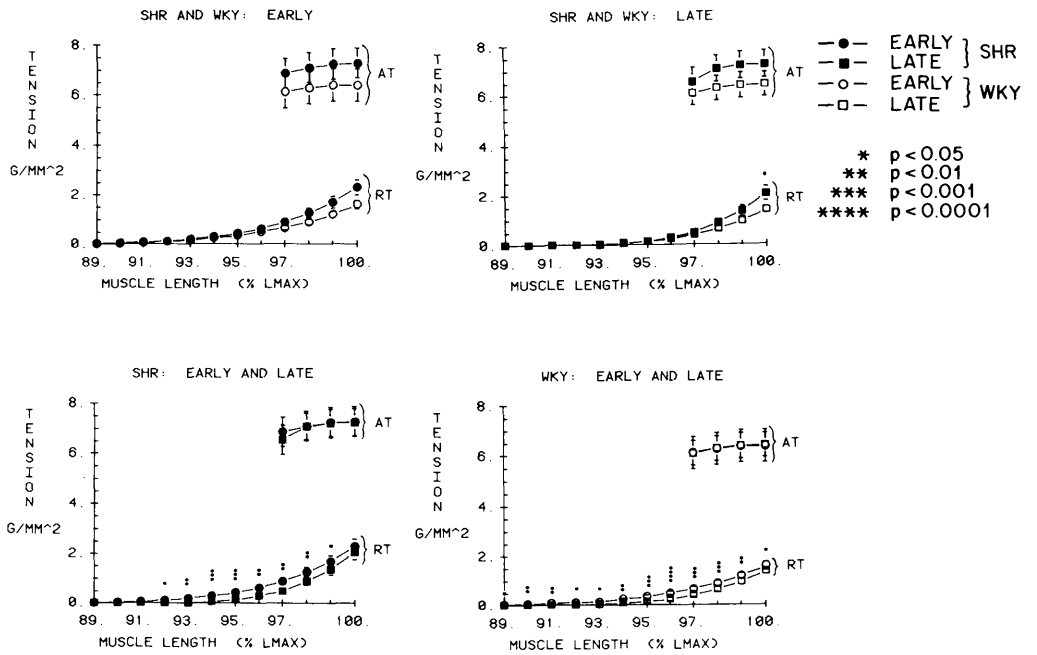

FIG. 1. Active and passive (or resting) length–tension relations for muscle preparations from 18-month-old spontaneously hypertensive rats (SHR, $n = 15$) and age-matched normotensive Wistar–Kyoto rats (WKY, $n = 13$), measured at 65 ± 3 min (early) and 200 ± 5 min (late) following sacrifice. Upper panel: strain effects—early (left) and late (right). Differences between SHR and WKY were statistically insignificant. Lower panel: time effects—SHR (left) and WKY (right). Passive tension decreased significantly with time, and passive stiffness increased significantly ($P < 0.01$, SHR; $P < 0.001$, WKY).

in WKY and 92–99% of L_{max} in SHR. In contrast, peak active tension was stable over time (Fig. 1, bottom panel).

Passive stiffness indices averaged 0.461 ± 0.058 for SHR early, 0.347 ± 0.038 for WKY early, 0.620 ± 0.105 for SHR late, and 0.533 ± 0.055 for WKY late. No significant differences in the passive stiffness indices were present between strains. Between early and late measurements, the passive stiffness indices increased significantly in both SHR ($P < 0.01$) and WKY ($P < 0.001$).

Discussion. It was discovered in the present study that the time of measurement was an extremely important factor in evaluating the performance of muscle preparations. The papillary muscles underwent an equilibration period of $\frac{1}{2}$ hr, and over 1 hr elapsed prior to initial measurements. Yet, it appears that preparations never attained totally equilibrated performance during the study, which encompassed over 3 hr. Between early and late measurement sequences, in both SHR and WKY, preparations demonstrated decreased passive tension, increased passive stiffness, and abbreviated isometric responses. Had less exacting procedures relative to time been followed, false differences between groups might have been suggested and/or differences which were present might have remained undetected. This study emphasizes the importance of recording parameters at specific times precisely referenced from time of sacrifice.

The only distinctions in isometric performance between the preparations from hypertrophied and control strains of animals were an increased EMD and TPT in the SHR. Other investigators have observed an increased TPT in rats with aortic constriction (14), renal artery coarctation (9, 32), and after DOCA treatment (6). In contrast to these treatments which produce acute hypertension, there is no significant change in TPT in the SHR until 18 months despite considerable hypertrophy (2). The fact that a prolonged TPT is seen only after acute loading of the left ventricle or after

protracted hypertension in the SHR may be consistent with the suggestion (2, 3, 15) that changes in intrinsic muscle performance result from the load on the muscle and not from hypertrophy. Others, however, maintain that at least some alterations in myocardial mechanics are the result of hypertrophy itself (14).

Although the SHR is considered a model of essential hypertension in man (17–20), cardiac hypertrophy is thought by some not to be entirely the result of elevated blood pressure in the SHR. The SHR apparently begins to develop hypertrophy prior to the appearance of hypertension, and treatment data suggest at least a partial dissociation between blood pressure and hypertrophy in the SHR (33, 34). These observations support the possibility of genetic cardiomyopathy in the SHR, which might be expected to diminish myocardial performance. The present study, however, demonstrates no depression of isometric performance in the isolated left ventricular papillary muscle of the SHR.

After studying left ventricular papillary muscles from renal artery banded rats at 5 to 30 weeks postoperation, Capasso *et al.* (9) predicted that longer-term studies would demonstrate a depression of force development. Depressed force development of isolated muscle preparations in late stages of chronic hypertension may occur in the SHR as well. The present study, however, presents no evidence for impaired force development in the SHR at the relatively advanced age of 18 months.

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