McAllister, Richard M., Kelli L. Luther, and P. Charles Pfeifer. Thyroid status and response to endothelin-1 in rat arterial vessels. Am J Physiol Endocrinol Metab 279: E252–E258, 2000.—We have previously reported that changes in thyroid status are associated with significant alterations in skeletal muscle blood flow during exercise and that changes in endothelium-dependent vasodilation may contribute to these blood flow abnormalities. The purpose of this study was to test the hypothesis that altered endothelium-dependent vasoconstriction is also associated with changes in thyroid status. To test this hypothesis, rats were rendered hypothyroid with propylthiouracil (Hypo, n = 14) or hyperthyroid with triiodothyronine (Hyper, n = 14) over ~3 mo. Treatment efficacy was confirmed by altered (P < 0.05) citrate synthase activity in several hindlimb skeletal muscles from Hypo and Hyper, compared with that in muscles from euthyroid rats (Eut, n = 12). Vascular rings were prepared from abdominal aortae, and responses to several vasoactive agents were determined in vitro. As found previously, maximal acetylcholine-induced vasorelaxation was modulated by thyroid status (Eut, 47 ± 9; Hypo, 28 ± 6; Hyper, 68 ± 5%; P < 0.05). Contractile responses of vascular rings with intact endothelium to the endothelium-derived constrictor endothelin-1 (ET-1), however, were similar among groups across a range of ET-1 concentrations. In addition, maximal responses [Eut, 3.75 ± 0.47; Hypo, 2.72 ± 0.25; Hyper, 3.22 ± 0.42 g; not significant (NS)] and sensitivities (Eut, 8.12 ± 0.09; Hypo, 8.10 ± 0.06; Hyper, 8.28 ± 0.09 –log M; NS) to ET-1 were similar among groups. If these findings from the conduit-type abdominal aorta extend into resistance vasculature, it appears that changes in endothelium-dependent vasoconstriction do not contribute to skeletal muscle blood flow abnormalities associated with thyroid disease states.

hypothyroidism; hyperthyroidism; acetylcholine; vasodilation; vasoconstriction

THYROID DISEASES ARE ESTIMATED to affect ~5% of the population (34). Two common thyroid diseases, hypothyroidism and hyperthyroidism, are both characterized by exercise intolerance (20). Poor exercise tolerance in hypothyroidism, undoubtedly makes an important contribution to inadequate skeletal muscle perfusion during exercise (26). In addition, alterations in vascular function may contribute to poor perfusion of muscle. Consistent with this possibility, we have reported (5) that hypothyroidism is associated with blunted endothelium-dependent relaxation of isolated arterial vessels. Conversely, left ventricular function (26), endothelium-dependent vasorelaxation (22, 28), and skeletal muscle blood flow during exercise (9, 23) are all augmented in hyperthyroidism. Enhanced perfusion of active muscle suggests that other factors (e.g., impaired thermoregulation) must account for exercise intolerance in this disease (20).

In addition to synthesizing relaxing factors (e.g., nitric oxide), the endothelium can synthesize substances that induce vascular smooth muscle contraction. The best characterized of these substances is endothelin-1 (ET-1), a 21-amino acid polypeptide with potent vasoconstrictor ability (36). Effects of thyroid diseases on endothelium-dependent vasoconstriction are unknown. Data are, however, available for hypertension, a disease having hemodynamic similarities with hypothyroidism (15, 20). Vascular smooth muscle contraction induced by ET-1 has been reported to be greater in hypertensive patients (11) and in a rodent model of hypertension (3) compared with normotensive controls. Thus hypothyroidism may be associated with inadequate perfusion of skeletal muscle during exercise for two reasons related to vascular function. First, blood flow to active muscle may be inadequate because of blunted endothelium-dependent vasodilation (5). Second, augmented vasoconstriction in response to ET-1 may reduce muscle blood flow. The second possibility is important to investigate, because it has been reported that ET-1 contributes to the control of resting skeletal muscle blood flow (12, 35) and that plasma ET-1 concentration increases with exercise (19). Hyperthyroidism, on the other hand, may be characterized by augmented muscle blood flow during exercise because of enhanced endothelium-dependent vasore-
relaxation (22, 28) and/or lesser ET-1-induced vasoconstriction.

This study was designed to test two hypotheses. First, we hypothesized that the vascular smooth muscle contractile response to ET-1 is augmented in hypothyroidism. Second, we hypothesized that hyperthyroidism is associated with a decreased contractile response to ET-1. In addition, we wished to determine which ET receptor subtype(s) mediates contraction of vascular smooth muscle induced by ET-1 in arterial vessels of euthyroid, hypothyroid, and hyperthyroid rats. Previous work had suggested that the ET_A receptor subtype is primarily responsible for mediating the smooth muscle contractile response to ET-1 in normal vasculature (10, 35).

METHODS

Experimental animals. Male Sprague-Dawley rats (Charles River) initially weighing 150–175 g were housed in a room with controlled temperature (20–21°C) and light (12:12-h light-dark). Rats were randomly assigned to one of three groups: euthyroid control (Eut), hypothyroid (Hypo), and hyperthyroid (Hyper). Eut were slightly food restricted (~90% of normal bulk food intake) to match their body weights with those of Hypo and Hyper. Rats in the latter two groups were allowed to consume food ad libitum.

Treatments. Hypothyroidism was induced by ~3-mo treatment with propylthiouracil (Sigma-Aldrich) in the drinking water (0.04 g/100 ml), as done previously (5, 21). Hyperthyroidism was induced by intraperitoneal injections of triiodothyronine (T_3, sodium salt, Sigma-Aldrich; 300 μg/kg) on alternate days over ~3 mo, as done previously (8, 14, 22, 23). These treatments and other experimental procedures were approved by the Kansas State University Institutional Animal Care and Use Committee.

Determination of treatment efficacy. Effectiveness of propylthiouracil and T_3 treatments was assessed by determination of left ventricular weight and by estimation of skeletal muscle oxidative capacity, as done previously (5, 8, 14, 21–23). Oxidative capacity was estimated by determination of citrate synthase activity in several hindlimb muscles. These muscles included the vastus lateralis (red section), vastus lateralis (white section), and soleus, which are composed primarily of fast oxidative glycolytic, fast glycolytic, and slow oxidative muscle fibers, respectively (4). Citrate synthase activity was determined spectrophotometrically by the method of Srere (31).

Preparation of arterial vascular rings. Pentobarbital sodium (65 mg/kg) administered intraperitoneally was used to anesthetize rats. They were then killed by decapitation, and abdominal aortae distal to the renal arteries were quickly dissected. These segments were placed in Krebs bicarbonate buffer solution (4°C; see Solutions and drugs) after precontraction of a denuded vascular ring by norepinephrine (NE, 10^{-7} M).

Length-tension relationship. Aortic vascular rings were adjusted to optima of their individual length-developed tension relationships, as done previously (5, 22). In brief, two fine stainless steel wires were passed through the lumen of each vascular ring. One wire was connected to an isometric force transducer (Harvard Apparatus); the other wire was connected to a micrometer microdrive (Stoelting). Isometric force was continuously monitored by means of a computerized data acquisition system (MacLab). Each vascular ring/wire combination was submerged in Krebs bicarbonate buffer solution (37°C) contained in a 20-ml tissue bath.

Repeated exposures to 60 mM of KCl at increasing length permitted vascular rings to be adjusted to optima of their individual length-developed tension relationships. Length was changed by stretching rings in 5–10% of passive outside diameter) increments with the micrometer microdrives. After each exposure to and determination of developed tension in response to 60 mM KCl, the buffer solution was replaced to allow for washout of the contractile effect of KCl before further stretching and assessing developed tension in response to 60 mM KCl at a greater length. Upon attainment of optimal stretch, a 1-h period of stabilization was allowed.

Pharmacological studies. After the stabilization period, concentration-dependent contractile responses to NE were determined (10^{-7}–10^{-4} M, in one-half log increments), as done previously (5, 22). Concentration was increased by cumulative addition of NE to tissue baths. A recovery period of 90–120 min, during which buffer solution was changed at 5- to 10-min intervals, was allowed to reattain resting tension in all vascular rings.

Endothelium-dependent vasorelaxation was then determined, as done previously (5, 22). Vascular rings were precontracted with NE (10^{-7} M). This concentration of NE was used to ensure that developed isometric tension was similar among groups before assessment of relaxation responses. Upon attainment of stable tension development, a maximally effective dose of the endothelium-dependent agent acetylcholine [10^{-4} M (25)] was administered. A recovery period of ~30 min was allowed, permitting reattainment of resting tension by all vascular rings. Buffer solution was changed at 5- to 10-min intervals during this recovery period.

After determination of endothelium-dependent relaxation, concentration-dependent contractile responses to ET-1 were determined (10^{-10}–10^{-7} M, in one-third log increments), as done previously (24). Concentration was increased by cumulative addition of ET-1 to tissue baths. In selected experiments, ET receptor antagonists were used to determine roles of ET_A and ET_B receptor subtypes in mediating the contractile response to ET-1. The ET_A-selective receptor antagonist BQ-123 (10^{-6} M) and the ET_B-selective receptor antagonist BQ-788 (10^{-6} M) were used (10). These agents were administered to one of the two vascular rings with intact endothelium from each rat 30 min before determination of contractile responses to ET-1. A recovery period of 90–120 min, during which buffer solution was changed at 5- to 10-min intervals, was allowed to reattain resting tension in all vascular rings after determination of concentration-dependent contractile responses to ET-1.

Finally, endothelium-independent vasorelaxation was determined, as done previously (5, 22). Vascular rings were precontracted with NE (10^{-7} M). After stable isometric tension development was attained, a maximally effective dose of the endothelium-independent agent sodium nitroprusside [10^{-4} M (25)] was administered.

Solutions and drugs

Solutions

5% to acetylcholine (10^{-2} M; see Solutions and drugs) after precontraction of a denuded vascular ring by norepinephrine (NE, 10^{-7} M).

Length-tension relationship. Aortic vascular rings were adjusted to optima of their developing tension relationships, as done previously (5, 22). In brief, two fine stainless steel wires were passed through the lumen of each vascular ring. One wire was connected to an isometric force transducer (Harvard Apparatus); the other wire was connected to a micrometer microdrive (Stoelting). Isometric force was continuously monitored by means of a computerized data acquisition system (MacLab). Each vascular ring/wire combination was submerged in Krebs bicarbonate buffer solution (37°C) contained in a 20-ml tissue bath.

Repea...
Solutions and drugs. Krebs bicarbonate buffer solution consisted of (in mM): 131.5 NaCl, 5.0 KCl, 1.2 NaH2PO4, 1.2 MgCl2, 2.5 CaCl2, 11.2 glucose, 13.5 NaHCO3, 0.003 propranolol, and 0.025 EDTA. Propranolol was included in the buffer to antagonize β-adrenoceptor-mediated vasorelaxation. Upon equilibration with a 95% O2-5% CO2 gas mixture, the buffer solution was of pH 7.4.

Stock solutions of most vasoactive agents were prepared in distilled water. Stock solutions of ET-1 and BQ-788 were prepared in 1% (vol/vol) glacial acetic acid and 1% (vol/vol) DMSO solutions, respectively, as recommended by vendors. Stock solutions of NE and ET-1 were serially diluted with distilled water. Appropriate aliquots of stock solutions or serial dilutions were added to tissue baths to achieve desired concentrations of vasoactive agents. Most agents were purchased from Sigma-Aldrich. ET-1 was obtained from Peninsular Laboratories, and BQ-123 and BQ-788 were purchased from American Peptide.

Statistical analysis. All data are presented as means ± SE. Responses to contractile agents (NE, ET-1) are expressed in grams of developed tension, meaning the increase in isometric tension above resting level (that caused by stretch of vascular ring alone). Responses to vasorelaxing agents (acetylcholine, sodium nitroprusside) are expressed in relative terms, i.e., as a percentage of developed tension induced by the precontracting agent NE. Vasorelaxation of vascular rings with intact endothelium was required to be ≥10% for inclusion in the data set. Relaxation of a vascular ring with intact endothelium of <10% was considered to indicate endothelial damage incurred during ring preparation. Data for appropriate vascular rings from an experimental animal were averaged before statistical analysis.

Citrate synthase activities, left ventricular weight-to-body weight ratio, vascular ring characteristics, and responses to vasorelaxing agents were compared among groups using one-way ANOVA, with the Tukey’s test used for post hoc analysis (32). Responses to agents inducing vascular contraction were compared among groups using two-way ANOVA, with the Tukey’s test used for post hoc analysis (32). Maximal responses and sensitivities (EC50 values) to agents inducing vascular contraction were compared among groups using two-way ANOVA with repeated measures on one factor (agent concentration). The Tukey’s test was used for post hoc analysis (32). Maximal responses and sensitivities (EC50 values) to agents inducing vascular contraction were compared among groups using one-way ANOVA, with the Tukey’s test used for post hoc analysis (32). Contractile agent concentration inducing 50% of maximal vascular contractile response was termed EC50.

RESULTS

Treatment efficacy. Propylthiouracil treatment successfully induced hypothyroidism. Citrate synthase activity, an estimate of oxidative capacity, was decreased in hindlimb skeletal muscles from Hypo compared with those from Eut (Fig. 1). The magnitude of reduction in citrate synthase activity ranged from ~30% in the vastus lateralis muscle (white section) to nearly 60% (P < 0.05) in the soleus. Conversely, citrate synthase activity was increased in muscles from Hyper compared with those from Eut, with the magnitude of augmentation ranging from slightly less than 10% in the vastus lateralis (white section) to nearly 50% (P < 0.05) in the red section of the same muscle (Fig. 1). These findings demonstrate that hyperthyroidism was induced by T3 treatment. In addition, Hyper exhibited left ventricular hypertrophy, as indicated by greater left ventricular weight-to-body weight ratio (Eut 1.86 ± 0.04, Hyper 2.36 ± 0.07 mg/g; P < 0.05). Hypo did not exhibit altered left ventricular size [1.78 ± 0.05 mg/g; not significant (NS) vs. Eut].

Vascular ring characteristics. Table 1 presents the characteristics of rings prepared from abdominal aorta of Eut, Hypo, and Hyper rats. Vascular rings from rats of different groups were of similar dimensions.

Table 1. Vascular ring characteristics

<table>
<thead>
<tr>
<th>Group</th>
<th>Outside Diameter, mm</th>
<th>Inside Diameter, mm</th>
<th>Axial Length, mm</th>
<th>Optimal Stretch, %</th>
<th>Resting Tension, g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euthyroid (n = 12)</td>
<td>1.58 ± 0.03</td>
<td>1.11 ± 0.03</td>
<td>2.93 ± 0.08</td>
<td>148 ± 2</td>
<td>3.39 ± 0.20</td>
</tr>
<tr>
<td>Hypothyroid (n = 14)</td>
<td>1.43 ± 0.04*</td>
<td>1.00 ± 0.04</td>
<td>2.73 ± 0.05</td>
<td>148 ± 2</td>
<td>2.84 ± 0.12*</td>
</tr>
<tr>
<td>Hyperthyroid (n = 14)</td>
<td>1.57 ± 0.05</td>
<td>1.10 ± 0.03</td>
<td>2.92 ± 0.07</td>
<td>146 ± 2</td>
<td>3.36 ± 0.16</td>
</tr>
</tbody>
</table>

Values are means ± SE. Optimal stretch, increase above passive outside diameter at which peak contractile response to 60 mM KCl occurred; resting tension, tension exhibited at optimal stretch, due to stretch of vascular ring alone. *P < 0.05 vs. Euthyroid, Hyperthyroid groups.
Vascular rings from Hypo, compared with those from Eut and Hyper, were of slightly smaller outside diameter and exhibited less resting tension at optimal stretch (Table 1). Calculated wall thickness, however, was similar among groups (Eut 0.23 ± 0.02, Hypo 0.21 ± 0.02, Hyper 0.24 ± 0.02 mm; NS).

Contractile responses to NE. Sensitivity to NE was reduced (P < 0.05) in Hypo (7.19 ± 0.09, -log M units) compared with both Eut (7.66 ± 0.07) and Hyper (7.63 ± 0.09). Maximal responses to NE tended (P = 0.054) to be reduced in Hypo (3.37 ± 0.30 g) and Hyper (3.19 ± 0.34 g) compared with Eut (4.38 ± 0.42 g).

Vasorelaxation responses. Relaxation responses to maximally effective doses of the endothelium-dependent agent acetylcholine and the endothelium-independent agent sodium nitroprusside are shown in Fig. 2. Contractile responses to NE (10⁻⁷ M), given to precontract vascular rings before administration of acetylcholine or sodium nitroprusside, did not differ among groups (data not shown). Endothelium-dependent vasorelaxation in rings with intact endothelium was modulated by thyroid status (P < 0.05 among groups), whereas endothelium-independent vasorelaxation in the same rings was similar among groups (Fig. 2).

Contractile responses to ET-1. Figure 3A illustrates contractile responses to ET-1 of vascular rings with intact endothelium from Eut, Hypo, and Hyper. Across the range of ET-1 concentrations tested, contractile responses were similar among groups. In addition, maximal responses to ET-1, irrespective of the ET-1 concentration at which they occurred, were similar among groups (Eut 3.75 ± 0.47, Hypo 2.72 ± 0.25, Hyper 3.22 ± 0.42 g; NS). Sensitivities to ET-1, as indicated by EC₅₀ values (-log M), were also similar among groups (Eut 8.12 ± 0.09, Hypo 8.10 ± 0.06, Hyper 8.28 ± 0.09; NS). Maximal responses to ET-1 were correlated with those to NE in all groups (Eut, r = 0.92; Hypo, r = 0.94; Hyper, r = 0.93; P < 0.05 for all).

Removal of endothelium did not affect contractile responses to ET-1 across the range of concentrations tested in any group (Fig. 3, B vs. A). Developed tension is that in response to endothelin-1 in excess of resting tension. Responses of endothelium-intact and -denuded vascular rings across the range of endothelin-1 concentrations tested did not differ among Euthyroid, Hyperthyroid, and Hypothyroid groups. Responses of endothelium-intact and -denuded vascular rings also did not differ from each other within each group.
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Table 2. Effects of ET receptor antagonists on responses to ET-1

<table>
<thead>
<tr>
<th>Group</th>
<th>ET&lt;sub&gt;A&lt;/sub&gt; Blockade</th>
<th>BQ-123</th>
<th>ET&lt;sub&gt;B&lt;/sub&gt; Blockade</th>
<th>BQ-788</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maximal response, g</td>
<td></td>
<td>Maximal response, g</td>
<td></td>
</tr>
<tr>
<td>Euthyroid (n = 4, 4)</td>
<td>3.42 ± 1.04</td>
<td>3.70 ± 0.73</td>
<td>4.88 ± 0.77</td>
<td>5.10 ± 0.75</td>
</tr>
<tr>
<td>Hypothyroid (n = 6, 5)</td>
<td>2.26 ± 0.46</td>
<td>3.18 ± 0.68</td>
<td>3.18 ± 0.17</td>
<td>4.09 ± 0.23*</td>
</tr>
<tr>
<td>Hyperthyroid (n = 6, 5)</td>
<td>3.40 ± 0.68</td>
<td>2.85 ± 0.61</td>
<td>2.93 ± 0.55</td>
<td>3.28 ± 0.45</td>
</tr>
</tbody>
</table>

Values are means ± SE; n denotes numbers of paired vascular rings studied in absence of (control) and in presence of endothelin (ET) receptor antagonist using ET<sub>A</sub> or ET<sub>B</sub> receptor antagonists, respectively. EC<sub>50</sub>, ET-1 concentration inducing 50% of maximal vascular contractile response. *P < 0.05, †P < 0.005 vs. control condition.

or ET<sub>B</sub> receptor blockade with BQ-788. ET<sub>A</sub> receptor blockade reduced sensitivity to ET-1 in Eut, Hypo, and Hyper. ET<sub>B</sub> receptor blockade, however, reduced sensitivity to ET-1 only in Hyper. ET receptor blockade generally did not alter maximal responses to ET-1.

DISCUSSION

The key new finding of this study is that changes in thyroid status are not associated with alterations in the vascular smooth muscle response to ET-1. Thus our hypothesis that hypothyroidism is associated with an increased contractile response to ET-1 was not confirmed. In addition, our hypothesis that a decreased vascular smooth muscle contractile response to ET-1 is characteristic of hyperthyroidism was not confirmed. Our findings suggest that altered responses to ET-1 do not contribute to the significant skeletal muscle blood flow abnormalities associated with thyroid diseases. This conclusion is necessarily tentative, because responses observed in a conduit vessel such as the abdominal aorta may not reflect those in resistance vessels (5, 22).

Animal models of thyroid diseases. As we (5, 21) and others (14) previously reported, propylthiouracil treatment reduced skeletal muscle oxidative capacity. This feature is a hallmark of hypothyroidism (20). Conversely, T<sub>3</sub> treatment increased muscle oxidative capacity, as both we (22, 23) and others (14) previously demonstrated. Hyper rats also exhibited left ventricular hypertrophy, as we (22, 23) and other investigators (8) observed in the past. These findings validate our animal models of hypo- and hyperthyroidism.

Importantly, vascular rings prepared from abdominal aortae of Hypo exhibited several characteristics that we had previously observed, including reduced sensitivity to NE, blunted endothelium-dependent relaxation, and unaltered endothelium-independent relaxation (5). Vascular rings from Hyper also exhibited characteristics previously reported, including a tendency toward reduced maximal response to NE, enhanced endothelium-dependent relaxation, and unchanged endothelium-independent relaxation (22).

Contractile responses to ET-1. Contrary to our hypotheses, the vascular smooth muscle contractile response to ET-1 was generally not altered by either hypo- or hyperthyroidism. Indeed, the only statistically significant finding was that the maximal response to ET-1 was generally not altered by either hypothyroidism or hyperthyroidism. Indeed, the only statistically significant finding was that the maximal response to ET-1 was generally not altered by either hypothyroidism or hyperthyroidism. Indeed, the only statistically significant finding was that the maximal response to ET-1 was generally not altered by either hypothyroidism or hyperthyroidism.

Maximal responses to NE were also not significantly augmented in Hypo (see RESULTS). Because NE and ET-1 utilize common intracellular signaling pathways (30), an unchanged response to ET-1 in hypothyroidism may be internally consistent. Indeed, maximal responses to NE and ET-1 were highly correlated in all experimental groups (see RESULTS). Interestingly, Criscione et al. (3) found increased pressor responses to NE in the mesenteric vascular beds of spontaneously hypertensive rats, whereas Haynes et al. (11) reported that venoconstrictor responses to NE were not different in their hypertensive patients compared with...
vascular smooth muscle contractile response to ET-1. This alternation is puzzling because it is inconsistent with the hemodynamic profile of hyperthyroidism (20). Furthermore, as is apparent in Fig. 3, the magnitude of elevation (<100%) in ET-1 concentration observed in these studies would not be predicted to increase the contractile response to ET-1 perceptibly. Thus we believe that altered ET-1 formation is unlikely to contribute to skeletal muscle blood flow abnormalities found in thyroid diseases.

ET receptor subtypes and contractile responses to ET-1. A secondary purpose of this study was to determine which ET receptor subtype(s) is responsible for mediating the vascular smooth muscle contractile response to ET-1 in thyroid disease states. Although some investigators have reported that both ET<sub>A</sub> and ET<sub>B</sub> receptors mediate the constrictor response to ET-1 in normal vasculature (29, 33), other studies have suggested that only the ET<sub>A</sub> receptor participates to any significant degree (10, 35). In addition, there are reports of endothelial ET<sub>B</sub> receptors that, when activated by ET-1, lead to the release of nitric oxide and/or vasodilatory prostaglandins that maybuffer the ET-1-induced constriction mediated by ET receptors on vascular smooth muscle (7, 13, 35).

Our findings indicate that it is the ET<sub>A</sub> receptor subtype that is primarily responsible for the constrictor response to ET-1 in rodent conduit-type vessels. The ET<sub>A</sub>-selective receptor antagonist BQ-123 reduced sensitivity to ET-1 in vascular rings from all experimental groups; in contrast, the ET<sub>B</sub>-selective receptor antagonist BQ-788 had minimal impact on responses to ET-1. The absence of ET<sub>B</sub> receptors on the endothelium may be vessel type (conduit vs. resistance), location, and/or species specific.

Physiological relevance. Skeletal muscle blood flow during exercise is significantly modified by thyroid status. Previous work has suggested that alterations in endothelium-dependent vasorelaxation contribute to blood flow abnormalities associated with thyroid diseases. The results of the present study indicate that altered endothelial-dependent vascular smooth muscle contraction at the conduit vessel level, on the other hand, does not contribute to abnormal skeletal muscle blood flow in thyroid disease states. Further studies at the level of resistance vasculature are required to confirm this notion.

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REFERENCES

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