Contractile Properties of Cardiac Muscle in Hyperthyroidism

ANALYSIS OF BEHAVIOR OF HYPERTHYROID CAT PAPILLARY MUSCLE IN VITRO RELEVANT TO THYROTOXIC HEART DISEASE

By Roger R. Taylor, M.B., M.R.A.C.P.

With the Technical Assistance of Peter Burrows

ABSTRACT

Right ventricular papillary muscles from hyperthyroid and normal cats were studied in vitro at 30°C, at contraction frequencies of 12, 30 and 60/min. At 12/min the contractility of hyperthyroid muscles was significantly greater than normal, as indicated by greater velocity of isotonic shortening, isometric tension development, and rate of tension development. Isotonically contracted muscle lengths were smaller and time to peak isometric tension less. At 60/min, velocity of shortening was still greater and time to peak tension less in hyperthyroid muscles, but isometric developed tension, rate of tension development, and isotonically contracted muscle lengths and shortening were not different. Increasing frequency from 12/min to 60/min resulted in immediate positive inotropic responses in both groups, but a smaller response in hyperthyroid than normal muscles. Over subsequent minutes, a slight decrease in contractility occurred in normal muscles but the decrease was significantly greater in hyperthyroid muscles. The difference in response to increasing frequency is attributed to more profound hypoxia in hyperthyroid muscles at high contraction frequencies. Predisposition of the muscle to hypoxia induced by hyperthyroidism then becomes an important determinant of the net effect of hyperthyroidism on myocardial contractility. The experimental situation is analogous to the coexistence, in vivo, of thyrotoxicosis and other conditions predisposing to coronary insufficiency, such as coronary artery disease or ventricular hypertrophy; that hyperthyroidism does not then augment contractile state in respect to tension development or muscle shortening helps explain the occurrence of thyrotoxic heart failure in response to the body's increased requirements for blood flow.

ADDITIONAL KEY WORDS
tension force velocity treppe contraction frequency hypoxia shortening active state thyroxine

Recent studies have emphasized that cardiac muscle of hyperthyroid animals frequently exhibits enhanced contractility, as evidenced by greater velocity of muscle shortening and rate of tension development and abbreviation of the time required to reach peak tension, with or without increase in absolute tension development, both in vitro (1, 2) and in vivo (3). Likewise, in clinical thyrotoxicosis, increase in rates of left ventricular ejection (4, 5) and circumferential shortening (4) and reduced isometric contraction (6, 7) and ejection (7) times suggest that the left ventricular contractile state is augmented, at least in respect to velocity and time-related parameters, in many subjects with thyrotoxicosis. Increase in myocardial contractility along with tachycardia usually enable the heart to meet the body's increased

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requirements for blood flow (3, 8), but, nevertheless, left ventricular or congestive cardiac failure may result from thyrotoxicosis. While it has long been considered that these complications occur particularly in the presence of other cardiovascular disease limiting the intact heart's adaptation to increased load (9, 10), it was thought appropriate to investigate certain aspects of the mechanical properties of cardiac muscle in hyperthyroidism.

Right ventricular papillary muscles with dimensions similar to those commonly studied in vitro (11-14) were obtained from normal and hyperthyroid cats and the behavior of isometric, afterloaded and purely isotonic contractions of the muscles was characterized in terms of passive and contracted length-tension relations and force (tension)-velocity relations. The muscles' response to increasing frequency of contraction was examined because tachycardia is characteristic of thyrotoxic heart disease. Responses to increasing frequency have been studied previously in hyperthyroid cat papillary muscle (1) and in guinea pig atrium (2) but the time course of the changes induced in contractility, which proved to be importantly different in muscles from hyperthyroid and normal cats, was not described in those reports.

The second aspect of muscle function particularly studied was the difference between contracted muscle length-tension relations resulting from isometric, purely isotonic, and afterloaded contractions (14), the last being to some extent analogous to ejecting contractions of the intact ventricle. The aim was to examine the hypothesis that the markedly abbreviated duration of active state in hyperthyroidism would particularly limit shortening in afterloaded and isotonic contractions, and hence possibly curtail ejection of the intact ventricle (14, 15).

**Methods**

Right ventricular papillary muscles were rapidly removed from thyroxine-treated (1 mg/kg im daily for 8 to 10 days) and untreated cats anesthetized with sodium pentobarbital (30 mg/kg ip). The muscle was placed in a water-jacketed glass bath containing Krebs-Ringer solution vigorously bubbled with 9% O2-5% CO2 (11) and maintained at a constant temperature of 30°C by a Tecam Tempunit TU 8 unit. The nontendinous end of the muscle was held in a Lucite clip attached to a rigid rod which passed through the base of the muscle bath to a force transducer (Statham Model C 1-4-350). The upper tendinous end of the muscle was secured by braided noncapillary silk (Ethicon 0000) to a magnesium lever of ratio 20 to 1. Displacement was measured by a rotary variable differential transducer (Schaevitz Engineering Model R 4 BSS) which formed the fulcrum of the lever. The lever had an experimentally measured moment of inertia of 1.35 g cm² which, together with the quoted inertia of the transducer, gave a value of 1.65 g cm² for the system, corresponding to an equivalent mass of 103 mg for the lever. Equivalent mass directly measured (16), using release with 0.1-g load, was 130 mg. The muscles were stimulated through platinum electrodes by square wave pulses of 7 msec and voltage just above threshold, delivered from a Nihon Kohden laboratory stimulator (model MSE-3). Recordings were made on a multichannel Sanborn (Hewlett Packard) direct writing recorder (7700 Series).

Appropriate mechanical stops permitted the study of isometric, afterload, and purely isotonic contractions. Each muscle was allowed to contract isometrically with 0.5-g preload for 1 hour. Three properties of the muscle were then examined:

1. The force-velocity relation at 0.5-g preload, that is, the inverse relation between total load (constant preload + variable afterload) and the initial velocity at which the muscle shortened against that load. Initial velocity was obtained from the continuous recording of an R-C differentiating circuit (time constant 4.5 msec) calibrated against the slope of the shortening recording. The initial velocity of shortening against 0.5-g preload alone, without afterload, is termed \( V_{max} \) and the maximum rate of isometric tension development at 0.5-g preload, \( (dT/dt)_{max} \).

2. Time to peak tension (TTPT) was measured from the stimulus artifact to peak tension.

3. The passive and active isometric length-tension relations obtained by increasing muscle length, with the muscle contracting isometrically, up to the length from which maximum tension \( (DT_{max}) \) was actively developed (optimum length).

4. The initial length, contracted length, and amount of shortening of the muscle contracting under constant total load while initial resting muscle length was increased between contractions.
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TABLE 1

Tension, Velocity and Time at 0.5-g Preload

<table>
<thead>
<tr>
<th>Stimulation</th>
<th>Thyroid state</th>
<th>( V_{\text{max}} ) (mm • sec^{-1} • mm^{-1})</th>
<th>DT (g/mm²)</th>
<th>((dT/dt)_{\text{max}}) (g/sec/mm)</th>
<th>TTPT (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/min</td>
<td>N</td>
<td>0.80 ± 0.17</td>
<td>4.77 ± 0.82</td>
<td>20.5 ± 4.4</td>
<td>402 ± 49</td>
</tr>
<tr>
<td></td>
<td>T</td>
<td>1.28 ± 0.06†</td>
<td>6.90 ± 1.12†</td>
<td>48.4 ± 8.2²</td>
<td>287 ± 28</td>
</tr>
<tr>
<td>30/min</td>
<td>N</td>
<td>1.13 ± 0.21</td>
<td>5.59 ± 1.09</td>
<td>29.6 ± 7.7</td>
<td>356 ± 29</td>
</tr>
<tr>
<td></td>
<td>T</td>
<td>1.61 ± 0.17†</td>
<td>6.98 ± 0.96*</td>
<td>56.3 ± 11.7†</td>
<td>257 ± 24</td>
</tr>
<tr>
<td>60/min</td>
<td>N</td>
<td>1.30 ± 0.15</td>
<td>5.71 ± 0.55</td>
<td>38.3 ± 6.2</td>
<td>283 ± 22</td>
</tr>
<tr>
<td></td>
<td>T</td>
<td>1.53 ± 0.24*</td>
<td>5.50 ± 1.07</td>
<td>45.7 ± 9.2</td>
<td>299 ± 34</td>
</tr>
</tbody>
</table>

Changes Induced by Changing Frequency

<table>
<thead>
<tr>
<th>Stimulation</th>
<th>Thyroid state</th>
<th>( V_{\text{max}} ) (mm • sec^{-1} • mm^{-1})</th>
<th>DT (g/mm²)</th>
<th>((dT/dt)_{\text{max}}) (g/sec/mm)</th>
<th>TTPT (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 → 30/min</td>
<td>N</td>
<td>+0.33 ± 0.09†</td>
<td>+0.82 ± 0.45†</td>
<td>+0.1 ± 4.7♭</td>
<td>−10.9 ± 7.4¶</td>
</tr>
<tr>
<td></td>
<td>T</td>
<td>+0.33 ± 0.11†</td>
<td>+0.08 ± 0.54</td>
<td>+7.9 ± 8.5*</td>
<td>−10.3 ± 5.7¶</td>
</tr>
<tr>
<td>30 → 60/min</td>
<td>N</td>
<td>−0.17 ± 0.08‡</td>
<td>+0.12 ± 0.65</td>
<td>+8.7 ± 5.3‡</td>
<td>−20.5 ± 4.7¶</td>
</tr>
<tr>
<td></td>
<td>T</td>
<td>−0.07 ± 0.20</td>
<td>−1.48 ± 0.67‡</td>
<td>−10.6 ± 15.5</td>
<td>−11.3 ± 8.8*</td>
</tr>
<tr>
<td>12 → 60/min</td>
<td>N</td>
<td>+0.50 ± 0.09‡</td>
<td>+0.94 ± 0.45‡</td>
<td>+17.8 ± 5.1‡</td>
<td>−29.0 ± 8.1¶</td>
</tr>
<tr>
<td></td>
<td>T</td>
<td>+0.27 ± 0.21*</td>
<td>−1.40 ± 0.76‡</td>
<td>−2.7 ± 15.0</td>
<td>−20.4 ± 9.7†</td>
</tr>
</tbody>
</table>

Values are means ± 1 SD. N = normal; T = hyperthyroid; \( V_{\text{max}} \) = initial velocity of isotonic shortening; DT = isometric developed tension; \((dT/dt)_{\text{max}}\) = maximum rate of isometric tension development; TTPT = time to peak tension; \( V_{\text{max}} = \) shortening in millimeters per second divided by muscle length in millimeters.

Levels of significance of differences between normals and hyperthyroids or with changes in rate: *P < 0.05; †P < 0.01; ‡P < 0.001; §Significance of differences between changes in hyperthyroid muscles and normal muscles.

(14). Initial length was increased by the micrometer stop from a length at which the muscle just failed to move the load (isometric contraction) through lengths at which the initial tension on the muscle was less than the load but the muscle developed tension and then shortened against the load (afterloaded contraction) to a length, determined by the load, at which the muscle was contracting purely isotonically, or until the optimum length was reached. A total load of 0.5 g was examined, then 1.0 g, 2.0 g, increasing by 1.0 g increments until shortening did not occur and only isometric contractions were obtainable at the optimum length. Examination of isometric, afterloaded and isotonic contractions in this way over a range of loads allowed comparison of their respective contracted length-tension relations (Fig. 2) as previously described (14). The equipment compliance and its influence on the measurements have been described (14). It is also worth considering whether equipment inertia could have been important in producing the discrepancies observed between muscle lengths in the different types of contraction. If this were so, the discrepancies should have been greatest when shortening occurred with the greatest velocity and acceleration in isotonic contractions, that is, in hyperthyroid rather than normal muscles and in normal muscles at lowest load. This was not so (Fig. 2).

Each of these three properties was examined at contraction frequencies of 12, 30, and 60/min. After each increase in frequency we waited 2 minutes before the force-velocity relation was obtained; this was then completed in 1 to 2 minutes, and the full protocol at each frequency required 12 to 24 minutes. Using the above protocol, seven muscles from hyperthyroid cats (serum thyroxine iodine > 20 μg/100 ml in each) were compared with seven muscles from normal cats (serum thyroxine iodine, 3.4 ± 1.4 (SD) μg/100 ml). The lengths of the muscles from hyperthyroid and normal cats were, respectively, 6.6 ± 1.0 mm and 6.5 ± 1.6 mm, the weights 5.4 ± 1.6 mg and 6.4 ± 2.4 mg, and their cross-sectional areas at optimum length 0.82 ± 0.23 mm² (range 0.56 mm² to 1.23 mm²) and 0.96 ± 0.21 mm² (0.67 to 1.22 mm²). A further four hyperthyroid and four normal muscles were used to document the time course of contractility changes following change in frequency from 12 to 60/min.

Force is expressed in grams. Tension is synonymous with stress and its units are g/mm². Load is used as a term to replace either force or tension when it particularly refers to the...
experimental loading of muscles. Results compared in different muscles are expressed in units appropriately normalized for the cross-sectional area or length of the individual muscle, that is $DT_{max}$ and $DT$ are expressed in $g/mm^2$, $(dT/dt)_{max}$ in $g/sec/mm^2$, $V_{max}$ in muscle lengths/sec (mm/sec/mm); resting and contracted muscle lengths are expressed as percent of optimum length.

The significance of the difference between group means was evaluated by using Student's $t$-test and changes induced by an intervention were evaluated with the paired $t$-test.

**Results**

Measurements of tension and velocity-related variables at 0.5-g preload are summarized in Table 1. Velocity of isotonic shortening $V_{max}$ was significantly greater and time to peak isometric tension ($TTPT$) shorter in the hyperthyroid than in the normal muscles at each frequency of stimulation. Isometric developed tension ($DT$) and the maximum rate of tension development $(dT/dt)_{max}$ were significantly greater in the hyperthyroid muscles at contraction frequencies of 12/min and 30/min, but not at 60/min. Hyperthyroid and normal muscles responded differently to changing frequency, especially between 30/min and 60/min, at which the change in each variable was significantly different between the two groups (Table 1).

In Figure 1, isometric developed tension is plotted against resting muscle length at contraction frequencies of 12/min (A) and 60/min (B). At 12/min, tension developed by the hyperthyroid muscles was significantly greater than normal at all muscle lengths while at 60/min it was variably depressed below normal due mainly to the large decrease in tension development in hyperthyroid muscles in response to the increase in frequency (Fig. 1, Table 1).

In Figure 2, total tension is plotted against contracted muscle lengths resulting from isometric and isotonic contractions. In both hyperthyroid and normal muscles the contracted length-tension relations depended on the mechanics of loading of the contractions in that the contracted length of each muscle at a given total load varied directly with its initial length. Contracted lengths were greater in...
purely isotonic than in isometric contractions at each load (Fig. 2) and were intermediate in afterloaded contractions. The discrepancies between contracted muscle lengths in isotonic and isometric contractions at 12/min were significantly less in hyperthyroid than in normal muscles at low tensions, 0.5 g/mm² ($P < 0.025$) and 1.0 g/mm² ($P < 0.05$), not different at 2.0 g and significantly greater in hyperthyroid muscles at 3.0 g/mm² ($P < 0.02$). Why there should be a discrepancy between contracted muscle lengths in different types of contractions is not exactly clear (14) but, empirically, the nature of the differences between discrepancies in hyperthyroid and normal muscles contracting at 12/min is consistent with the "shift to the left" in the contracted length-tension relations of hyperthyroid muscles at that frequency (Fig. 2) (14). At 30/min and 60/min the shift to the left of both the isometric and isotonically contracted length-tension relations of hyperthyroid muscles was abolished and then the discrepancies in the normal and hyperthyroid muscles were not significantly different at any level of tension (Fig. 2B). Therefore no effect on the discrepancies in question could be attributed to abbreviated duration of active state in the hyperthyroid muscles. As a further result of this, comparison of isotonically contracted lengths of hyperthyroid and normal muscles led to conclusions similar to those derived from other variables concerning contractility at each frequency. At 12 contractions/min, hyperthyroid muscles contracting isotonically reached shorter lengths than did normal muscles. With increasing frequency from 12/min to 60/min, the normal muscles...
shortened further and the hyperthyroid muscles less, so that at 60/min there was no significant difference between the two, and the hyperthyroid muscles then actually shortened, on the average, less than normal (Fig. 2).

The time course of contractility changes was documented in many of the muscles used in the preceding experiments at the end of the protocol but was more definitively examined in another four hyperthyroid and four normal muscles. Typical results of increasing frequency from 12/min to 60/min while tension (force) in isometric contractions at 0.5-g preload was recorded are shown in Figure 3A. In normal muscles, DT increased an average of 53% (range 36 to 76%) and then slowly fell over the next 10 minutes to reach the control value (−6 to +9%). In hyperthyroid muscles, DT increased 22% (1 to 29%), significantly less than in the normals (P < 0.05), and fell to reach a steady level of 45% (22 to 59%) below the initial value after 10 minutes, a response also significantly different from the normal (P < 0.005). These responses were reversible and reproducible when frequency was altered over 1 to 2 hours and results of decreasing frequency from 60 to 12/min are seen in Figure 3B. An immediate decrease in isometric tension development occurred in both normal and hyperthyroid muscles (following potentiation for one or two contractions), but in the hyperthyroid muscles, tension returned to 76% (38 to 118%) above the initial tension after 10 minutes, significantly different from the return of tension to the initial value in the normal muscles (P < 0.005). Similar biphasic responses were seen in amount and velocity of shortening when frequency was changed with the muscles contracting isotonically, and the delayed effects of changing frequency were also reflected in the tension-velocity relations.

Discussion

At 12 contractions/min, right ventricular papillary muscles from hyperthyroid cats developed significantly greater tension more rapidly in isometric contractions and exhibited greater initial velocity of shortening (V_max) and amount of shortening during isotonic contractions than did muscles from normal cats. The time to peak isometric tension (TTPT) was less in hyperthyroid muscles. These results are essentially similar to those of Buccino et al. under comparable conditions (1). However, at 60/min, tension development, rate of tension development, and isotonic shortening were not significantly different in the two groups although V_max was still greater and TTPT shorter in the hyperthyroid. Of course the measured variables only indirectly reflect the activity of the contractile elements of muscle which exert their effect.
through series elastic and viscous components and with which other components are in parallel (12, 17-19). There is evidence, however, which indicates that the function of series and parallel components is not appreciably altered by acute hyperthyroidism (1, 20). Attention is also drawn to the fact that force-velocity relations derived from isotonic and afterloaded contractions are obtained at constant external muscle length and at various times throughout contraction and take no account of the shortening of contractile element length which occurs during tension development nor of variation in intensity of active state during contraction (13, 17, 21-24). These problems can be largely overcome by the use of quick release techniques (13, 17, 18, 21-24) or by attempting to relate force-velocity relations to contractile element length (24), but even then it is likely that the estimated velocity cannot be precisely equated with contractile element velocity or external force with contractile element force because of the influence of parallel components (19). This present study was not intended to encompass these questions but rather to document the contractile activity of hyperthyroid and normal muscles in relatively simple terms of external velocity, shortening, and tension development, with particular emphasis on aspects which might be relevant to the function of the intact hyperthyroid heart.

Effects of thyroid state on frequency-induced changes in contractility of cardiac muscle in vitro have been reported previously (1, 2). In guinea pig atrial muscle at 28°C, Murayama and Goodkind (2) found that, at contraction frequencies of 100/min and below, hyperthyroid muscles developed more tension than normal muscles but tension increased less with increasing frequency so that it was not significantly different in the two groups between 100/min and 200/min. The optimum frequency was less in hyperthyroid than normal muscles. Buccino et al. (1) increased frequency from 6/min to 48/min in cat papillary muscle and found that the rate of tension development increased less in hyperthyroid than normal muscles and, with similar reductions in TTPT, developed tension increased in normals but fell slightly in hyperthyroid muscles. The present results are in general accord with these observations in that, some minutes after increasing frequency of contraction, a less positive inotropic effect was in evidence in hyperthyroid than in normal muscles, particularly in the high frequency range of 30 to 60/min over which tension development and shortening actually decreased significantly in the hyperthyroid muscles.

While the early positive inotropic response to increasing frequency of contraction (Treppe effect) was less apparent in hyperthyroid muscles, there was also a much greater subsequent depression of contractility. The time course of this indicates that it was not an integral part of the inotropic response to increasing frequency (25). The obvious explanation is that increasing frequency of contraction increased the muscle's oxygen consumption (26) and adequacy of oxygen diffusion became a limiting factor and that this was more critical in hyperthyroid muscle, which has been shown to have a greater oxygen consumption both in vitro (27, 28) and in vivo (29-31). Reversible depression of tension development occurs in muscle preparations subjected to hypoxia (32), and similar changes are observed if the O2-CO2 flow to cat papillary muscle is temporarily stopped. The cross section of muscles used in these experiments is as small as that used by most workers in studying the mechanics of cat ventricular muscle in vitro (11-14) since there is considerable difficulty in obtaining smaller muscles. However, it has been suggested that under many conditions muscles of the size used are not adequately oxygenated (33-35). Even at rest, the maximum cross-sectional area allowing adequate oxygenation may be as little as 0.3 mm² (33), although it is probably greater since quiescent muscles between 1 and 2 mm² are able to maintain their high energy phosphate stores after anaerobic metabolism has been eliminated with iodoacetic acid (36). Frequency of stimulation, by influen-
ing oxygen consumption, affects the critical size; Koch-Weser found kitten papillary muscles below 1.0 mm² to be adequate at 18.8 contractions/min, 38°C, but at 188/min only muscles below 0.6 mm² were satisfactory (34). Undoubtedly, the depressant effect of hypoxia was responsible for the greater secondary decrease in contractility following increasing frequency in hyperthyroid muscles, and it is also possible that the smaller initial Treppe response was due to the early appearance of such an effect.

Before the studies of Buccino et al. in cat papillary muscle (1) and Murayama and Goodkind in guinea pig atrium (2) observations on rat atrial and ventricular muscle in vitro had consistently shown less tension development by hyperthyroid than normal muscle (37-40). Since there is recent evidence indicating that the intrinsic response of rat cardiac muscle to thyroid hormone is the same as that of other mammals and man (41), these early findings must have been due to hypoxia, as suggested by Van der Schoot and Moran (40). The effects of hyperthyroidism on cardiac muscle at most contraction frequencies would perhaps resemble those observed here at 12/min if hypoxia could be avoided. The differences between tension-velocity relations of the intact left ventricle in acutely hyperthyroid and normal dogs with contraction frequency controlled at 150/min are similar to those in cat papillary muscle in vitro at 12/min (3).

Oxygen requirements of cardiac muscle in vitro are increased by hyperthyroidism (27, 28) and, additionally, in the intact circulation, sinus tachycardia or atrial fibrillation with rapid ventricular response contributes to the increase in myocardial oxygen utilization (29-31, 42), an increase which amounts to about 30 to 40% per unit mass of myocardium in the average thyrotoxic patient (30, 31) and may double in the severely hyperthyroid dog (29). In the latter, even without other cardiac disease, reduced myocardial extraction of carbohydrate substrates suggests hypoxia (29), which may also be responsible for functional and structural changes in the mitochondria of chronically hyperthyroid rats (43), and for diffuse degenerative or fibrotic changes throughout the myocardium in other experimental animals (44). The effect of superimposing coronary artery disease with limitation of myocardial blood flow and oxygen availability may be anticipated from the present in vitro study. Although the direct effect of hyperthyroidism is to increase myocardial contractility, under conditions of marginal oxygenation, hyperthyroidism also induces a more profound depressant effect of hypoxia, and contractility may not show a net increase. In the otherwise healthy animal and man with good myocardial perfusion, augmentation of contractility is one of the mechanisms by which the heart adapts to increased metabolic and flow load (3-8). Coronary artery disease of an extent which might not be particularly significant in the euthyroid patient would be expected to seriously impair this adaptive response. Similarly, hypertensive or valvular heart disease not only imposes an additional hemodynamic load but also results in ventricular hypertrophy with associated ischemia of variable degree, becoming especially important in the presence of thyrotoxicosis. It is when one of the above conditions coexists with thyrotoxicosis in the older age group, that clinical cardiac failure or angina occur (9, 10, 45). Presumably, other factors are also involved: the tachycardia, if excessive, may limit diastolic coronary blood flow and encroach upon ventricular diastolic filling, and atrial fibrillation results in loss of the normal mechanism for mitral valve closure and loss of the atrial contribution to ventricular filling (46).

This study was also designed to test the hypothesis that the marked abbreviation of active state, reflected by decreased time to peak tension (21-23), in hyperthyroidism might particularly limit shortening in afterloaded and isotonic contractions and that the difference between contracted length-tension relations in isotonic and isometric contractions (14) might be greater in hyperthyroid than in normal muscle. Such an effect, if it existed, could curtail shortening and ejection of the
intact hyperthyroid ventricle (15) and hence limit the latter's ability to deal with flow load. Hyperthyroidism was found to influence the difference between isotonic and isometric contracted length-tension relations at a contraction frequency of 12/min; at low loads the difference was diminished and at high loads it was increased. The effect, although significant, was small and characteristic of that associated with the change in position of the isometric length-tension relation, the shift to the left which was observed at this frequency (14). At 60/min, neither the isometric nor the isotonic contracted length-tension relations of hyperthyroid muscles, nor the differences between these relations, were significantly different from those of normal muscles. Therefore, no effect could be attributed to the abbreviation of active state resulting from hyperthyroidism. This is not to suggest that the reduced duration of active state is not important in other respects, for tension development and shortening depend on the resultant of intensity and duration of active state and would be more substantially increased if reduction in duration of active state did not accompany increase in its intensity.

In conclusion, predisposition of cardiac muscle to hypoxia is considered an important determinant of the net effect of hyperthyroidism on the contractile properties of cardiac muscle under conditions of marginal oxygenation. At high contraction frequencies, the in vitro preparation studied here is analogous to cardiac muscle in vivo in the presence of coronary insufficiency. That the ability to develop tension and shorten is not, in this circumstance, greater in hyperthyroid than in normal muscle helps explain the occurrence of thyrotoxic heart disease when metabolic and flow requirements are increased.

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