Influence of the Thyroid State on Left Ventricular Tension-Velocity Relations in the Intact, Sedated Dog

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A B S T R A C T The mechanical properties of left ventricular contraction were described in terms of tension, velocity, length, and time in closed-chest, sedated normal, hypothyroid, and hyperthyroid dogs. Heart rate was controlled at 150 beats/min, and instantaneous contractile element velocity was calculated from left ventricular pressure and its first derivative during isovolumic left ventricular contractions, produced by sudden balloon occlusion of the ascending aorta during diastole. Wall tension was derived from ventricular pressure and volume, the latter being obtained from the pressure-volume relation of the arrested ventricle, and tension-velocity relations were analyzed over a range of ventricular end-diastolic volumes. At any level of ventricular volume, the hypothyroid state was associated with a displacement of the tension-velocity relation of the left ventricle downwards and to the left, and the time to peak tension was prolonged (154 msec, normal 139 msec). In the hyperthyroid state, the tension-velocity relation of the left ventricle was displaced upwards and to the right, and the time to peak tension was reduced (80 msec). The changes in the tension-velocity relations indicate that the inotropic state of the left ventricle in the intact dog varies directly with the animal's thyroid state. This influence on myocardial contractility necessarily constitutes an important and integral part of the response of the intact circulation to altered thyroid state.

INTRODUCTION

In 1927 Blalock and Harrison found that cardiac output increased more than body oxygen utilization in thyroid-

fed dogs and postulated that the increased blood flow might have resulted in part from a direct effect of thyroid hormone on the heart (1). A direct effect on cardiac pacemaker tissue was demonstrated in 1931 when Yater (2) and Andrus (3) found higher spontaneous rates in perfused hearts from thyroxine-treated rabbits, and Markowitz and Yater (4) also found that thyroxine increased the spontaneous rate of cardiac tissue in a chick embryo devoid of formed neural elements. In contrast, the influence of thyroid state on the mechanics of contraction of isolated cardiac muscle has been completely documented only recently (5). In the intact experimental animal, and in man, the effects of altered thyroid state upon heart rate, total body or organ blood flow and metabolism (6–18), heart size, and the electrocardiogram have been investigated (19–22). However, there is little information on the manner in which hyper- and hypothyroidism affect the characteristics of contraction of the intact, *in situ* left ventricle.

It was recently shown that the contractile properties of the left ventricle of the intact, sedated dog can be characterized in terms of force, velocity, length, and time parameters (23), as can those of isolated skeletal (24–26) and cardiac muscle (27–29) and that these properties can be expressed in normalized terms for the intact, healthy dog (23). In this analysis tension-velocity relations were obtained during isovolumic contractions, produced by sudden balloon occlusion of the ascending aorta. Apart from shape changes, external muscle shortening does not occur during isovolumic ventricular contractions, although according to Hill's muscle model (24) contractile elements shorten to stretch series elastic elements with the development of tension. The rate of shortening of the contractile elements comprising the entire ventricle may then be derived from the rate of tension development and the stress-strain relation of the series elastic elements (30).

In the present study left ventricular tension-velocity relations were obtained in thyroxine-treated and radio-iodine-treated dogs and compared with those of untreated dogs. To exclude the influence of heart rate per se on the tension-velocity relation (31) heart rate was controlled at the same level in all experiments. Consistent changes were found in the tension-velocity relations, those in the hypothyroid dogs representing a negative inotropic influence, and those in the hyperthyroid dogs a positive inotropic influence. These changes in the contractile properties of the intact left ventricle appear to reflect a direct influence of thyroid hormone on the ventricular myocardium.

METHODS

Mongrel dogs weighing between 15.0 and 26.8 kg were prepared before study as previously described (23). In brief, a median sternotomy was performed under pentobarbital anesthesia, the left lateral aspect of the pericardium was opened from apex to base, and its lower free edge was sutured to the left chest wall to facilitate later percutaneous puncture of the left ventricle. The pericardium was left widely open. In some experiments a ½-inch band of Teflon tape was placed around the ascending aorta to provide support for the balloon inflations. Electrodes were then sutured to the right atrial appendage, the ends of the lead wires implanted subcutaneously, and the chest closed with drainage. The 15 dogs constituting the normal control group were those described previously (23). Five dogs were given a single intraperitoneal injection of radioactive iodine [131]I (1 mc/kg) and studied 6 months later; 5 dogs were given l-thyroxine (1 mg/kg per day) by subcutaneous injection for 10–20 days before study. As previously (23), for the experimental procedure the hyperthyroid animals were sedated with morphine (3 mg/kg), promazine (1.5 mg/kg), and promethazine (1.5 mg/kg) by intramuscular injection. The hypothyroid dogs received these drugs in half dosage. Local anesthesia with xylocaine was used for all catheter insertions.

Aortic pressure was measured through a polyethylene cannula passed into the thoracic aorta from a femoral artery and left ventricular pressure was obtained through a short, stiff, polyethylene cannula (PE #220) inserted by direct percutaneous puncture using a No. 19 spinal needle as a trocar, and attached directly to a pressure transducer. Intraventricular pressure was referred to the level of the mid-left ventricular cavity determined directly at the completion of each experiment. Intrapleural pressure (IPP) was measured through a self-retaining Foley catheter inserted through the right chest wall, and left ventricular (LV) transmural pressure, which was used in all calculations, was obtained by subtraction of IPP from the measured LV pressure. The first derivative of LV pressure, LV dp/dt, was obtained with an analog differentiating circuit.[1] All pressures were measured with Statham P23Db transducers and recorded with the electrocardiogram on a multichannel oscillograph[2] at a paper speed of 100 mm/sec. Cardiac output was measured in duplicate by superior vena caval injection of Indocyanine green dye with aortic sampling; the standard deviation of

cardiac output measurements by the method of paired measurements was 0.25 liters/min.

A rubber balloon mounted at the tip of a metal cannula was passed through the left carotid artery and placed in the ascending aorta just above the aortic valve (23, 32). The balloon was rapidly inflated during diastole with 5–18 ml of saline by a power injector[3] triggered from the electrocardiogram. Beats were analyzed only if they showed features characteristic of isovolumic contractions: a smooth LV pressure contour, a steady, uninterrupted fall in LV dp/dt after its peak, and a progressively falling aortic pressure. The period of occlusion lasted from one to three contractions, and all hemodynamic variables promptly returned to control levels. All isovolumic beats used for analysis were obtained during expiration.

The left ventricular end-diastolic volume (EDV), from which isovolumic beats originated, was derived from the transmural end-diastolic pressure (LVEDP) and the passive pressure-volume relationship of the KCl or anoxia-arrested ventricle, determined after sacrifice of the animal. The application of this method to the measurement of end-diastolic volume in the closed-chest animal has been described in detail in recent communications (23, 33). A study in progress in the closed-chest anesthetized dog indicates that an acceptably close agreement exists between left ventricular volume measurements made by this method and those made using a biplane cineangiographic technique. In six dogs, end-diastolic volumes calculated from biplane cineangiograms were compared with the passive pressure-volume (PV) curves obtained after anoxic cardiac arrest in the same six animals. The mean regression equation was: PV volume = 1.14 (±0.12) cine volume − 5.33 (±6.8) ml. A significant linear relationship between the volumes calculated from the passive pressure-volume curve and those calculated from the biplane cineangiograms was obtained in each animal (P < 0.01) and the correlation coefficients in the six animals were: 0.99, 0.97, 0.97, 0.95, 0.93, 0.87, and 0.75.

Calculation of myocardial wall tension and contractile element velocity. Left ventricular wall tension (stress) was calculated from the formula:

$$T = \frac{P \cdot r}{2h} \text{ g/cm}^2$$

where P = transmural ventricular pressure in grams per cubic centimeter, r = internal radius in centimeters, and h = wall thickness in centimeters. The internal radius of the left ventricle was obtained from the cavity volume, assuming a spherical ventricular shape. Wall thickness was calculated by assuming the mass of left ventricular muscle to be evenly distributed around its contents. The mass was determined at the completion of each experiment. The units of T, g/cm² are those of stress. The term tension is used interchangeably with the term stress, and is expressed as total tension, end-diastolic tension, and the difference between these, active tension.

As detailed previously (23) the rate of elongation of the series elastic (SE) component (dl/dt) and the contractile element (CE) shortening velocity (V_{CE}) are considered to be essentially equal in isovolumic contractions, and since in an isovolumic contraction dT/T closely approximates dp/p, where p is transmural ventricular pressure, then dp/$K \cdot$p = dl and (dp/dt)/$K \cdot$p = dl/dt = V_{CE} cm/cm per sec (muscle lengths/sec or circumferences/sec). K was taken to be 28 in all experiments in accord with

TABLE I
Initial Hemodynamic Measurements Before Control of Heart Rate and End-Diastolic Volume[*]

	Body wt‡	LV wt‡	Heart rate,	Aortic pressure	Cardiac output, liters/min	EDV	SV/EDV	LVEDP	Peak isovolumic pressure	Total isovolumic tension
	kg		*beats/min*	*mm Hg*	*(ml/min per kg)*	*ml*		*mm Hg*	*mm Hg*	*g/cm²*
Normal	19.3 ±2.5	5.25 ±0.56 (101.3)	125 ±38	133/93 ±20/17	2.44 ±0.86 (124 ±33)	40.5 ±10.3	0.50 ±0.13	7.1 ±2.3	251 ±55	332 ±105
Hyperthyroid	20.8 ±3.5	5.25± 0.74 (109.2)	276 ±20§	131/79 ±10/9	4.01 ±1.37‖ (189 ±39)‖	27.9 ±2.1¶	0.51 ±0.17	3.6 ±1.0‖	214 ±49	208 ±68¶
Hypothyroid: Before atropine	18.8 ±2.5	4.12 ±0.65§ (77.5)	74 ±12§	124/91 ±25/11	1.34 ±0.25¶ (72 ±14)‖	29.3 ± 5.7¶	0.62 ±0.09	7.3 ±1.7	243 ±29	321 ±26
After atropine			116 ±12	116/90 ±13/9	1.49 ±0.26¶ (82 ±15)¶	21.7 ± 7.7‖	0.62 ±0.12	4.7 ±1.7	215 ±49	236 ±75

Abbreviations: wt = weight, LV = left ventricle, EDV = left ventricular end-diastolic volume, SV/EDV = left ventricular stroke volume/end-diastolic volume ratio, LVEDP = transmural left ventricular end-diastolic pressure.

[*] Values are means ±1 SD.

‡ Body weight refers to weight at the time of preparative surgery in each group, that is before changing thyroid status. Left ventricular weight is referred to this body wt, i.e., expressed as g/kg body wt; the values in parentheses represent the average total LV weights in each group.

§ Significantly different from normal, $P < 0.001$.

‖ Significantly different from normal, $P < 0.01$.

¶ Significantly different from normal, $P < 0.05$.

values found in the dog's intact left ventricle (34, 35) and with the lowest value of K found in cat isolated papillary muscle (30). In separate experiments, using a quick release method the series elasticity of cat papillary muscle was found to be unchanged by induction of the hyperthyroid state, and by ventricular hypertrophy,[4] supporting the use of a single elasticity constant in the different animals of the present study.

Control measurements were made with the dogs resting quietly in the supine position. In the hypothyroid dogs measurements were repeated after the intravenous injection of atropine (0.4 mg). After these measurements the dog's blood was exchanged with fresh blood obtained from donor dogs lightly anesthetized with sodium methohexital.[5] In the normal and hypothyroid animals the previously implanted right atrial electrode leads were attached to a stimulator[6] and heart rate was subsequently controlled at average levels of 150.6 ±5.6 (SD) and 148.4 ±3.8 beats/min, respectively, in the two groups. Isovolumic contractions were then obtained over a wide range of transmural end-diastolic pressures obtained by infusion of previously exchanged donor blood. In the hyperthyroid animals, in which the spontaneous heart rates were above 150 beats/min, the right cervical vagus trunk was stimulated (six square wave pulses per sec, 3 msec duration) to produce cardiac slowing, and isovolumic contractions were induced 30 sec after a stable heart rate had been attained, at an average rate of 150.2 ±9.6 (SD) (range 142–166) beats/min.

[4] Parmley, W. W., J. F. Spann, Jr., R. R. Taylor, and E. H. Sonnenblick. 1968. The series elasticity of cardiac muscle in hyperthyroidism, ventricular hypertrophy, and heart failure. *Proc. Soc. Exp. Biol. Med.* **127**: 606.

[5] Brevital sodium. Eli Lilly and Company, Indianapolis, Ind.

[6] American Electronic Laboratories, Inc., Colmar, Pa., model 104 A.

During the experimental procedure the rectal temperatures of all dogs ranged between 35° and 40°C; the maximum level in the hyperthyroid dogs was 40°C and the minimum in the hypothyroid animals was 35°C. The range in the euthyroid dogs was 36°–38°C.

The serum protein–bound iodine of the ^{131}I-treated animals had decreased over 6 months from 3.5 ±1.4 (SD) to 0.8 ±0.3 mg % and the serum cholesterol had increased from 159 ±10 to 353 ±57 mg %. The serum protein–bound iodine of the hyperthyroid group was 21.3 ±7.2 mg % and the cholesterol 103 ±5 mg %. The hyperthyroid animals lost 1.0–2.3 kg weight between thoracotomy and the experimental procedure and the hypothyroid animals gained 0.2–5.0 kg.

Wall tensions were compared in the groups of animals at common levels of V_{CE} in each of three groupings of LVEDP, and V_{CE} also was compared at the lowest common levels of wall tension (100 g/cm²) at which an inverse relationship between V_{CE} and wall tension existed. When several observations were made on a given parameter in any one animal, the mean of those observations was used to calculate the group mean. In some instances when observation required subdivision, i.e. on the basis of LVEDP, not every animal contributed an observation to a particular group. Significance of the difference between group means was determined by two-tailed Student's t test.

RESULTS

The values, in each experimental group, for animal body weight at the time of preparative surgery, left ventricular weight relative to this body weight, and for the hemodynamic measurements made before cross-transfusion and control of heart rate are shown in Table I. In the hyperthyroid animals the heart rate and cardiac output were significantly higher than normal ($P < 0.001$,
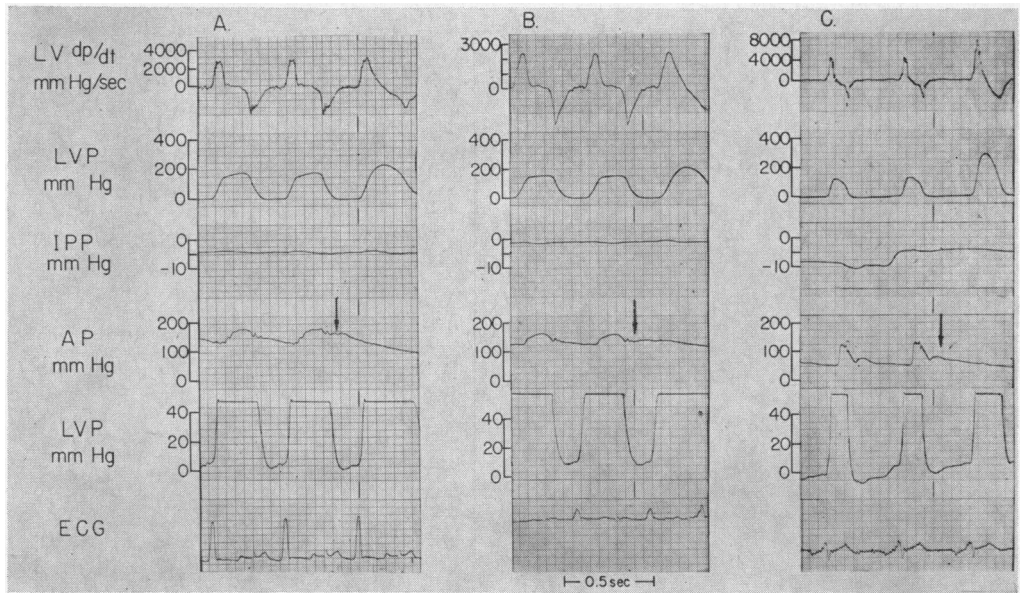
FIGURE 1 Representative recordings from normal, hypothyroid, and hyperthyroid dogs. The observations in the normal dog (A), hypothyroid dog (B), and hyperthyroid dog (C) were made at transmural left ventricular end-diastolic pressures 10.0, 10.3, and 10.2 mm Hg and heart rates 145, 148, and 150 beats/min, respectively. Arrows indicate points at which balloon has been inflated. LVP = left ventricular pressure; LV dp/dt = rate of change of LVP; IPP = intrapleural pressure; AP = aortic pressure; ECG = electrocardiogram.

$P < 0.01$), and in the hypothyroid animals heart rate and cardiac output were significantly lower than normal ($P < 0.001, P < 0.05$).

Observations after cross-transfusion and control of heart rate. Fig. 1 shows characteristic tracings from normal (A), hypothyroid (B), and hyperthyroid dogs (C) at similar transmural left ventricular end-diastolic pressures (10.0, 10.3, and 10.2 mm Hg) when heart rates were controlled (145, 148, and 150 beats/min). In an expiratory phase the aortic balloon was rapidly inflated during diastole (marked with arrow). The normal isovolumic contraction attained a pressure of 241 mm Hg in 145 msec, the hypothyroid 216 mm Hg in 153 msec, and the hyperthyroid 296 mm Hg in 85 msec. The maximum rates of pressure rise (peak LV dp/dt) were 3078, 2231, and 7431 mm Hg, respectively. While peak dp/dt in the isovolumic contraction of (C) is 7431 mm Hg/sec, that in the ejecting contraction is 4001 mm Hg/sec. Such a difference in dp/dt between ejecting and isovolumic contractions was prominent in two of the five hyperthyroid animals but did not occur in the normal or hypothyroid animals. Peak dp/dt in ejecting beats in the LVEDP range 6–12 mm Hg was significantly higher than normal in hyperthyroid animals ($P < 0.001$), but not different from normal in the hypothyroid group ($P > 0.1$).

Fig. 2 shows tension plotted against time throughout another set of typical isovolumic contractions. In the nor-

mal, hypothyroid, and hyperthyroid contractions total isovolumic tension (Po) was 363, 289, and 390 g/cm², respectively, and time to peak tension (TTP) was 130, 150, and 70 msec. Relaxation was slower in the hypothyroid state, prolonging the total duration of contraction, and it was more rapid in the hyperthyroid state, abbreviating the total duration of left ventricular contraction.

Fig. 3 shows tension-velocity relations derived from isovolumic contractions in representative normal, hypothyroid, and hyperthyroid dogs. In the normal contraction an approximately hyperbolic relation was established after 30–40 msec and existed until shortly before peak tension was reached. A qualitatively similar relation obtained in contractions of the hypothyroid ventricle but the relation was displaced downwards and to the left from the normal. In contrast, the inverse relation between tension and velocity in the hyperthyroid ventricle was not obviously hyperbolic, but, despite this, the inverse relation which did exist showed a marked displacement upwards and to the right from normal.

Analysis of pooled data. The time to peak pressure and tension averaged 139 ±3 (mean ±SE) msec (range 125–155 msec) in the normal, was significantly greater than normal in the hypothyroid animals, 154 ±2 (148–161) ($P < 0.01$), and less than normal in the hyperthyroid animals, 80 ±3 msec (68–85) ($P < 0.001$).

Increasing left ventricular end-diastolic pressure, vol-

ume, and fiber length increased Po in the normal, hypothyroid, and hyperthyroid ventricles, and comparisons of Po and tension-velocity relations were made with these observations grouped according to LVEDP and according to end-diastolic tension. Table II shows Po values for the LVEDP groups 5–7 mm Hg, 7–10 mm Hg, and 10–15 mm Hg. The average Po in the hypothyroid dogs was lower than the normal in each group but this difference was significant only for the 10–15 mm Hg LVEDP group ($P < 0.05$). The average Po in the hyperthyroid dogs was consistently greater than normal; it was significantly greater than normal in the 5–7 mm Hg LVEDP group ($P < 0.05$) and was significantly greater than Po in the hypothyroid dogs at each LVEDP level (Table II). Table II also shows the maximum V_{CE} measured at the lowest common level of tension. In the hypothyroid animals V_{CE} at 100 g/cm² tension was significantly less than normal in the 10–15 mm Hg LVED group and was reduced in the other two groups (although this depression did not quite achieve statistical significance [$0.05 < P < 0.1$]). In the hyperthyroid animals V_{CE} at 100 g/cm² of tension was significantly greater than the normal ($P < 0.001$) and the hypothyroid values ($P < 0.001$).

Fig. 4 summarizes the mean tension-velocity relations obtained by calculating the mean tensions at the indicated selected velocities in the normal, hypothyroid, and hyperthyroid animals. The curves in the hypothyroid animals are displaced downwards and to the left from the normal and those in the hyperthyroid animals are displaced upwards and to the right. There was a significant difference in tension development at the highest common velocity between the hyperthyroid and normal and the hypothyroid and the normal groups. As indicated above (Table II), velocities at the lowest common tension were significantly higher than control in the hyperthyroid group and lower than control in one of the hypothyroid groups, and although estimation of maximum velocities at zero tension (V_{max}) by extrapolation were not made, this finding and the shape of the mean curves (Fig. 4) suggest that an alteration in V_{max} was present. The tension velocity relations were also grouped and analyzed according to end-diastolic tension, and the differences were similar to those observed with LVEDP grouping.

DISCUSSION

The hemodynamic measurements made in the resting state show a decrease in the heart rate and cardiac output characteristic of the hypothyroid state, and an increase in these variables in the hyperthyroid state similar to those previously described in animals and in man (1, 6–18). The hemodynamic and derived mechanical data in the resting state, in which heart rate and filling pres-
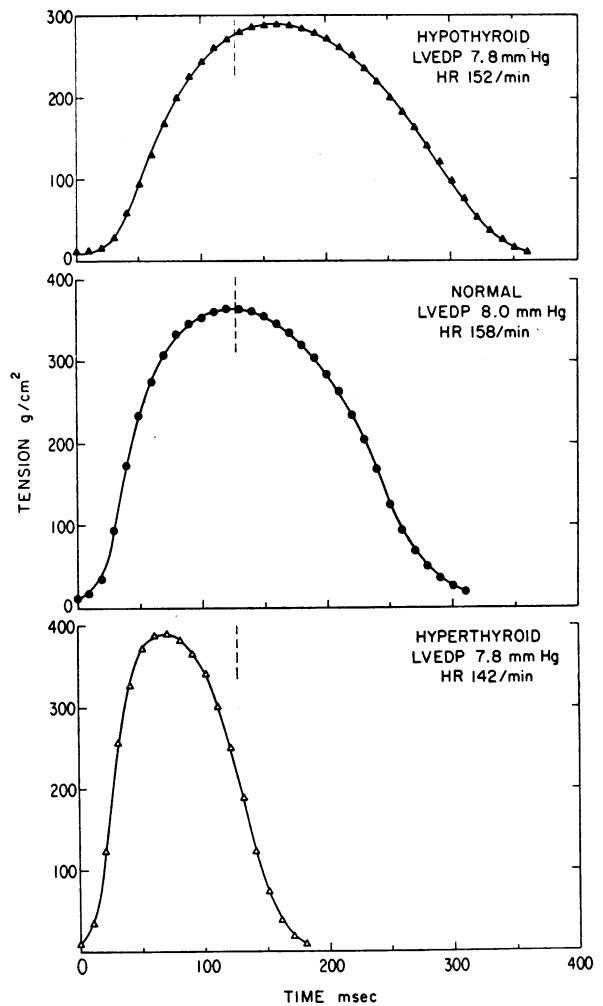

FIGURE 2 Tension plotted against time throughout representative isovolumic left ventricular contractions. The contractions from a hypothyroid dog (upper panel), a normal dog (center panel), and a hyperthyroid dog (lower panel) are at similar transmural left ventricular end-diastolic pressures (LVEDP) and heart rates (HR). The vertical broken lines indicate the point in time at which peak ventricular tension is attained in the normal dog.

sure were not modified, emphasize some of the problems which make comparisons between groups or individuals difficult under these conditions. For example, isovolumic contractions of the hyperthyroid left ventricle at spontaneous heart rate and filling pressure developed less tension than did contractions of the normal ventricle (Table I). This can be accounted for by the lower left ventricular end-diastolic pressure, end-diastolic volume and muscle fiber length (23, 36, 37) and no valid conclusion can be drawn concerning the inotropic state of the muscle. In addition, recently it has been shown that increasing contraction frequency decreases time to peak
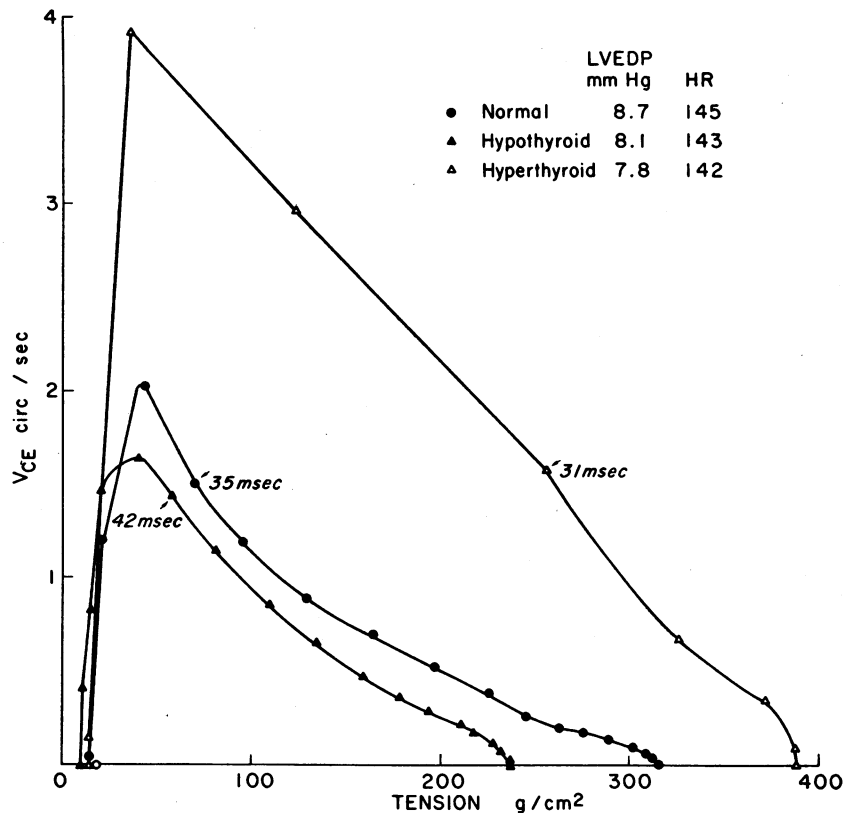
	LVEDP mm Hg	HR
● Normal	8.7	145
▲ Hypothyroid	8.1	143
△ Hyperthyroid	7.8	142

FIGURE 3 Contractile element velocity (V$_{CE}$) plotted against tension at 10 msec intervals throughout isovolumic left ventricular contractions in representative normal, hypothyroid, and hyperthyroid dogs. The time from the first appearance of mechanical activity is indicated once on each curve. Abbreviations as in Fig. 2.

tension and increases the rate of tension development and shifts the force-velocity relation in the intact left ventricle (31). The resting state proved, then, of little

TABLE II
Left Ventricular Tension and Contraction Velocity with Heart Rate Controlled

	LVEDP	LVEDP	LVEDP
A. Total isovolumic tension			
g/cm²*	5–7 mm Hg	7–10 mm Hg	10–15 mm Hg
Normal	289 ±13	348 ±17	409 ±21
Hyperthyroid	359 ± 5	398 ±23	431 ±18
Hypothyroid	241 ±10	299 ±18	324 ±11
B. V$_{CE}$ at tension of 100 gm/cm²			
Norml	1.38 ±0.10	1.60 ±0.10	1.74 ±0.10
Hyperthyroid	2.63 ±0.35	2.95 ±0.24	2.87 ±0.20
Hypothyroid	1.06 ±0.08	1.23 ±0.10	1.29 ±0.07

* Values are means ±1 SE. LVEDP = transmural left ventricular end-diastolic pressure. V$_{CE}$ = contractile element velocity.

value in the assessment of the effect of thyroid state on ventricular contractility.

Analysis of isovolumic left ventricular contractions showed that the thyroid state markedly influences the contractile properties of the left ventricle. At any level of passive ventricular filling, the tension-velocity relation of the hypothyroid left ventricle was characterized by a shift downwards and to the left and the hyperthyroid ventricle by elevation upward and to the right of the tension-velocity relation. The relatively small changes in Po in each situation were undoubtedly due in part to reciprocal changes in the duration of active state, since the time to peak tension, which approximately parallels active state duration (38) was increased in the hypothyroid and decreased in the hyperthyroid ventricles. Hence, it seems likely that had normal duration of active state been available to the hyperthyroid ventricle, Po would have been consistently higher than normal. Conversely, had a prolonged duration of active state not been available in the hypothyroid animals, Po undoubtedly would have been reduced more consistently. In the hyperthyroid ventricles, active state was apparently so
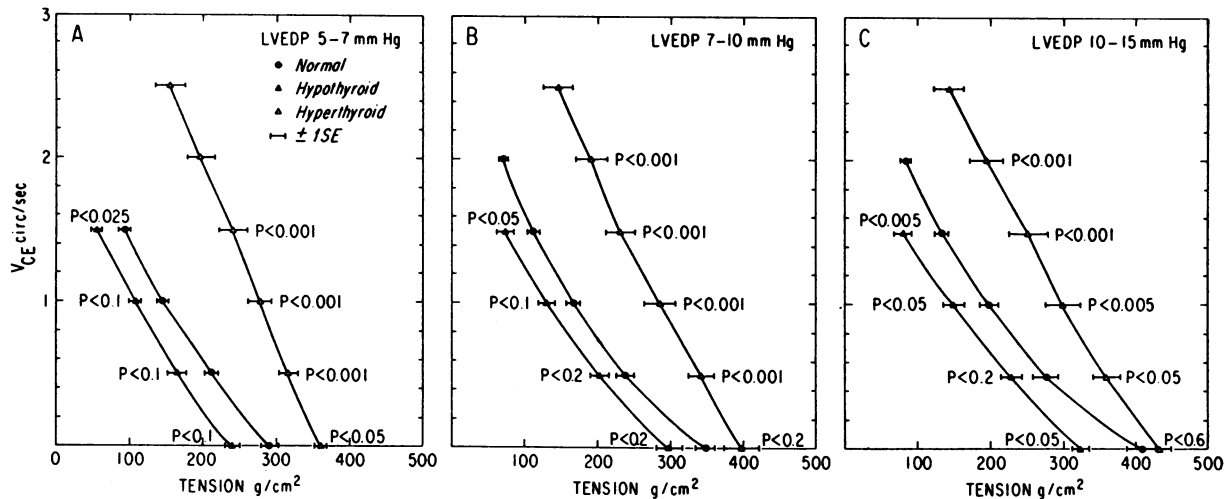
FIGURE 4 Mean tension-velocity relations in normal, hypothyroid, and hyperthyroid dogs at each of three levels of transmural left ventricular end-diastolic pressure (LVEDP). P values refer to the significance of the differences between the means in the hypothyroid and hyperthyroid animals and those in the normal animals.

abbreviated that no relative plateau of active state occurred (39), and hence the inverse relation between tension and velocity differed in configuration from those observed in the normal and hypothyroid ventricles (Fig. 3).

The changes in the tension-velocity relations of the intact left ventricle correspond closely to those recently described by Buccino et al. in papillary muscles isolated from hyperthyroid and hypothyroid cats (5) and conform to the general features observed with positive and negative inotropic influences respectively (23, 27, 28, 32, 37). Previously, there had been no consensus on the nature of the effects of thyroid hormone on the contractile mechanism even in isolated preparations. Peacock and Moran found tension development to be greater than normal in right ventricular strips from hypothyroid rats (40), but their thyroidectomized rats were calcium treated. Benforado and Wiggins found little change in tension development by hypothyroid rat right ventricular strips (41); Meijler reported that less than normal tension was developed in the ventricle of hypothyroid rats studied in a Langendorff preparation (42); Hirvonen and Lybeck found that tension development was subnormal at 25°C but normal at 41°C in atrium isolated from hypothyroid rats (43). Myocardium isolated from hyperthyroid animals, on the other hand, usually has been found to develop less than normal tension in similar preparations (40, 43–45). As indicated by Van der Schoot and Moran (45), this latter finding may be an artifact resulting from anoxia, to which some isolated preparations would be especially prone in the hyperthyroid state. Additionally, temperature and frequency

of contraction may affect the rate of tension development, time to peak tension, and hence total tension development in a relatively different manner in normal, hypothyroid and hyperthyroid muscle (5), and differences in these factors may also help to explain the divergent results of previous studies.

While the effects of thyroid state upon the mechanical characteristics of myocardial contraction have been unclear in vitro until recently, even less information has been available in the intact animal. The hyperthyroid state is associated with an increase in left ventricular mean ejection rate and circumferential shortening rate (46) and a reduced isometric contraction time (47), changes suggesting a positive inotropic effect but difficult to evaluate in the presence of tachycardia. In the hypothyroid state, studies on the intact circulation have been predominantly clinical. Myxedema heart disease, with radiological enlargement of the cardiac silhouette and electrocardiographic changes, with or without congestive cardiac failure, was described by Zondek in 1918 (19) and Fahr in 1925 (20). In more recent reports the rarity of evidence for cardiac failure has been emphasized (16, 17, 21, 22) and yet in the present study the contractility of the markedly hypothyroid left ventricle was depressed. Therefore, it would appear that, despite this impaired function, the left ventricle is usually able to satisfy the diminished metabolic demands of the body, although if additional demands or limitations are placed on the ventricle as, for example, by hypertensive vascular disease or coronary artery disease (21), then ventricular function may become inadequate with ensuing fluid retention and clinical cardiac failure. In

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the hyperthyroid state, the positive inotropic influence of hyperthyroidism per se, as well as tachycardia (48), may enable the heart to meet with increased demands of the body for blood flow, although again, cardiac hypertrophy and/or congestive cardiac failure can occur spontaneously or when other disease is superimposed (49).

As indicated earlier, it was important in the present study to make comparisons of the left ventricular tension-velocity relations at the same heart rate in the normal, hyperthyroid, and hypothyroid animals. Therefore, in the intact animal with uncontrolled heart rate, the thyroid-dependent changes in myocardial function found in this study would presumably have been potentiated by the concurrent changes in heart rate (31). A frequency of 150 beats/min was selected, but, with right atrial stimulation at this rate in the hypothyroid dogs, administration of atropine was required to prevent atrioventricular block. Conversely, since the spontaneous frequency was greater than 150 beats/min in the hyperthyroid dogs, graded right vagal stimulation was required to slow to 150 beats/min. Although some controversy exists concerning the cardiac effects of such stimulation, recent experiments have indicated that vagal stimulation produces a negative inotropic effect on the left ventricle (50, 51); atropine administration to the hypothyroid dogs would be expected to result in a positive inotropic effect (51), and, both the vagal and anti-vagal responses would have tended to oppose those observed experimentally. These interventions could not, therefore, have been responsible for the observed alterations in the tension-velocity relations, but could have attenuated these changes. It is emphasized that the derived tension-velocity relations represent those of the entire left ventricle, acting as a unit to develop intracavitary pressure. Thus, an increase in the rate of conduction of the ventricular depolarization wave, with greater synchronicity of contraction of ventricular muscle bundles, could have contributed to the changes observed in the hyperthyroid ventricles, while opposite changes could have contributed to the response in the hypothyroid ventricles (52). This effect is unlikely to have been responsible for changes of the magnitude observed (53), and the alterations are ascribed predominantly to an effect on the contractile properties of individual muscle fibers. Moreover, the changes observed in the intact ventricle with changing thyroid state are similar to those observed in isolated cardiac muscle in which field stimulation was used (5), and activation was not sequential.

Another variable which could have contributed to the observed differences in the tension-velocity relations was body temperature. It was possible to cool two hyperthyroid dogs from rectal temperatures of 39°C and 40°C to 37°C by external application of ice, without obvious change in tension-velocity relations. It was not attempted to raise the temperatures of the hypothyroid dogs, but even the extremes of temperature observed (35°C in the hypothyroid to 40°C in the hyperthyroid) could not have been responsible for the magnitude of changes which occurred in the tension-velocity relations; moreover, hypothermia to lower levels (30°C) produces an inconsistent change in V_{max} and an increase in Po in the left ventricle (32).

The present study did not aim to elucidate further the mechanisms whereby altered thyroid state influences myocardial function. In the intact animal there is some evidence that the metabolic and general hemodynamic effects of thyroid hormone are partly mediated by the sympatho-adrenal system (7, 10, 11), although this evidence is not conclusive (12, 13, 18). The thyroid-induced changes in the function of the isolated cat papillary muscle are observed after catecholamine depletion (5), suggesting that thyroid hormone affects myocardial function independently of the myocardial level of neuro-effector hormone. However, it is appreciated that, in the intact animal, other factors, such as changes in the delivery of humoral catecholamines to the heart or alterations in their inactivation (54) may be operative and the response to thyroid hormone thereby modified.

Increasing ventricular filling shifts the tension-velocity relation to the right with an increase in Po but without an apparent change in estimated V_{max} (23, 37). Therefore, to compare tension-velocity relations in different animals is was necessary to make comparisons at similar levels of left ventricular filling, or muscle fiber length. In the intact heart, end-diastolic tension, i.e. stress, is analogous to the initial resting tension or preload of isolated muscle. Under conditions in which the passive extensibility of individual fibers is unchanged, as appears to be the case in altered thyroid states (5, 44), but in which chamber distensibility may be altered by hypertrophy or chronic slippage of fibers, end-diastolic stress should represent one theoretically valid reference for mechanical parameters. Thus, end-diastolic stress should reflect end-diastolic sarcomere length, the specific length determinant of myocardial contraction (55). On the other hand, reference to ventricular circumferential length, or some function thereof, would not be valid because circumferential length relative to sarcomere length could be changed, for example, by the addition of contractile units in series or by fiber slippage. Likewise, ventricular volume, or volume normalized for body weight, would provide a less satisfactory reference point. This is exemplified by the changes observed here in the hypothyroid animals: ventricular volume was reduced to the same extent, i.e., the ventricle was proportionately reduced in size and the normal relation between pressure and tension was maintained (Table I). Therefore, in

the present study, mechanical parameters were normalized according to end-diastolic pressure and it is of interest that the latter, simpler measure appeared entirely adequate under these experimental conditions.

The calculation of V_{CE} is dependent upon the value ascribed to the series elasticity (SE) constant. In the different thyroid states, it is possible that secondary changes in cardiac connective tissue could have altered the elastic properties of the myocardium. In a separate study, using a quick release technique, the effect of chronic changes in the myocardium on the series elastic constant (K) was examined. In these studies there was no significant difference in K in papillary muscles removed from normal cats, cats with hyperthyroidism, or with chronic hypertrophy and congestive failure.[4] Although the hypothyroid state was not specifically examined, from these data it seems unlikely that myxedema would significantly influence the SE, since even the structural changes that accompany hypertrophy did not alter the constant.

In conclusion, it has been shown that the thyroid state importantly influences the contractile properties of the left ventricular myocardium, which have been characterized in this study in terms of tension, velocity, length, and time. It is suggested that these changes constitute an integral and important part of the response of the intact circulation to variable thyroid state.

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