Augmentation of Myocardial Oxygen Consumption in Hyperthyroid Cats

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ABSTRACT

To clarify the effects of hyperthyroidism on myocardial oxygen consumption (VO\textsubscript{2}), a polarographic method was employed to compare the VO\textsubscript{2} of isolated papillary muscles from 13 normal euthyroid cats with that of 11 hyperthyroid cats. Basal VO\textsubscript{2} was greater in the hyperthyroid group (3.03 ± 0.20 vs. 2.36 ± 0.19 SE filtering dry weight \cdot hour\textsuperscript{-1}, P<0.05). In muscles studied under afterloaded isotonic conditions, hyperthyroidism shifted the force-velocity curve upward and to the right, with an increase in both extent and velocity of shortening at equivalent loads. These changes in myocardial behavior in hyperthyroidism were associated with an increase in myocardial VO\textsubscript{2}. Isometrically contracting muscles from hyperthyroid animals demonstrated significant increases in both developed tension (6.3 ± 0.7 vs. 4.7 ± 0.4 g/mm\textsuperscript{2}, P<0.05) and rate of tension development (32.6 ± 3.5 vs. 19.4 ± 1.5 g/mm\textsuperscript{2} \cdot second\textsuperscript{-1}, P<0.01), as compared to the euthyroid group. Myocardial VO\textsubscript{2}, expressed per g/mm\textsuperscript{2} isometric developed tension, was significantly greater in the hyperthyroid group (0.641 ± 0.09 vs. 0.42 ± 0.04 milliliters \cdot mg dry wt \cdot beat\textsuperscript{-1}, P<0.02). Thus, experimental hyperthyroidism augments myocardial VO\textsubscript{2} whether measured in resting or contracting cardiac muscle. This increase can be attributed, at least in part, to the altered contractile function of the heart in hyperthyroidism.

ADDITIONAL KEY WORDS: cat papillary muscle, muscle mechanics, contractile state, external work, force-velocity relations, myocardial metabolism, tension development, 1-thyroxine

The most characteristic effect of thyroid hormone on cellular function is its regulation of energy metabolism (1). In general, the metabolic rate of most body tissues is directly related to the circulating level of thyroid hormone (2). In the heart, however, this relationship is not clear. Investigations utilizing isolated noncontracting cardiac tissue slices from hyperthyroid animals have repeatedly demonstrated an increased oxygen consumption (VO\textsubscript{2}) (3-7). However, attempts to determine the effects of hyperthyroidism on the VO\textsubscript{2} of intact, working cardiac muscle have given conflicting results, with some investigators reporting an increased VO\textsubscript{2} (8, 9) and others finding normal values (10-13). The heart is an aerobic organ and can
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cats (1.8 to 3.6 kg) and 10 cats (2.0 to 3.6 kg) and oxygen consumption. Correlation of changes in mechanical behavior during contraction (14). Such mechanical factors as tension development (15-19), external work (20-22), and contractile state (23-28) have been identified as important determinants of myocardial energy utilization. Heart rate is also important since it determines the number of times per minute that these mechanical factors are in force. In addition, the basal or resting rate of myocardial metabolism accounts for a significant though relatively small portion of the total myocardial energy needs (18, 21, 29).

Alterations of the contractile properties of cardiac muscle as characterized by an increased intrinsic velocity of contraction \( V_{\text{max}} \), an increased rate of tension development, and a decreased duration of active state have been repeatedly demonstrated in experimental hyperthyroidism (20-33). Under appropriate experimental conditions, these alterations in contractile function in hyperthyroidism would be expected to augment myocardial VO\(_2\).

Accordingly, the present study was performed to determine if myocardial oxygen consumption is altered in hyperthyroidism and to define, insofar as possible, the mechanical factors responsible for any observed changes. Correlation of changes in mechanical behavior with changes in oxygen consumption is difficult in the intact heart because of its complex architecture and the difficulty in isolating a single variable. Therefore, we utilized the isolated papillary muscle of cats because its simplified geometry and mechanical controls allow a more precise and quantitative measurement of myocardial mechanics and oxygen consumption.

Methods

MEASUREMENT OF MYOCARDIAL MECHANICS

Studies were performed with 13 normal adult cats (1.8 to 3.6 kg) and 10 cats (2.0 to 3.6 kg) made hyperthyroid by the intraperitoneal injection of 1-thyroxine (0.75 mg/kg · day) for 10 to 17 days. The cats were anesthetized with intraperitoneal pentobarbital (25 mg/kg) and blood was obtained for the determination of serum protein-bound iodine and cholesterol. The hearts were then removed and right ventricular papillary muscles rapidly excised and transferred to a petri dish for placement of 4.0 noncapillary silk ties. Each muscle was mounted in a bundle muscle bath perfused with an oxygenated Krebs-Ringer solution (pH 7.4) containing Na\(^+\), 145; K\(^+\), 3.7; Ca\(^{2+}\), 2.5; Mg\(^{2+}\), 1.2; Cl\(^-\), 125; HPO\(_4\)\(^{2-}\), 1.2; SO\(_4\)\(^{2-}\), 1.2; HCO\(_3\)\(^{-}\), 2.5; and glucose, 5.6 mm. The details of this myograph have previously been presented (27). The muscle was attached via its tendinous end to either a Schilling isometric transducer (34) or a Statham force transducer (Model G-1000) mounted on an adjustable screw stand. This arrangement allowed the study of either afterloaded isotonic or isometric contractions. A preload of 0.3 g determined initial muscle length for isotonic contractions. Experiments on isometrically contracting muscles were performed at L\(_{\text{max}}\), the length at which active tension was maximal. Average resting tension at L\(_{\text{max}}\) was the same for both muscle groups, 1.2 g/mm². Temperature in the muscle bath was maintained at 26°C. Electrical field stimulation at a frequency of 30/min was delivered via electrodes placed parallel to the muscle using square wave pulses of 5-msec duration at a voltage 10 to 20% above threshold (3 to 6 V). Using an identical stimulation technique, Coleman and co-workers have shown that papillary muscles function normally after depletion of their endogenous norepinephrine stores by chronic extrinsic cardiac denervation (35). This finding indicates that the suprathreshold stimuli used in the present study do not liberate significant amounts of norepinephrine from sympathetic fibers in papillary muscles. Each muscle was allowed to stabilize for at least 40 minutes before myocardial mechanics and oxygen consumption were measured. Only thin, approximately cylindrical papillary muscles were used. Average muscle cross-sectional area in the two groups was identical, 0.74 mm².

Measurements of papillary muscle contractile function and oxygen consumption were obtained simultaneously during periods of contraction lasting 5 to 10 minutes. After a brief initial treppe effect, contractile function in each muscle remained essentially unchanged during the contraction period. Either the maximal velocity of isotonic shortening, dll/dtl, or rate of isometric tension development, dT/dtl, was obtained by electronic differentiation with an R.C. circuit and displayed along with muscle shortening or isometric developed tension on an oscillograph.
recorder at a paper speed of 100 mm/sec. Mean data for mechanical parameters were calculated by analyzing a single representative contraction per muscle at each experimental load.

MEASUREMENT OF OXYGEN CONSUMPTION

The technique used to measure papillary muscle oxygen consumption has been described in detail in a previous publication (27). Briefly, a Krebs-Ringer solution equilibrated with 95% O2-5% CO2 was circulated past the muscle situated in the central tubular chamber of the muscle bath. The effluent from the muscle chamber was withdrawn through a capillary containing a Clark type oxygen electrode.1 The electrode was calibrated during each experiment by changing the gas mixture equilibrating the solution from 95% O2-5% CO2 to 90% O2-5% CO2-5% N2. Gas mixtures were analyzed either with a Haldane apparatus (30) or by gas chromatography. Papillary muscle oxygen consumption was calculated using the solubility constant of oxygen in water at 26 °C, the calibration curve, and the deflection in the oxygen tension record produced during periods of rest or contraction. The oxygen consumption associated with contraction was determined at each load by stimulating the muscle for 5 to 10 minutes and integrating the curve for decreased oxygen tension with respect to the duration of stimulation. Resting or basal oxygen consumption was measured by noting the base-line deflection produced in the oxygen tension record after installation of the muscle in the bath.

The results are expressed as the mean ± SE. Statistical tests of significance were performed using the t-test of differences between group means (37). Differences between the groups were considered significant when P<0.05.

Results

CHARACTERIZATION OF THYROID STATE

All cats injected with 1-thyroxine lost weight (0.60 ± 0.05 kg) during the 10- to 17-day treatment period. Protein-bound iodine averaged 4.5 ± 0.4 μg/100 ml in the euthyroid animals and was always greater than 20 μg/100 ml even in the hyperthyroid group (P<0.01). Serum cholesterol was significantly less in the hyperthyroid animals, 54 ± 4 mg/100 ml, than in the euthyroid controls 78 ± 7 mg/100 ml (P<0.01).

RESTING OXYGEN CONSUMPTION

The resting myocardial VO2 was measured in 11 muscles from the euthyroid and 10 muscles from the hyperthyroid cats. Muscles from the hyperthyroid animals averaged 3.03 ± 0.20 μl/min mg dry wt • hour-1 compared to 2.36 ± 0.19 μl/min mg dry wt • hour-1 for muscles from the euthyroid group (P<0.05).

OXYGEN CONSUMPTION DURING AFTERLOADED ISOTONIC CONTRACTIONS

Force-velocity curves, muscle shortening, and VO2 were determined in 13 muscles from the euthyroid controls and 10 muscles from the hyperthyroid cats. The mean results for each group are depicted in Figure 1. Hyperthyroidism caused a shift in the force-velocity curve upward and to the right with augmentation of both the intrinsic velocity of shortening (Vmax) and isometric load (P0). The velocity of muscle shortening with only the preload on the lever averaged 0.71 ± 0.08 muscle lengths/sec in the euthyroid group and 1.24 ± 0.17 muscle lengths/sec in the hyperthyroid animals (P<0.01). Furthermore, muscles from hyperthyroid cats shortened more at equivalent loads than muscles from euthyroid animals. Therefore, external work, calculated as the product of load × shortening, was increased in the hyperthyroid group. Thus, values for both velocity of shortening and external work at comparable loads were increased by experimental hyperthyroidism. These alterations in mechanical behavior in muscles from hyperthyroid animals were associated with significant increases in myocardial VO2 over the entire range of loads studied.

Analysis of isometric contractions at the apex of the length-active tension curve (Fig. 2) revealed marked differences in contractile function between the euthyroid and hyperthyroid groups. Experimental hyperthyroidism was associated with an increased tension development, an increased maximal rate of tension development, and a decreased time to peak tension. Average myocardial VO2 for the eight muscles from hyperthyroid cats studied under isometric conditions was 3.73 ± 0.33

1Constructed by Mrs. Zena McCallum.

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Effects of experimental hyperthyroidism on myocardial mechanics and oxygen consumption (VO₂) measured simultaneously under afterloaded isotonic conditions. Mean results ± se from 13 papillary muscles from euthyroid cats and 10 muscles from hyperthyroid animals are compared. Ordinates are velocity of shortening (top panel), shortening (middle panel) and VO₂ (bottom panel). Abscissa is total load.

Myocardial VO₂ per g/mm² developed tension was significantly greater in muscles from euthyroid cats averaging 1.99 ± 0.25 µliter • mg dry wt⁻¹ • beat⁻¹ (P < 0.01). Since myocardial VO₂ has a direct linear relation to isometric tension development (18, 35), the data for isometric contractions were compared by expressing VO₂ as a function of developed tension.
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Effects of experimental hyperthyroidism on isometric contractile function. Measurements made at a contraction frequency of 30/min at $L_{	ext{max}}$.

Discussion

The results of the present investigation demonstrate that experimental hyperthyroidism in cats causes a marked augmentation of myocardial VO₂, whether measured in resting or contracting cardiac muscle. The increase in resting myocardial VO₂ noted here is consistent with the findings of several earlier studies in which a variety of noncontracting cardiac muscle preparations were used (4-7). Our demonstration of an increase in myocardial VO₂ per gram of muscle per contraction in hyperthyroidism agrees with the results of Rowe and co-workers (8), but differs from the findings of most investigators who have previously examined this problem. Rowe et al., using the technique of coronary sinus catheterization, showed that myocardial VO₂ per contraction was increased in hyperthyroid patients. Leight and co-workers (9), employing a similar technique, also found an elevated myocardial VO₂ per minute in hyperthyroidism, but these investigators made no correction for heart rate. In a comparable study, Bing et al. (12) reported that myocardial VO₂ per contraction was normal in hyperthyroid patients. Dock and Lewis (10) used a rat heart-lung preparation and McEachern (11) utilized isolated guinea pig atria to demonstrate no differences in myocardial VO₂ per gram of muscle per contraction between euthyroid and hyperthyroid animals. More recently, Piatnek-Leunissen and Olson (13) have observed that the VO₂ per 100 g of ventricle per contraction was normal in dogs with experimental hyperthyroidism. However, unlike the present investigation, all of the above mentioned studies were performed under experimental conditions which did not allow complete control or accurate measurement of the mechanical factors now known to be important determinants of myocardial oxygen consumption during contraction. Consequently, interpretation of the results of these earlier experiments is difficult, and variations of the mechanical conditions under which the hearts were working perhaps account for the conflicting results obtained.
The examination of papillary muscle function under afterloaded isotonic conditions revealed marked differences between the normal and hyperthyroid groups. Hyperthyroidism caused a marked shift upward and to the right of the muscle force-velocity curve with increases in both $V_{\text{max}}$ and isometric load. These alterations in muscle force-velocity relations indicate that myocardial contractility is increased in hyperthyroidism. We recognize that force-velocity curves obtained by measuring the velocity of muscle shortening in a series variably afterloaded isotonic contractions do not precisely represent the true force-velocity relation of the contractile element (38, 39). However, the complexity of the quick-release techniques required for a more precise analysis of contractile element function precludes their use in studies measuring VO$_2$. The hyperthyroid-induced augmentation of myocardial contractile state was always associated with an increased VO$_2$. However, muscles from the hyperthyroid animals also shortened more at equivalent loads; therefore, they performed more external work than did the muscles from euthyroid animals. Thus, under isotonic conditions, changes occurred in both contractile state and external work precluding assessment of their individual contribution to the augmentation of myocardial VO$_2$ in hyperthyroidism.

The analysis of isometric contractions in which muscle shortening and external work were eliminated provided a more precise definition of the role played by enhanced contractility in determining myocardial VO$_2$ in the hyperthyroid animals. The development of tension in isometric contractions is due to the interaction of a passive series elastic component and an active contractile element (40). Since the series elastic component of cardiac muscle is not altered by hyperthyroidism (41), the increased rate of tension development noted in muscles from hyperthyroid cats can be correlated directly with an increased intrinsic velocity of contractile element shortening ($V_{\text{max}}$) (42). A 68% increase in the rate of tension development in muscles from hyperthyroid cats was associated with a 52% increase in myocardial VO$_2$ per g/mm$^2$ of tension development. Thus, it seems likely that augmentation of the contractile state is an important determinant of the increased myocardial VO$_2$ caused by hyperthyroidism.

Factors unrelated to the mechanics of contraction may also be implicated to explain the increased myocardial energy needs in hyperthyroidism. The administration of large doses of thyroxine has been shown to uncouple the process of oxidative phosphorylation (1, 43). As a result of this uncoupling, increased amounts of oxygen are consumed by the cell to maintain adequate high-energy phosphate stores. However, the dose of thyroxine required (20 to 40 mg/kg per day) to produce uncoupling far exceeds that used in the present study (0.75 mg/kg per day). Furthermore, normal oxidative phosphorylation was found in cardiac mitochondria from dogs treated with similar doses of thyroxine for 5 to 27 months (13). Thus, it seems unlikely that uncoupling of oxidative phosphorylation contributed to the differences in myocardial VO$_2$ observed in the present study. Wang and Bernmiloud (44) have reported that hearts from hyperthyroid rats had an increased adenosine triphosphatase activity in cellular fractions containing mitochondria. Similar results have been reported from human skeletal muscle (45). An increased activity of this enzyme in hyperthyroidism could account for a portion of the increase in resting energy needs noted in the present investigation, but probably would have little effect on the VO$_2$ associated with cardiac muscle contraction.

Recently it has been demonstrated that high-energy phosphate utilization for the performance of mechanical work was inefficient in papillary muscles removed from hyperthyroid cats (46). The mechanism of this increased energy utilization unrelated to mechanical variables was not explained, but uncoupling of oxidative phosphorylation was excluded by measuring energy utilization after high-energy phosphate production had been blocked by exposure of the muscle to iodoacetic acid and nitrogen. The design of...
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the present study precluded any attempt to quantify the contribution of inefficient energy utilization to the increased myocardial VO_2 of hyperthyroid myocardium, but such a contribution remains a possibility.

The basal VO_2 at 26°C of 2.36 µliter • mg dry wt^-1 • hour^-1 reported here in normal papillary muscles is equivalent to 1.0 ml • 100 g left ventricle^-1 • min^-1. This value compares favorably with the 1.2 to 1.7 ml • 100 g left ventricle^-1 • min^-1 generally accepted to represent basal VO_2 in the intact heart at 37°C (14). Basal VO_2 of most tissues increases with increasing temperature. Thus, the slightly lower VO_2 noted here may possibly be explained by the lower temperature at which the measurements were made. The VO_2 of normal muscles contracting isometrically at a rate of 30/min in the present study (1.99 µliter • mg dry wt^-1 • beat^-1) is equivalent to 1.5 ml • 100 g left ventricle^-1 • min^-1. The VO_2 of contracting intact hearts has been found to range between 1.5 to 15 ml • g left ventricle^-1 • min^-1 (14). The relatively low value reported here may be partially explained by differences in the temperature at which measurements were made but more important is the fact that most studies with the intact heart were performed at heart rates greater than 100/min compared to the rate of 30/min used in the papillary muscles. Extrapolating the data in papillary muscles to a heart rate of 100/min gives a VO_2 of 5.0 ml • 100 g left ventricle^-1 • min^-1. Thus, similar values for myocardial VO_2 are found whether measurements are made in the isolated papillary muscle or in the intact heart.

These experiments demonstrate that experimental hyperthyroidism in cats is associated with a significant augmentation of myocardial VO_2 whether measured in resting or contracting cardiac muscle. The association of an increased myocardial VO_2 with the alterations in cardiac muscle mechanics characteristic of the hyperthyroid state is consistent with previous studies indicating that tension development, external work, and contractile state are important determinants of cardiac energy utilization.

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