Original Contributions

Myocardial characteristics of thyroxine stimulated hypertrophy
A structural and functional study

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Summary: The effects of thyroxine-stimulated hypertrophy (TSH) were studied in the porcine left ventricular myocardium. Hypertrophy was produced in six adult pigs by administration of triiodothyronine (1 mg/kg; i.v) for eight days. Six pigs served as controls. The degree of hypertrophy, determined by left ventricular-to-body weight ratio, was 47%. With hypertrophy there was a significant increase in heart rate, blood pressure and myocardial blood flows. Minimal coronary resistance measured during adenosine infusion was lower in the TSH group compared with the control group. Anatomic studies revealed a balanced proliferative response of mitochondria, myofibrils and the t-tubular system during TSH. Analysis of the microvasculature indicated that the capillary and arteriolar beds both experienced growth which paralleled myocyte growth during TSH. These results suggest that thyroxine administration promotes angiogenesis in the microvascular bed which provides a partial anatomic rationale for the lowered minimal coronary resistance.

Key words: hyperthyroidism, myocardial hypertrophy, microvasculature, ultrastructure, myocardial blood flow

Introduction

Adaptive growth of the heart in response to hypertrophic stimuli involves functional and morphological changes which are predictable depending upon the stimuli and its duration. Pressure overload hypertrophy is associated with temporal changes in the subcellular organelles (6, 28), abnormalities of the coronary vasculature (6, 7), with altered coronary flow, and increased coronary resistance (6, 7). Similarly, volume overload hypertrophy demonstrates alterations of the subcellular organelles (31), with reduced coronary capillarity (32, 38), reduced coronary flow reserve (3, 38), with normal coronary resistance (3), or normal coronary flow, and normal coronary resistance (14). Exercise induced hypertrophy elicits no change in the subcellular organelles (1, 2), with some alterations in the coronary vasculature (1, 2, 8, 27), accompanied by a normal or increased coronary reserve (8, 19). Thyroxine induced hypertrophy has unique characteristics regarding ultrastructure (11, 20), decreased collagen content (13), while results concerning coronary vascular anatomy suggest growth (9, 15), and increased coronary blood flow (9, 18).
Since thyroxine-induced hypertrophy involves unique adaptational functional characteristics which are unlike those associated with volume or pressure overload induced hypertrophy this study was initiated to re-examine some of the early structural and functional responses of the myocardium during thyroxine-induced hypertrophy. Specifically to investigate the response of the myocyte, myofibrils, and mitochondria, and to correlate the coronary microvascular bed with changes in myocardial blood flow and minimal coronary resistance during this acute growth stimulus. Additionally, we wanted to examine the effect thyroxine-induced hypertrophy has upon the arteriolar segment of the coronary vascular tree. This portion of the coronary vasculature has not yet been investigated but may have a profound influence upon the regulation of coronary blood flow and vascular resistance.

Materials and methods

Twelve farm pigs approximately four months old, weighing 29.0 ± 8.0 kg were studied; six animals served as a control (C) group and six pigs comprised the experimental thyroxine-stimulated hypertrophy (TSH) group.

Animals in the normal and experimental group were anesthetized with ketamine (25 mg/kg), atropine (1/60 g), and thioamytal sodium (20 mg/kg). Anesthesia was maintained with 1% halothane and O₂. An incision was made in the neck and catheters were placed aseptically in the external jugular vein and the external carotid artery. Distal ends of the catheters were tunneled subcutaneously toward the spine and exited through the skin in the interscapular area, where they were capped with infusion plugs and filled with a saline/heparin solution to ensure patency. The animals received five days of prophylactic oral antibiotics (sulfamethoxazole-trimethoprim). Testing began following recovery from surgery (about five days). Catheters were flushed and reinstilled with heparin five times each week.

Following control measurements, the animals were given 1.0 mg/kg of triiodothyronine (T₃) by intravenous injection daily (early morning) for eight consecutive days. Blood pressure and heart rates were measured daily.

Myocardial blood flow and minimal coronary resistance

At the conclusion of the study, the eighth day of T₃ administration, the six hyperthyroid and six control animals were sedated with thioamytal sodium, intubated and anesthetized with halothane (1%) delivered by a pressure-cycled ventilator. A left thoracotomy was performed and catheters were placed in the left atrium for the administration of microspheres and measurement of left atrial pressure. When the animals were stable, with arterial blood gases and pH within the normal range, blood pressures and heart rates were continuously recorded on a Hewlett-Packard eight-channel ink recorder (Model 7848-A). Blood samples were simultaneously obtained from the aortic and coronary sinus catheters and analyzed electrometrically for blood gases and pH, and spectrometrically for hemoglobin concentration. For determination of myocardial blood flow, a dose of 3.0 × 10⁶ microspheres 15 ± 3 μm in diameter, labeled with either ⁴⁸Sn, ⁴⁶Sc, or ⁴¹Cr was suspended in 0.5 ml of 10% dextran in saline. This microsphere technique was previously used by this laboratory (34). Myocardial blood flow measurements were made at rest, during adenosine infusion (1.0 mg/kg/min), and during adenosine and phenylephrine (10–20 μg/kg/min) infusion, while heart rate and blood pressures were continuously monitored. Mean arterial pressure fell approximately 50 mm Hg during adenosine infusion, but only fell approximately 16 mm Hg during phenylephrine and adenosine infusion, although there was no significant difference between groups. In order to insure that the dose of adenosine produced maximal vasodilation of the coronary bed, a dose response curve for adenosine was carried out in 3 control and 3 hyperthyroid pigs. This required the use of three additional microspheres (⁴⁸Ca, ¹⁰⁹Ru, and ⁴¹Nb). Minimal coronary resistance was calculated for adenosine infusion levels of 0.6, 0.8, 1.0 and 1.2 mg/kg/min in the six pigs. Minimal coronary resistance was achieved in both groups of pigs at the 1.0 mg/kg/min dosage level of adenosine infusion. Minimal coronary resistance was calculated as:

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\frac{\text{mean arterial pressure} - \text{mean left atrial pressure}}{\text{myocardial blood flow}}
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