culating activity. Electrophoretically faster immunoglobulins contained passive cutaneous anaphylactic activity but no detectable flocculating titer. A pure platelet suspension from sensitized rabbits did not release histamine when challenged with antigen. Histamine release did occur in the presence of whole washed blood when similarly challenged. A significant increase in histamine release was noted when normal blood platelets in a suspension of washed sensitized cells were added to antigen.

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The Series Elasticity of Cardiac Muscle in Hyperthyroidism, Ventricular Hypertrophy, and Heart Failure (32753)

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The three-component model for muscle proposed by A. V. Hill (1) has been useful in describing the contractile activity of cardiac muscle *in vitro* (2) and *in vivo* (3). The contractile element (CE) of this model is assumed to be freely extensible at rest, but with activation it shortens according to a characteristic inverse relation between the velocity of shortening and the load (4). The CE is in series with an elastic element (SE) so that during isometric contraction, the activated CE shortens and stretches the SE, the rate of tension development (dP/dt) being determined by the CE velocity and the stress strain relation of the SE (1). Thus the external manifestations of CE activity depend to a large extent on the properties of the SE.

Although the stiffness of the SE is unaffected by inotropic interventions, or the course of active state (5,6), it does become somewhat stiffer following damage from segmental compression (7). With the recent application of cardiac muscle mechanics to the study of pathologic states such as hyperthyroidism, cardiac hyperthophy and failure (8–10), a quantitative knowledge of the SE compliance in these conditions is required if CE velocity and work are to be evaluated. Accordingly the present study was undertaken to measure the series elasticity of papillary muscles from cats with hyperthyroidism, cats with cardiac hypertrophy, and those with cardiac hypertrophy and heart failure.

Methods. Right ventricular papillary muscles from three groups of cats (1.5–2.5 kg) were used. Hyperthyroidism was induced in six cats by the intraperitoneal injection of l-thyroxine (1 mg per kg per day) for 10–14 days (10). Serum protein bound iodine (PBI) and cholesterol determinations were made at the time of sacrifice. In a second group of 15 cats, right ventricular hypertrophy with or without heart failure was produced

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by banding the pulmonary artery with clips of diameter 2.8 or 3.5 mm which produced 90% and 80% constriction, respectively (11). The right and left ventricles were weighed when the cats were killed 28–55 days (av 35.5 days) postoperatively. A third group of 17 cats served as normal controls.

After each cat was anesthetized with intraperitoneal sodium pentobarbital (50 mg/kg), right ventricular papillary muscles were rapidly removed from the heart and placed in a muscle bath containing Krebs-Ringer solution aerated with 95% O_2 and 5% CO_2 at a constant temperature of 30°C. The muscles were stimulated (AEL laboratory stimulator model 104A) 12 times per min via platinum mass electrodes placed parallel to the muscle. The stimulus duration was 7 msec with voltages 20% above threshold. The details of the isotonic lever system and quick release air jet apparatus have been described previously (6).

After 1 hour of equilibration, force-velocity curves were obtained (2). The SE extension curves were then obtained by an isotonic quick release method (6,12). All measurements were made in triplicate at various preloads, following which length–tension curves were obtained. At the conclusion of each experiment the equipment compliance was determined by the quick release method and used as a correction factor for the SE extension curves (6). Muscle lengths and wet weights were determined and average cross-sectional areas calculated. Maximum velocity of shortening (V_{max}) was calculated by extrapolation from the force–velocity curves, using a form of the Hill equation (4). Time to peak tension was measured from the stimulus artifact to the peak of tension development. All results are expressed as the mean ± 1 SEM.

Results. The serum PBI of each cat receiving l-thyroxine was greater than 30 μg/100 ml and the average cholesterol for the group was 58 $\pm$ 11 mg/100 ml at the time of sacrifice. Normal cat PBI and cholesterol values are 4.3 $\pm$ 0.2 μg/100 ml and 101 $\pm$ 10 mg/100 ml (10). In the group with pulmonary artery constriction there was marked right ventricular hypertrophy in each cat, and 10 of these

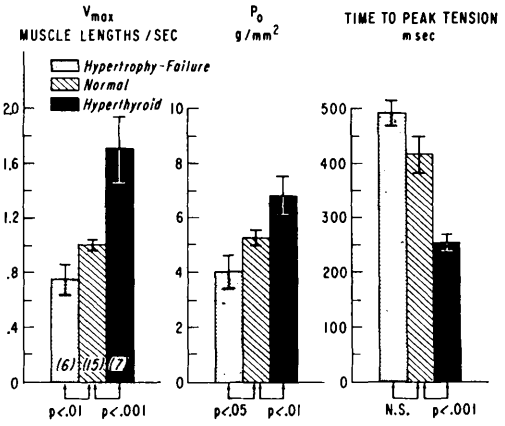

FIG. 1. Maximum velocity of shortening (V_{max}), maximum isometric tension (P_0), and time to peak tension for the three groups. The number of muscles in each group are indicated by the number in parentheses. The p values refer to the significance of the differences between each experimental group and the normal. The vertical bars represent $\pm$ 1 SEM.

15 cats had pleural and peritoneal fluid as a manifestation of overt congestive heart failure. The ratio of right ventricular weight in grams to the preoperative body weight in kilograms averaged .83 $\pm$ .04 gm/kg in the cats with pulmonary artery constriction, while this value averagered .55 $\pm$ .02 gm/kg in normal cats ($p < .001$).

The effects of hyperthyroidism and cardiac hypertrophy and failure on muscle mechanics are illustrated in Fig. 1. Only the results from muscles with cross-sectional areas less than 1.5 mm^2 were used for these averages in order to exclude any muscles which may have limitation of oxygen diffusion. In the papillary muscles from hyperthyroid cats, the maximum velocity of shortening (V_{max}) and maximum tension development at the apex of the length tension curve (P_0) were significantly increased while time to peak tension was reduced. In the hypertrophy-failure group both V_{max} and P_0 were reduced while time to peak tension was slightly but not significantly prolonged.

The load-extension curves of the SE for the three groups were compared at similar preloads corrected for cross-sectional area since the apparent stiffness of the series elastic is preload dependent (6). The curves with pre-

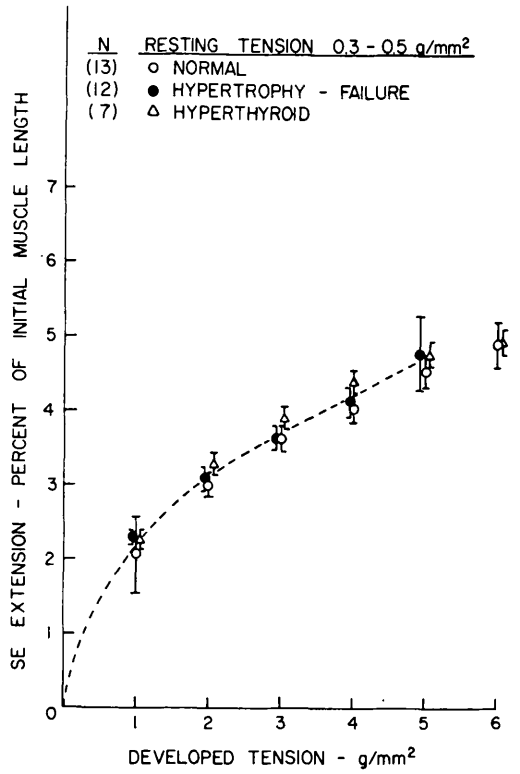

FIG. 2. Average SE extension curves for the normal, hyperthyroid, and hypertrophy failure groups. Resting tension is 0.3–0.5 gm/mm² in all muscles. The verticle bars represent ± 1 SEM.

loads of 0.3–0.5 gm/mm² are shown in Fig. 2. Series elastic extension has been expressed as a percentage of initial muscle length and plotted as a function of tension development which is normalized for cross-sectional area. The SE extension curves were identical for the three groups starting from resting tensions of 0.3–0.5 gm/mm² and this was also the case with resting tensions of 0.1–0.3 gm/mm².

Since no difference could be demonstrated between the three experimental groups, the results from all muscles were combined to provide normalized myocardial series elastic extension curves at preloads ranging from 0.1–0.5 gm/mm² (Fig. 3). The equation for the inverse slope (dP/dL) of these exponential curves at any developed tension P is $dP/dL = \mathrm{KP} + \mathrm{C}$, and the appropriate K and C values are shown on the figure.

Discussion. Alterations in the properties of the series elastic (SE) could potentially alter muscle function since the contractile elements (CE) are required to stretch the series elastic elements in the development of external tension. In terms of a mechanical model of muscle (Fig. 3), the rate of isometric tension development (dP/dt) is dependent on the CE velocity (dL/dt) and the stiffness of the SE (dP/dL), i.e., $dP/dt = dL/dt \cdot dP/dL$. Thus any change in the rate of tension development could theoretically be due to a change in CE velocity and/or a change in the compliance of the SE. Further, calculations of CE velocity derived from dP/dt depend on a quantitative knowledge of the properties of the SE component. In the present study the large changes in V_{max}, P_0, and time to peak tension were

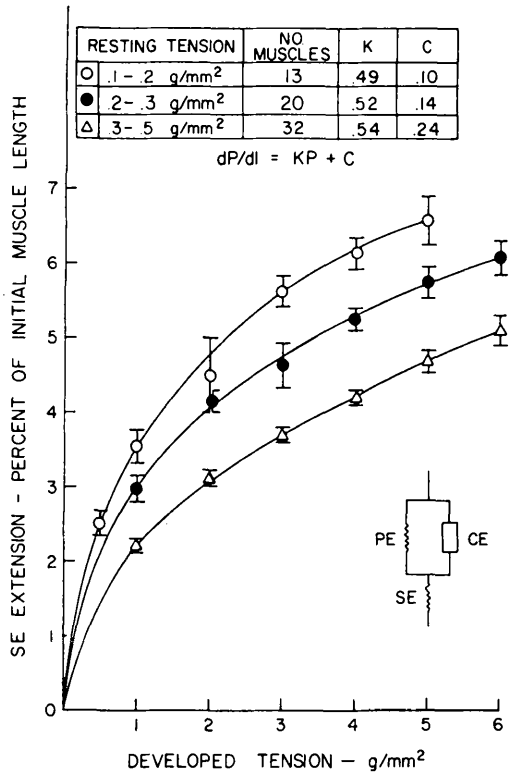

FIG. 3. Normalized series elastic extension curves for resting tensions of 0.1–0.2, 0.2–0.3, and 0.3–0.5 gm/mm². The averages are derived from normal, hyperthyroid, and hypertrophy-failure muscles at each preload. The calculated K and C values for the inverse slope (dP/dL) of each curve are indicated. The three component model to fit this data is illustrated. CE = contractile element; SE = series elastic element; and PE = parallel elastic element.

similar to those previously noted for hyperthyroidism (10) and hypertrophy-failure (9). Since the SE compliance was unchanged, alterations in the velocity of shortening and in force development can be attributed to changes in the performance of the CE.

The length-passive tension curves of the papillary muscle in hyperthyroidism (10) and hypertrophy-failure (9) have been studied previously and shown to be unaltered. Thus it would appear that both the parallel elastic and series elastic elements of heart muscle are essentially unaffected by these pathological states, just as they are unaffected by changes in inotropic state (5, 6). The SE may, however, be altered in some pathological states; for example, damage to papillary muscles by transient segmental compression increases SE stiffness (7).

The present study further defines the properties of the normal SE. Previous measurements of SE have been limited to preloads of 0.5 gm/mm^2 and were incompletely normalized (6). The SE extension curves of Fig. 3 provide quantitative normalized values for cardiac muscle series elasticity at preloads between 0.1 and 0.5 gm/mm^2. The constant K remains unchanged as previously shown (6) while C increases with preload (Fig. 3). This supports the view that the SE is working on a stiffer portion of the same exponential extension curve at higher resting tensions (6).

In summary, the series elasticity of the cat papillary muscle as measured by isotonic quick release methods was shown to be normal in hyperthyroidism and in cardiac hypertrophy and failure, despit large changes in V_{max}, P_0, and the time to peak tension. The alterations in muscle mechanics in the abnormal states, therefore, can be attributed to changes in the properties of the contractile mechanism.

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