Thyroxine-Induced Left Ventricular Hypertrophy in the Rat
Anatomical and Physiological Evidence for Angiogenesis

William M. Chilian, Roger D. Wangler, Kevin G. Peters, Robert J. Tomanek, and Melvin L. Marcus

SUMMARY. We examined anatomical and physiological responses of the left coronary vascular system to thyroxine-induced myocardial hypertrophy. Wistar-Kyoto rats (1 and 5 months old) were administered thyroxine (0.25 mg/kg per day) or the saline vehicle (sham-treated controls) for 2 months. At the ages of 3 and 7 months, each group of animals was used for one of three experimental protocols: (1) determination of numerical capillary density in perfusion-fixed hearts, (2) measurement of coronary reactive hyperemic responses following a 20-second coronary occlusion (peak-to-resting blood flow velocity) as an index of coronary reserve, and (3) assessment of myocardial perfusion under resting conditions and during maximum coronary dilation (dipyridamole infusion) for the calculation of minimum coronary resistance per unit weight of the left ventricle or minimum coronary resistance of the total left ventricle. In both groups of thyroxine-treated animals, the left ventricular weight-to-body weight ratio increased by 35-40%. Capillary density of the 3- and 7-month-old Wistar Kyoto controls was 4467 ± 352 (mean ± SEM) and 4029 ± 143 capillaries/mm², respectively, but was increased significantly in the thyroxine-treated animals to 6052 ± 409 capillaries/mm² (3-month) and 4654 ± 201 capillaries/mm² (7-month). In both age control groups, the peak-to-resting blood flow velocity ratio was about 2.2. This index of coronary reserve was not changed in the thyroxine-treated animals. Myocardial perfusion measurements were limited to the 7-month-old animals. These measurements indicated that minimum coronary resistance per unit weight of myocardium in the control rats (0.13 ± 0.02 mm Hg x min/ml per 100 g) was not different from the thyroxine-treated rats (0.08 ± 0.02 mm Hg x min/ml per 100 g). The minimum resistance of the entire left ventricle was significantly less in the thyroxine-treated animals than in the controls. These data indicate that in thyroxine-induced hypertrophy, there is a disproportionate increase in the capillary bed and an appropriate increase in the cross-sectional area of the resistance vessels concomitant with the hypertrophy of the myocardium. Thus, angiogenesis during thyroxine-induced hypertrophy maintains normal coronary vasodilator reserve despite increased myocardial mass and augmented metabolic demands.

MYOCARDIAL hypertrophy is usually associated with abnormalities of the coronary vascular system. There is a decrease in coronary vasodilator reserve in the left ventricle (Rembert et al., 1978; Bache et al., 1981; Wangler et al., 1982) and right ventricle (Murray and Vatner, 1980; Manohar et al., 1981) and an increase in minimum coronary resistance per unit weight of myocardium (Mueller et al., 1978; Holtz et al., 1979; Wicker et al., 1980; Einzig et al., 1981; Wangler et al., 1982). Coronary vascular lesions associated with myocardial hypertrophy have also been anatomically confirmed. Capillary density is reported to decrease (Rakusan, 1966; Rakusan, 1971; Lund and Tomanek, 1978; Anversa et al., 1979; Breish et al, 1980; Tomanek and Hovanec, 1981). Although some investigators report that the size of the epicardial coronary arteries increases appropriately during myocardial hypertrophy (Hutchins et al., 1977; Hort, 1981), Stack et al. (1983) report that epicardial coronaries do not enlarge during pressure overload-induced hypertrophy. The general impression from these studies is that hypertrophy, secondary to pressure-overload, adversely affects the coronary vascular system. It is possible, however, that the interaction between the coronary vasculature and the myocardium may depend on the stimulus causing the hypertrophy. Thyroxine-induced cardiac hypertrophy is uniquely characterized by several biochemical and anatomical parameters which separate it from other models of cardiac hypertrophy. Increased activity of myosin adenosine triphosphatase (ATPase) (Goodkind et al., 1974) results from a shift to the V₁ (fastest) myosin ATPase isozyme (Litton et al., 1982).
During thyroxine-induced hypertrophy, there also is an increased number of cardiac β-adrenergic receptors (Ciraldi and Marinetti, 1978), an increased mitochondrial volume per myocyte (Page, 1973; Craft-Cormney and Hansen, 1980), and a decreased amount of collagen in the ventricular wall (Edgren, 1976). Because of these unusual features of thyroxine-induced cardiac hypertrophy, we reasoned that the response of the coronary system to such hypertrophy may be quite different from that during hypertrophy secondary to pressure-overload. Within this context, the goal of this study was to define more precisely the factors that may modulate the functional and anatomical responses of the coronary vascular system to cardiac hypertrophy. Our specific hypotheses were: (1) that the signal which provokes cardiac hypertrophy modulates the response of the coronary vascular system, and (2) that the response of the coronary vascular system is related to the age of the animal when the hypertrophy is induced. The latter hypothesis was considered because several previous studies of models of pressure-overload hypertrophy have indicated that the interaction between coronary vascular growth and muscle enlargement is age-dependent (Archie et al., 1974; Vlahakes et al., 1980; Manohar et al., 1982).

We assessed the functional responses of the coronary system with measurements of myocardial perfusion and coronary blood flow velocity: in control and thyroxine-hypertrophied ventricles. We determined the anatomical response of the coronary system to hypertrophy by comparing capillary numerical density in control and hypertrophied hearts.

**Methods**

**Experimental Model**

Age-matched, male Wistar-Kyoto rats (WKY) were studied at 3 and 7 months of age. The two sham groups (3-month and 7-month WKY) received saline vehicle (0.25 ml), sc, daily for 2 months prior to study. The two experimental groups [3-month and 7-month thyroxine-treated WKY (TH-WKY)] received thyroxine (0.25 mg/kg per day, sc, in 0.25 ml of saline) for 2 months prior to study. All rats had access to food and water ad libitum and were maintained under identical ambient conditions.

**Myocardial Perfusion Measurements**

**Preparation**

The 7-month-old treated and control rats were weighed, then anesthetized with ketamine (10 mg/kg, ip) and acepromazine (1 mg/kg, ip). Arterial catheters (PE 10) were placed in both femoral arteries and in the brachial artery. One femoral catheter was advanced 6–8 cm, retrograde, and the other was advanced 1–2 cm. The brachial catheter was connected to a Statham P23Db strain gauge for measurements of arterial pressure. The right jugular vein was isolated and catheterized for fluid and drug administration. The right carotid artery was catheterized, and this catheter was advanced retrograde across the aortic valve into the left ventricle, confirmed by the left ventricular pressure pulse. All catheters consisted of the intravascular (PE 10 tubing) portion, which was telescoped to an extravascular (PE 50 tubing) portion. After the surgical procedures were completed, heparin (250 μg/kg) was administered iv.

**Microsphere Technique**

Myocardial perfusion was measured by injecting nuclide-labeled (46Sr, 51Sc, 113Ce) microspheres (9 μm) into the left ventricle. Before injection, the microspheres were agitated for several minutes on a vortex mixer. Approximately 5–8 × 10^5 microspheres were injected over a 10-second period and were flushed with 0.25 ml of warm (35–37°C) saline. Two arterial reference samples were obtained simultaneously from the femoral arterial catheters at a withdrawal rate of 0.18 ml/min. The withdrawal started 15 seconds before injection of microspheres and continued for 90 seconds after the saline flush was completed. Blood from a strain-matched donor was infused to replace the volume taken for the reference samples.

After the experimental protocol was completed, the heart was excised, weighed, and placed in 9% formalin. After preservation in the fixative (approximately 3–5 days), the heart was reweighed (and corrected for any weight changes from the initial wet weight), the great vessels and atria were trimmed from the ventricles, and the right ventricle was dissected free from the left ventricle. The left ventricular sample and the arterial reference samples were placed in γ-counter, counted for 5 minutes, and these data were recorded on paper tape. The paper tape was processed, and isotope separation and flow computation were performed by a computer.

Myocardial blood flow was calculated from the formula:

\[
MBF = \frac{Cm \times 100 \times Wr}{Cr}
\]

where \(MBF = \) myocardial blood flow or myocardial perfusion (ml/min × 100 g), \(Cm = \) counts per unit time/g of myocardium, \(Cr = \) counts per unit time of arterial reference sample, and \(Wr = \) withdrawal rate of the pump (ml/min). Blood flow determinations were discarded if the activity in the reference samples differed by more than 10% (2 of 21 measurements).

Coronary resistance was calculated as (1) resistance per unit weight of myocardium (quotient of mean arterial pressure and myocardial blood flow), and (2) resistance of the entire left ventricle (quotient of mean arterial pressure and absolute flow, ml/min, to the left ventricle not normalized for weight).

**Experimental Protocol**

Myocardial blood flow was measured in anesthetized rats twice: before and after maximal vasodilation subsequent to dipyridamole infusion (2.0 mg/kg per min). During the course of the experiment, arterial pressure and heart rate were monitored continuously. Left ventricular pressure was also monitored, except during the microsphere injections. Dipyridamole, a coronary vasodilator, was infused through the jugular catheter beginning 10 minutes before the perfusion measurement and continuing during the microsphere injection and arterial reference sample withdrawal. We have shown previously that this dose and administration protocol produce maximal coronary dilation in the rat (Wangler et al., 1982). Following this blood flow measurement, the animal was killed with intravenous KCl, and the heart was removed.

Blood gases were monitored throughout the exper-
Coronary Reserve Measurements

Experimental Preparation and Protocol

We measured coronary blood flow velocity in anesthetized (methoxyflurane), open-chest rats with a Doppler velocimeter modified from the method of Hartley and Cole (1974). Rats were ventilated at a positive end-expiratory pressure (1–2 cm water) with a Harvard rodent respirator. Supplemental oxygen was administered to maintain \( P_{\text{O}_2} \) within normal limits (100–150 mm Hg), and arterial \( P_{\text{CO}_2} \) and \( \text{pH} \) were maintained within normal ranges by varying the rate of respiration. Doppler probes consisted of a 20 MHz piezoelectric crystal, 1 mm in diameter, housed in a silicon suction cup. The probe was secured to the left anterior descending artery with a 6–8 mm vacuum. Once the probe was attached, the crystal was oriented at approximately 45° to the blood column.

Arterial pressure (Statham, 23 Db) from a femoral catheter, along with coronary blood flow velocity, was recorded on an oscillographic recorder. Once steady state recordings of pressure and blood flow velocity had been obtained, the left anterior descending artery was occluded for 20 seconds by gentle pressure on the proximal portion of the artery. This occlusive zero had to match the electronic zero of the Doppler, or the study was excluded. The occlusion was released after 20 seconds, and the maximum peak coronary blood flow velocity was measured during this hyperemic period. Arterial blood gases and \( \text{pH} \) were measured before the assessment of coronary reserve.

After the experiment, the rat was killed, weighed, and the heart was excised. After the great vessels, atria, and right ventricle were removed, the left ventricle was weighed.

Calculation of Coronary Reserve

A directional pulsed Doppler capable of measuring phasic and mean coronary blood flow velocity in rats (Wangler et al., 1981) was used to assess coronary reserve, i.e., the relationship between coronary blood flow under resting conditions and that during maximum coronary dilation. This relationship can be estimated from measurements of coronary blood flow velocity during coronary reactive hyperemia following a 20-second occlusion. Coronary reserve was estimated from the following expression:

\[
CR = \frac{PBFV}{RBFV}
\]

where \( CR \) = coronary reserve (arbitrary units), \( RBFV \) = resting coronary blood flow velocity (kHz shift) and \( PBFV \) = peak blood flow velocity (kHz shift).

Measurements of Capillary Numerical Density

Experimental Preparation

Animals were anesthetized with methoxyflurane and ventilated via an endotracheal tube with a mechanical respirator. Methoxyflurane was vaporized in a chamber connected in parallel to the inspiration tube and was administered as needed by opening the parallel circuit. Details concerning preservation of cardiac tissue have been described in previous communications (Tomanek and Karlsson, 1973; Tomanek, 1977). In brief, following cardiac arrest in diastole with procaine, the heart was perfused via a cannula positioned retrograde in the ascending aorta, and the aorta distal to the cannula was ligated. Approximately 100 ml of a glutaraldehyde fixative solution (Tomanek and Karlsson, 1973) were perfused through the system at a pressure of 120 mm Hg, and the heart was removed. The left ventricle was weighed and immersed in the glutaraldehyde fixative. Using a stereomicroscope, several tissue specimens were dissected from the left ventricular epicardium and were placed in separate vials containing the glutaraldehyde fixative for 2–3 hours. An \( \text{OsO}_4 \) (1%) solution was used for postfixation; then the tissues were imbedded in Epon.

Microscopic Analysis

Capillary numerical density (number of capillaries per square millimeter) in the tissue samples was obtained from projected images of 1-μm sections stained according to the method of Richardson (1960). All capillaries within three or four fields, each containing about 700–800 capillaries, were counted. Perfusion-fixation facilitated the counting of capillaries, since they were fixed in an open position and were therefore easily identified.

Statistical Analysis

All comparisons were made using unpaired \( t \)-tests, employing the Bonferroni inequality for any multigroup comparison. A probability value of 0.05 or less was accepted as statistical significance. All data are reported as mean ± SEM.

Results

Left Ventricular Weight and Body Weight

Figure 1 shows body weight and left ventricular weight-to-body weight ratio in the experimental groups. In both 3- and 7-month-old animals, thyroxine administration increased the left ventricular weight-to-body weight ratio (LV:BW) and decreased body weight. The percent increase in the left ventricular weight-to-body weight ratio was about 40% in both age groups. Left ventricular mass in the 3-month-old thyroxine-treated animals was 32% higher (\( P < 0.05 \)) (768 ± 43 mg) than in the sham-

![Figure 1: Body weight (g) and left ventricular weight-to-body weight ratio (LV:BW (mg/g)) for the 3- and 7-month-old WKY and thyroxine-treated WKY (TH-WKY). All data are shown as mean ± SEM.](image-url)
TABLE 1
Hemodynamics of 3- and 7-Month-old WKY and TH-WKY

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<th>3-Mo</th>
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<td></td>
<td>WKY</td>
<td>TH-WKY</td>
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<td></td>
<td>Open-chest</td>
<td>Closed-chest</td>
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<td>(n = 7)</td>
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<tr>
<td>Heart rate (beats/min)</td>
<td>343 ± 11</td>
<td>448 ± 10*</td>
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<td>Mean arterial pressure (mm Hg)</td>
<td>80 ± 2</td>
<td>105 ± 4*</td>
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<th>Microsphere studies (7-Mo)</th>
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<tr>
<td>Control</td>
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<tr>
<td>WKY</td>
<td>334 ± 13</td>
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<tr>
<td>TH-WKY</td>
<td>408 ± 19*</td>
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<td>Mean arterial pressure (mm Hg)</td>
<td>113 ± 4</td>
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<th>Dipyridamole</th>
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<td>WKY</td>
<td>405 ± 18</td>
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<tr>
<td>TH-WKY</td>
<td>525 ± 21</td>
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Values are mean ± SEM.
* P < 0.05 age-matched WKY vs. TH-WKY.
† P < 0.05 dipyridamole vs. control.

Treated controls (583 ± 29 mg). Among the 7-month-old animals, left ventricular mass was 17% greater (P < 0.05) in those that had been thyroxine-treated (931 ± 59 mg) than in the controls (793 ± 40 mg).

Hemodynamics

Table 1 shows heart rate and mean arterial pressure in both anesthetized open-chest rats (Doppler measurements) and anesthetized closed-chest rats (microsphere measurements). We found that in both open- and closed-chest animals, thyroxine treatment resulted in increased heart rate (P < 0.05) and mean arterial pressure (P < 0.05). Dipyridamole infusion produced disparate hemodynamic results in the control and thyroxine-treated animals. In the thyroxine-treated animals, both arterial pressure and heart rate increased significantly during dipyridamole infusion, whereas, in the control animals, arterial pressure decreased and heart rate increased.

Capillary Numerical Density

Figure 2 illustrates numerical capillary density in 3- and 7-month-old WKY and TH-WKY. The thyroxine-treated animals had higher numerical capillary densities than their age-matched WKY counterparts. Furthermore, the 3-month-old thyroxine-treated rats had a higher numerical capillary density than the 7-month thyroxine-treated rats. There was no age-related change in the control WKY. The difference between the treated and nontreated 3-month-old group was 30%, whereas that for the 7-month-old group was 17%. Capillary diameters were not different among the experimental groups. In the 3- and 7-month-old WKY, the capillary diameters were 6.17 ± 0.09 and 6.17 ± 0.14 μm, respectively. In the 3- and 7-month-old TH-WKY, capillary diameters were 6.18 ± 0.11 and 6.36 ± 0.23 μm, respectively.

Coronary Blood Flow Velocity

Figure 3 summarizes the maximum peak-to-resting blood flow velocity data in the open-chest animals after a 20-second occlusion of the left anterior descending artery. There were no differences in this index of coronary reserve following thyroxine treatment and the age-matched WKY. Also, there were no age-related differences in the peak-to-resting blood flow ratio.

Myocardial Perfusion

Table 2 shows myocardial perfusion at rest and during dipyridamole infusion, and minimum coronary resistance. At rest and during maximum coronary dilation with dipyridamole, perfusion was greater in the thyroxine-treated animals. Minimum coronary resistance per unit weight of myocardium was not different in the thyroxine-treated WKY rats vs. that in the control WKY rats. Minimum coronary resistance of the entire left ventricle was less in the thyroxine-treated animals than in the control WKY (P < 0.05).
The major conclusion of this study is that the left ventricular coronary circulation in the thyroxine-treated rat is normal or supernormal, despite considerable hypertrophy. This is based on three observations. First, the peak-to-resting blood flow velocity ratio, which is an index of vasodilator reserve, was the same in both age groups of the control and thyroxine-treated WKY. Second, minimum coronary resistance per unit weight of the left ventricle was equivalent in the control and thyroxine-treated animals, and minimum coronary resistance of the total left ventricle was less in the thyroxine-treated rats than in the WKY controls. Third, capillary density was higher in the 7-month- and 3-month-old animals with thyroxine-induced hypertrophy of the left ventricle than in their controls. Our conclusions critically depend on the methodology we employed to measure the anatomical and physiological indices of coronary reserve. To this end, we will briefly critique our experimental approaches.

For estimates of physiological indices of the coronary vascular system and estimates of the vascular cross-sectional area, we used measurements of coronary blood flow velocity (Doppler) and myocardial perfusion (microspheres). These techniques have received extensive evaluation in our laboratory (Falsetti et al., 1975; Marcus et al., 1981a, b). We have successfully applied these techniques to hemodynamic measurements of the coronary circulation in the rat (Wangler et al., 1981, 1982). Furthermore, Wangler et al. (1981) reported that changes in coronary blood flow velocity measurements are highly correlated with changes in microsphere measurements of myocardial perfusion in rats. In the present study and in former studies on rats (Wangler et al., 1982), we administered microspheres into the left ventricle rather than the left atrium. Wicker and Tarazi (1982) have recently challenged the validity of intraventricular injection of microspheres for accurate measurements of coronary blood flow in rats. They reported that left atrial injections of microspheres provided less variable measurements of myocardial perfusion than intraventricular injections. However, there was no significant difference in the mean values of perfusion from either injection site. Furthermore, in our studies, left ventricular injection of microspheres was employed in both the control and experimental rats. Hence, we are confident that inadequacies in the methods utilized to assess physiological responses of the coronary vessels could not be responsible for the differences observed in the control and thyroxine-treated animals.

Gerdes et al. (1979) reported that capillary density decreases in the thyroxine-hypertrophied heart. The treatment was maintained for 2 months, as in our study; however, the extent of hypertrophy was greater in their study, as evidenced by the LV:BW ratio of 4.9, whereas, in our study, the LV:BW ratio was 3.2–3.5. An interesting aspect of their report was that the LV:BW ratio increased by 69%, yet the capillary density decreased by only 18%. This suggests some degree of capillary angiogenesis in their experimental model. Our results in thyroxine-treated rats with less severe left ventricular hypertrophy indicate that capillary density is slightly augmented (17%).

Another interesting aspect of our data is that the capillary density of the 3-month-old thyroxine-treated animals was greater than that of the 7-month-old thyroxine-treated animals. This implies that the anatomical response of the coronary vascular system to thyroxine-induced hypertrophy is age-dependent. Other laboratories (Archie et al., 1974; Vlackes et al., 1980; Manohar et al., 1982) have also found that the response of coronary system secondary to pressure-overload induced hypertrophy was age-dependent. Thus, despite many di-
The divergent attributes of pressure-overload hypertrophy and thyroxine-induced hypertrophy, a similar aspect is that the response of the coronary vascular system is dependent on the age of the animal when the hypertrophic stimulus is applied.

An important implication of our results is that the stimulus (or stimuli) that produces hypertrophy may modulate the response of the coronary system. Pressure-induced left ventricular hypertrophy is associated with a decrease in coronary reserve in both animals (Rembert et al., 1978; Murray and Vatner, 1980; Bache et al., 1981; Wangler et al., 1982; Wicker et al., 1983) and man (Wusten et al., 1977; Marcus et al., 1981a, 1982), an increase in left ventricular minimal coronary reserve per unit weight of myocardium (Mueller et al., 1978; Holtz et al., 1978; Bache et al., 1981; Einzig et al., 1981; Wangler et al., 1982; Wicker et al., 1983), and a decrease in capillary density (Rakusan, 1966, 1971; Lund and Tomanek, 1978; Anversa et al., 1979; Breisch et al., 1980; Tomanek and Hovanek, 1981). Volume overload-induced hypertrophy is associated with decreased coronary reserve in man (Hiratzka et al., 1982); however, coronary resistance per unit weight of myocardium in animals with volume overload hypertrophy has been reported to be normal (Gascho et al., 1981). In exercise-induced hypertrophy, capillary density is generally reported as being normal (Mandache et al., 1971; Ljungquist and Unger, 1972).

It is difficult to compare the results of the present study with those in the literature because of several factors: (1) different types of species used as the experimental model, e.g., dogs, rats, cattle, ponies (Mueller et al., 1978; Manohar et al., 1981, 1982; Wangler et al., 1982), (2) different stimuli used to provoke the hypertrophy, e.g., pressure overload, volume overload, exercise (Gascho et al., 1981; Mandache et al., 1981; Wicker et al., 1983), (3) age when the hypertrophy is induced, e.g., fetus, neonate, adult (Vhlakes et al., 1980; Archie et al., 1982; Manohar et al., 1982), and (4) the duration of the hypertrophy (Tomanek and Hovanek, 1981; Wangler et al., 1982). Consequently, we will restrict comparisons of the present results to those of previous studies from our laboratory employing the same experimental methodology (Wangler et al., 1982; Tomanek et al., 1982; Peters et al., 1984) using a different model of left ventricular hypertrophy (pressure-overload) in similarly aged spontaneously hypertensive rats (SHR). Thus our comparisons will specifically address the question: does the stimulus that provokes ventricular hypertrophy modulate the response of the coronary vasculature? These comparisons of the present results with those of Tomanek et al. (1982), Peters et al. (1984), and Wangler et al. (1982) are shown in Figure 4.

Figure 4 summarizes comparisons between 7-month-old SHR, WKY, and TH-WKY. The degree of left ventricular hypertrophy (indicated by the LV/BW ratio) was comparable in the SHR and TH-WKY. In the SHR, the numerical capillary density was approximately 20% lower than that in the parent WKY strain (P < 0.05) (Tomanek et al., 1982). In contrast, the TH-WKY had a higher numerical capillary than WKY (P < 0.05). We found coronary reserve (peak-to-resting blood flow velocity) in the TH-WKY to be equal to that of WKY controls, whereas it was depressed significantly in SHR (P < 0.05) (Peters et al., 1984). Minimum coronary resistance of the total left ventricle was decreased in TH-WKY from the WKY (P < 0.05); whereas minimum resistance in SHR and WKY were not different (Wangler et al., 1982). The data in Figure 4 emphasize that despite a similar degree of hypertrophy in SHR and TH-WKY, the response of the coronary vascular system is markedly different; namely, in the SHR, the effect of hypertrophy in the coronary vascular system is adverse, whereas in the TH-WKY, the coronary vascular system is either normal or actually above normal. Thus, the stimulus that provokes hypertrophy strongly influences the functional and anatomical responses of the coronary vascular system.

Although, we have evidence for angiogenesis in thyroxine-induced hypertrophy, the mechanism(s) responsible for this growth of the vasculature is (are) not elucidated by the present study. Thyroxine has been reported to increase directly capillary density in skeletal muscle (Romanul and Pollock, 1969; Romanul, 1971). Thus, thyroxine may directly stimulate angiogenesis in the hypertrophying heart. There also is evidence that increased myocardial blood flow, produced by chronic dipyridamole administration, results in augmented incorporation of [3H]thymidine in capillaries in the heart, and, thus, vascular growth (Hudlicka, 1982). In our study, thyroxine...
administration was associated with an increased resting myocardial blood flow. Thus, another possible mechanism for angiogenesis in our study could be the functional myocardial hyperemia associated with hemodynamic changes due to thyroxine administration.

In conclusion, when thyroxine is the stimulus for left ventricular hypertrophy, there is an appropriate increase in the vascular cross-sectional area to match the increase in the myocardial mass. This increase in vascular cross-sectional area enables the thyroxine-hypertrophied heart to have normal coronary dilator reserve, despite the increased muscle mass and augmented metabolic demands.

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References


Hirotaka LF, Doty DB, Eastham CL, Marcus ML (1982) Pressure versus volume overload has different effects on coronary rese (abstr). Circulation 66 (suppl II): 354


Rakusan K, Poupou O (1966) Differences in capillary supply of...
hypertrophic and hyperplastic hearts. Cardiologica 49: 293-298
Rembert JC, Kleinman LH, Fedor JJ, Wechsler AS, Greenfield Jr
JC (1978) Myocardial blood flow distribution in concentric left
Richardson KC, Jarett L, Finke EH (1960) Embedding in epoxy
resins for ultrathin sectioning in electron microscopy. Stain
Technol 35: 313-323
Romanul FCA (1971) Reversal of enzymatic profiles and capillary
supply of muscle fibers in fast and slow muscles after cross-
nervation. In Muscle Metabolism during Exercise, edited by
B Fernow, B Saltin. New York, Plenum Press, pp 21-32
Romanul FCA, Pollock M (1969) The parallelism of changes in
oxidative metabolism and capillary supply of skeletal muscle
fibers. In Modern Neurology, edited by S Locke. Boston, Little-
Brown, pp 203-213
of left ventricular mass to geometry of the proximal coronary
arteries in the dog. Am J Cardiol 51: 1728-1731
Tharp GD, Wagner CT (1982) Chronic exercise and cardiac vas-
Tomanek RJ (1979) The role of prevention or relief of pressure
overload on the myocardial cell of the spontaneously hyperten-
sive rat. Lab Invest 40: 83-91
Tomanek RJ, Hovanec JM (1981) The effects of long-term pressure-
overload and aging on the myocardium. J Mol Cell Cardiol
13: 471-488
Tomanek RJ, Karlsson UL (1973) Myocardial ultrastructure of
young and senescent rats. J Ultrastruct Res 42: 201-220

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