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Low Thyroid Function Leads to Cardiac Atrophy With Chamber Dilatation, Impaired Myocardial Blood Flow, Loss of Arterioles, and Severe Systolic Dysfunction

Y.-D. Tang, J. A. Kuzman, S. Said, B. E. Anderson, X. Wang and A. M. Gerdes

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Effects of induced hyperthyroidism in normal and cardiomyopathic hamsters

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Kuzman, James A., Tracy A. Thomas, Kathryn A. Vogelsang, Suleman Said, Brent E. Anderson, and A. Martin Gerdes. Effects of induced hyperthyroidism in normal and cardiomyopathic hamsters. *J Appl Physiol* 99: 1428–1433, 2005. First published June 23, 2005; doi:10.1152/jappphysiol.00515.2005.—Thyroid hormones (TH) enhance cardiac function and reverse gene changes typical of pathological hypertrophy. However, reports in humans, but not animals, indicate that excess TH can cause heart failure. Also, the effects of TH on normal and cardiomyopathic hearts are likely to be different. The goal of this study was to characterize the effects of prolonged hyperthyroidism on cardiac function, chamber and cellular remodeling, and protein expression in both normal and cardiomyopathic hearts. Hyperthyroidism was induced in 3-mo-old normal BIO F1B and dilated cardiomyopathic BIO TO2 hamsters. After TH treatment for 10 days and 2 mo, hemodynamics, echos, myocyte length, histology, and protein expression were assessed. After 10 days and 2 mo, there were no differences between TO2-treated (Tx) and TO2-untreated (Untx) hamsters in chamber diameters or left ventricular function. After 2 mo of treatment, however, F1B-Tx showed evidence of dilated heart failure vs. F1B-Untx. Chamber diameters were increased, and ejection fraction and positive and negative changes in pressure over time were reduced. In F1B-Tx and TO2-Tx hamsters, β -myosin isoform expression was reduced, whereas α -myosin increased significantly in F1B-Tx only. In TO2-Tx hamsters, the percent of viable myocardium was increased, and percent fibronecrosis was reduced vs. TO2-Untx. Myocyte length increased with TH treatment in both hamster strains. We conclude that 1) excess TH can induce heart failure in normal animals as observed in humans, 2) reversal of myosin heavy chain expression does not necessarily improve heart function, and 3) excess TH altered cellular remodeling but did not adversely affect chamber function or dimensions in TO2 hamsters.

thyroid hormone; heart failure; TO2 hamster

THYROID HORMONE (TH) has profound effects on the cardiovascular system, including tachycardia, hypertrophy, and enhanced function (1, 16). TH stimulates myocyte hypertrophy, which is often associated with enhanced function. The mechanism behind this effect of TH is unknown, but many studies have implicated changes in expression of myosin heavy chain (MHC) isoforms and Ca^{2+} handling proteins (2, 12, 15). Although enhanced cardiac function is the most recognized outcome of hyperthyroidism, dysfunction has also been reported. Case studies have described patients with dilated cardiomyopathy in which hyperthyroidism is the primary cause (13, 14, 26, 32, 34). Interestingly, restoring normal levels of TH often reverses the dilatation and dysfunction, making hyperthyroid cardiomyopathy a potentially curable form of heart failure. To our knowledge, there have not been any

animal studies showing that hyperthyroidism can result in overt heart failure. A recent study suggested that, after 1 mo of TH treatment, cardiac function begins to decline (7). However, ejection fraction (EF) in the thyroid-treated group (Tx) was still higher than in the sham group (Untx). Because many of the studies suggesting TH-related dilated cardiomyopathy have been patient case studies, the underlying pathophysiological mechanisms of TH-induced heart failure are poorly understood.

BIO TO2 hamsters develop a dilated cardiomyopathy due to a mutation in δ -sarcoglycan. These hamsters have altered microcirculation, causing ischemia that results in myocyte loss and replacement fibrosis (24, 29). Because TH can stimulate angiogenesis and cause vasodilation (4, 25), the impaired coronary circulation might be improved with TH treatment, which could potentially reduce myocyte loss and replacement fibrosis. In addition, TH represses collagen expression in the heart, which could reduce extracellular matrix remodeling compared with controls (3, 33). Therefore, the effects of TH may be distinctly different in a cardiomyopathic model compared with controls. Of additional importance in selection of this model, we have recently found that BIO TO2 hamsters develop subclinical hypothyroidism (e.g., normal T3 but elevated thyroid-stimulating hormone) (8).

The goal of this study was to characterize the effects of prolonged hyperthyroidism on cardiac function, chamber and cellular remodeling, and protein expression in both a control and cardiomyopathic animal model. Because TH has such a wide variety of effects on cardiac tissue, the remodeling pattern due to hyperthyroidism in these two animal strains is likely to be different.

MATERIALS AND METHODS

Experimental design. BIO TO2 hamsters, an animal model of dilated cardiomyopathy due to a mutation in δ -sarcoglycan, develop progressive chamber dilation, myocardial fibronecrosis, and death by ~ 10 mo of age (27). Three-month-old male BIO F1B (controls) and BIO TO2 hamsters were obtained from Bio Breeders (Watertown, MA). Based on mean body weight (BW), F1B and TO2 hamsters were randomized into Tx and Untx groups. Animals in the Tx group were fed pellets containing 0.1% grade I desiccated TH (Sigma no. T1251). The pellets containing TH were made by Bio-Serv (Frenchtown, NJ). After 10 days of treatment, 10 hamsters from each group were killed to determine the short-term effects of TH treatment. Additional hamsters were killed after 2 mo of treatment to determine the long-term effects. At the end of the treatment period, echo and hemodynamic data were collected and hearts were removed. Myocytes were isolated from seven animals in each group. In the remaining animals,

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hearts were sectioned transversely and slices were snap frozen or immersion fixed in 10% formalin for histological analysis. Isolated cell aliquots were fixed in glutaraldehyde (myocyte length measurements, 40 cells/heart) and snap frozen (protein analysis).

Echocardiography. Echocardiography was performed in animals just before they were killed. Animals were anesthetized with 1.5% isoflurane. The chest was shaved, and the animals were placed on a warming pad to maintain normal body temperature. Echocardiographic gel was applied to the left hemithorax. Echos were performed using a Hewlett-Packard Sonos 2000 (7.5-MHz transducer). The transducer was lightly placed on the left hemithorax, and two-dimensionally targeted M-mode echocardiograms were obtained from short-axis views of the left ventricle at the level of the papillary muscle tips. M-mode tracings were used to measure left ventricular dimensions in systole and diastole along with EF.

Hemodynamics and mechanics. To obtain hemodynamic measurements, a Millar ultraminiature pressure transducer catheter (model SPR-835, 1.4 Fr, Houston, TX) was fed through the right carotid artery into the left ventricle. Data were collected and processed electronically using a Digi-Med Heart Performance Analyzer (Micro-Med, Louisville, KY). The following data were collected: heart rate, peak systolic pressure, and positive/negative change in pressure over time (dP/dt).

Western blot. Frozen whole left ventricular tissue was powdered in liquid nitrogen and RIPA buffer with protease cocktail inhibitor (EMD Biosciences, San Diego, CA), 1 mM PMSF, and 1 mM sodium orthovanadate. Each sample was incubated at 4°C for 15 min and sonicated to completely homogenize the tissue. Cell lysates were centrifuged at 14,000 rpm for 15 min. The supernatant was collected, aliquoted, and stored at -80°C until time of use. Protein concentrations of cell lysates were determined by a bicinchoninic acid protein assay. Samples were then mixed with Laemmli buffer containing 5% β -mercaptoethanol, and 10 μ g of protein were loaded onto SDS-PAGE gels. Protein was transferred to polyvinylidene difluoride membranes and detected by antibodies specific to SERCA2a (1:1,000; Santa Cruz Biotechnology, Santa Cruz, CA) and MHC- α/β . Hybridomas producing antibodies specific to MHC- α (BA-G5 hybridoma; American Type Culture Collection, Manassas, VA) and MHC- β (A4.951 hybridoma; American Type Culture Collection) were cultured, and the medium was collected and used for Western blotting. Resultant bands were detected through chemiluminescence (Pierce, Rockford, IL) and quantified using a Versadoc Imaging System model 3000 (Bio-Rad, Hercules, CA).

Histology. Formalin-fixed transverse sections were frozen, cryosectioned at 5 μ m, stained with hematoxylin and eosin, and examined in the 2-mo treatment group. Because of calcifications in TO2 hamsters, frozen sections with more uniform hardness provided better-quality sections than paraffin blocks. The percentages of viable ventricular myocytes and areas of fibronectic replacement were determined morphometrically by point-counting morphometry as described previously (9, 10). Histological sections were viewed under a microscope with a color video camera, and data were collected from 10 randomly selected fields from each animal.

T3 assay. Blood samples were separated into serum aliquots and frozen. T3 levels were measured using a solid-phases competitive

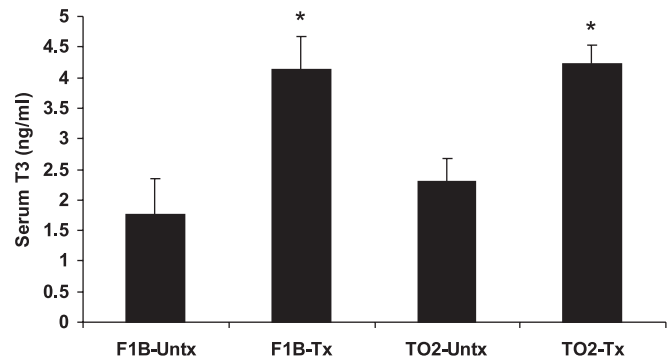


Fig. 1. Serum T3 levels measured by ELISA in 2-mo-old hamsters; $n = 8$ hamsters in each group. Tx, treated animals; Untx, untreated animals. * $P \leq 0.05$ vs. Untx animals of same strain.

ELISA kit from Bio-Quant (San Diego, CA), according to the manufacturers protocol.

Statistics. All data are expressed as means with standard deviation. Two-tailed unpaired t -tests were used to determine whether there were significant differences between Tx or Untx groups. No comparisons were made between the F1B and TO2 models.

RESULTS

Physical parameters. TH treatment for 10 days did not affect BW but significantly increased heart weight (HW) and HW/BW (Table 1). After 2 mo of treatment, BW was increased in F1B-Tx only. There was, however, a tendency for an increase in BW in the Tx groups. This effect has been previously reported in cardiomyopathic hamsters (28). HW and HW/BW were both significantly increased with long-term TH. Also, levels of T3 were significantly increased in both animal models with treatment (Fig. 1).

Echocardiography. TH treatment for 10 days (Tx) had no significant effects on echo parameters in either hamster strain (Fig. 2). After 2 mo, there was a dramatic effect on chamber remodeling in F1B-Tx. There were significant increases in left ventricular inner dimensions in both systole and diastole. EF was also significantly reduced in F1B-Tx. Thus echo data indicated that hyperthyroidism causes cardiac dilatation and dysfunction in control hamsters. Interestingly, there were no differences in chamber dimensions or EF between TO2-Untx and TO2-Tx.

Hemodynamics. After 10 days of treatment, heart rate was significantly increased in both F1B-Tx and TO2-Tx (Fig. 3). The +dP/dt increased in TO2-Tx and tended to increase in F1B-Tx (not significant). There was also a strong tendency for increased left ventricular end-systolic pressure in TO2-Tx. These results show that short-term treatment caused tachycardia and tended to enhance function. After 2 mo of treatment,

Table 1. Changes in heart and body weight

| | HW, mg | | BW, g | | HW/BW | |
|----------|---------------|---------------|---------------|---------------|-----------------|-----------------|
| | 10 days | 2 mo | 10 days | 2 mo | 10 days | 2 mo |
| F1B-Untx | 419 \pm 29 | 517 \pm 44 | 126 \pm 7.3 | 161 \pm 14 | 3.3 \pm 0.12 | 3.2 \pm 0.18 |
| F1B-Tx | 478 \pm 26* | 745 \pm 64* | 130 \pm 6.7 | 174 \pm 19* | 3.7 \pm 0.18* | 4.3 \pm 0.31* |
| TO2-Untx | 339 \pm 19 | 368 \pm 26 | 107 \pm 8.7 | 108 \pm 17 | 3.2 \pm 0.16 | 3.5 \pm 0.54 |
| TO2-Tx | 401 \pm 24* | 558 \pm 81* | 108 \pm 8.5 | 118 \pm 10 | 3.7 \pm 0.16* | 4.7 \pm 0.46* |

Values are means \pm SD. HW, heart weight; BW, body weight; Untx, untreated; Tx, treated. * $P \leq 0.05$ vs. age-matched Untx animals of the same strain.

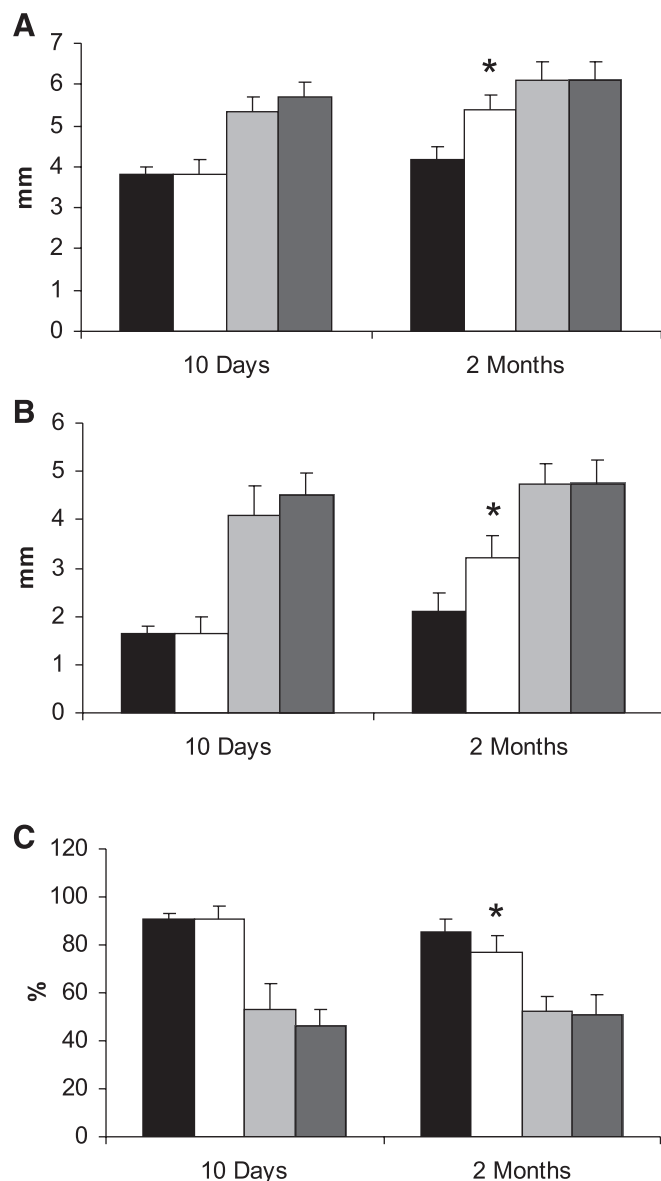


Fig. 2. Measurements obtained through echocardiography. *A*: left ventricular internal dimension during systole. *B*: left ventricular internal dimension during diastole. *C*: ejection fraction. Black bars, F1B-Untx ($n = 20$); white bars, F1B-Tx ($n = 18$); light gray bars, TO2-Untx ($n = 20$); dark gray bars, TO2-Tx ($n = 12$). * $P \leq 0.05$ vs. Untx animals of same strain.

heart rate was not different from Untx animals. F1B-Tx had significantly reduced $+/-dP/dt$ vs. F1B-Untx, but there were no changes in these parameters in TO2-Tx vs. TO2-Untx.

Cell shape and histology. After 10 days of treatment, there were no significant changes in myocyte length in F1B-Tx or TO2-Tx (Fig. 4A). However, 2 mo of treatment with TH induced cell lengthening in both F1B-Tx and TO2-Tx. The percentage of fibronecrosis was examined in the 2-mo treatment groups. Areas of fibrosis or necrosis were not found in any F1B hamsters. Fibronecrosis was extensive in TO2-Untx compared with F1B-Untx. The amount of fibrosis and necrosis was significantly reduced in TO2-Tx compared with TO2-Untx after 2 mo of treatment (Fig. 4B).

Western blot analysis. After 2 mo, TH had typical effects on the expression of genes important for normal cardiac function

including MHC- α , MHC- β , and SERCA. Figure 5 shows that TH increased protein expression of MHC- α in F1B-Tx. MHC- β expression was reduced in both F1B-Tx and TO2-Tx. SERCA2a was increased in TO2-Tx.

DISCUSSION

There were three key findings in this study. First, it was shown that hyperthyroidism can cause cardiac dilatation and ventricular dysfunction in normal animals. Typical of heart failure, chamber dilatation in these animals was associated with excessive myocyte lengthening. Second, even with onset of chamber dysfunction, F1B-Tx animals displayed a genetic phenotype normally associated with improved function ($\uparrow \alpha$, $\downarrow \beta$ MHC isoforms). This suggests that reversal of MHC expression, believed to be beneficial, does not always translate into improved cardiac function. Last, unlike the situation with normal animals, hyperthyroidism induced in cardiomyopathic animals did not accelerate progression of chamber dilatation or dysfunction. At the cellular level, however, it appears that the potential detrimental effect of accelerated myocyte lengthening was countered by reduced fibronecrosis.

F1B-Tx had increased internal dimensions and chamber dysfunction (evident by reduced EF and $+/-dP/dt$). These results are similar to those reported in case studies from patients with Grave's disease (13, 34). Increased myocyte length, without evidence of fibronecrosis, was the key cellular change leading to chamber dilatation in F1B-Tx hamsters. Interestingly, despite the onset of systolic pump dysfunction in F1B-Tx hamsters, MHC isoforms shifted to a more energetic profile (e.g., increased MHC- α and reduced MHC- β). Although TH is known to increase expression of MHC- α and reduce expression of MHC- β , heart failure is associated with the converse. Because the myosin isoform switch is believed to play a key role in chamber function, it might be predicted that TH would increase MHC- α and decrease MHC- β during the early period where cardiac function is increased, but eventually this change would be reversed as cardiac dysfunction ensued. In many studies, reversal of the fetal pattern of MHC expression has been used as a marker for improved cardiac function (17, 18), and it has been suggested that MHC isoform changes contribute to disease progression in human dilated cardiomyopathy (19). Our data suggest that changes in expression of MHC isoforms are not required for changes in ventricular function and may not always be a good molecular marker of cardiac function.

TO2 cardiomyopathic hamsters have large areas consisting of necrotic, fibrotic, and calcified tissue. It appears that development of both fibronecrotic areas and myocyte lengthening may contribute to cardiac dilatation in this model. TH dramatically reduced the amount of fibronecrosis. Although it has not yet been proven that TH actually reverses fibrosis and promotes angiogenesis in TO2 hamsters, other studies have demonstrated anti-fibrotic (3, 33) and proangiogenic actions of TH (5, 30). In the present study, we believe that TH prevented myocyte loss and development of ischemic lesions. It is likely that early lesions of this type in Untx TO2 hamsters may contribute to chamber dilatation as they become very pliant and extended before being stiffened by collagen deposition. However, further work is needed to confirm this hypothesis.

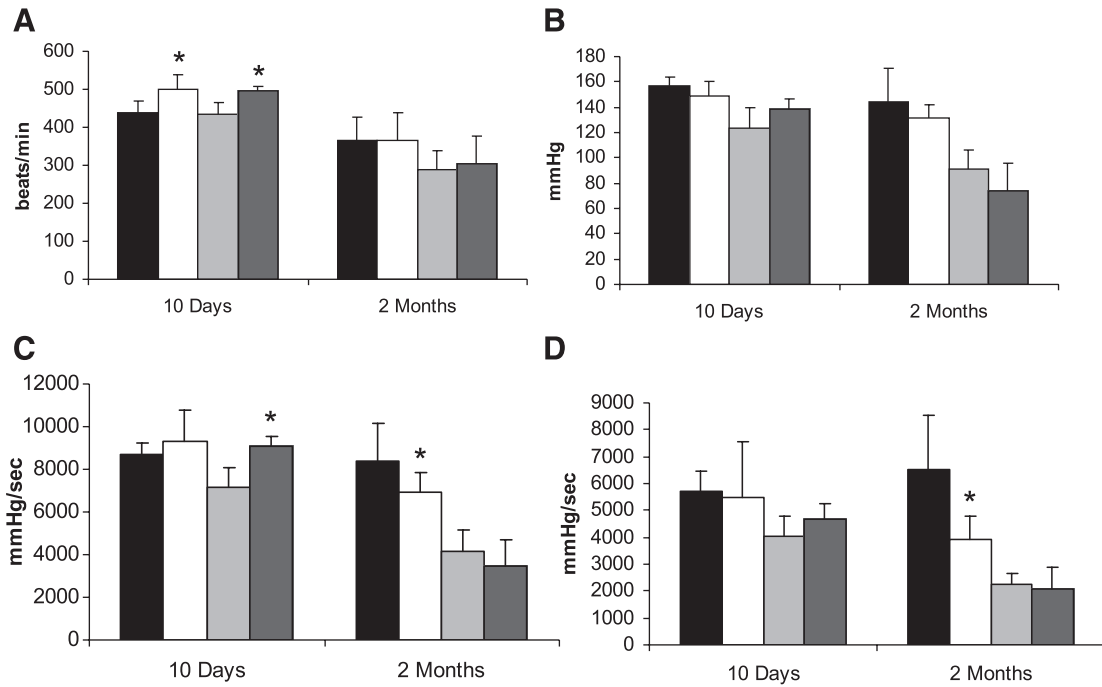


Fig. 3. Hemodynamic measurements obtained through left ventricular catheterization. *A*: heart rate. *B*: left ventricular end systolic pressure. *C*: positive change in pressure over time. *D*: negative change in pressure over time. Black bars, F1B-Untx ($n = 15$); white bars, F1B-Tx ($n = 14$); light gray bars, TO2-Untx ($n = 16$); dark gray bars, TO2-Tx ($n = 10$). * $P \leq 0.05$ vs. Untx animals of same strain.

Thyroid-induced tachycardia is one of the most widely used clinical parameters for identification of hyperthyroidism. In this study, 10 days of TH caused a significant increase in heart rate. After 2 mo of TH, however, heart rate was not different between Tx and Untx hamsters of either strain. These data suggest that heart rate is increased in the early stages of hyperthyroidism but at later stages may decline into the normal

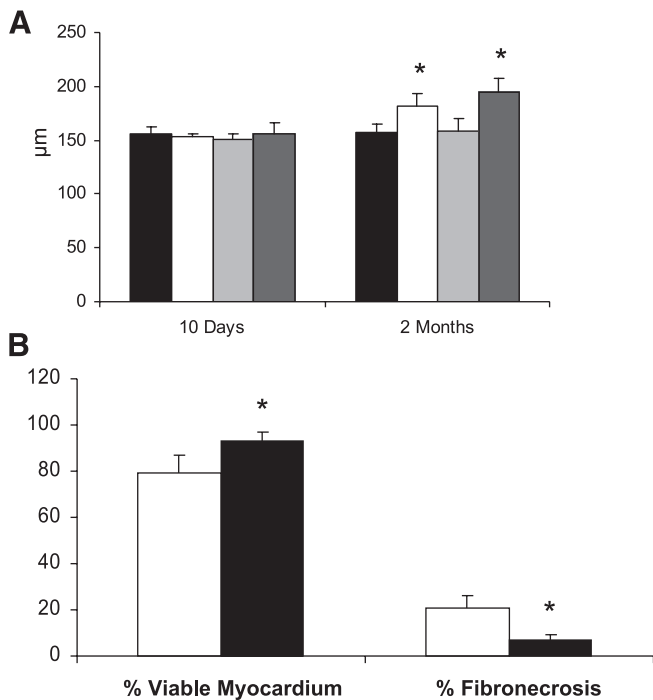


Fig. 4. *A*: myocyte length measurements from hamsters after treatment with thyroid hormone for 10 days and 2 mo. Black bar, F1B-Untx ($n = 7$); white bar, F1B-Tx ($n = 7$); light gray bar, TO2-Untx ($n = 7$); dark gray bar, TO2-Tx ($n = 7$). *B*: measurement of fibronecrosis in TO2 hamsters after treatment with thyroid hormone for 2 mo. White bars, TO2-Untx ($n = 4$); black bars, TO2-Tx ($n = 4$). * $P \leq 0.05$ vs. Untx animals of same strain.

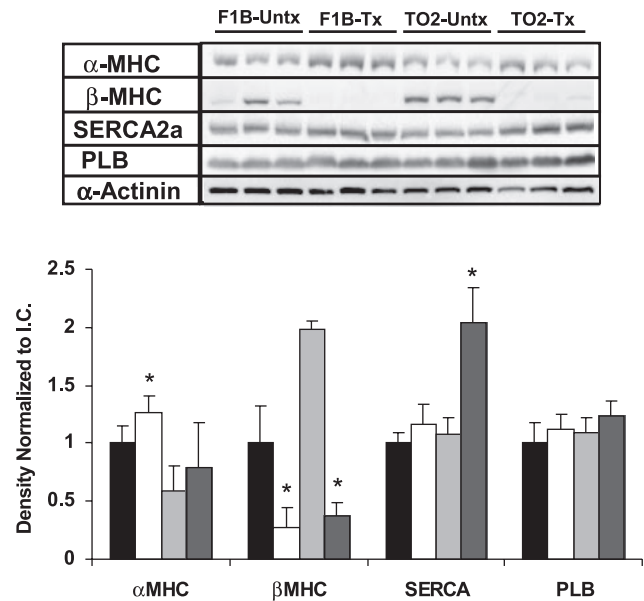


Fig. 5. Representative blots (*top*) and densitometry (*bottom*) ($n = 6$) using whole heart tissue extracts from 2-mo-old hamsters. Black bar, F1B-Untx; white bar, F1B-Tx; light gray bar, TO2-Untx; dark gray bar, TO2-Tx. MHC, myosin heavy chain; I.C., internal control. * $P \leq 0.05$ vs. Untx animals of same strain.

range with progression to failure. Therefore, heart rate may not always be a good predictor of hyperthyroidism when the disease has been present for prolonged periods of time. In fact, our results raise the possibility that it may be easy to overlook hyperthyroidism as a cause of heart failure in this situation. Although this may occur in very few cases, clinicians should be aware of the possibility since this type of heart failure may be easily cured with anti-thyroid treatment.

There is a need for better inotropic drugs to treat severe heart failure. TH is well known for its inotropic effect and could potentially be used in heart failure patients. However, care must be taken to prevent overdosing, which would lead to undesirable side-effects. Interestingly, this study suggests that induced hyperthyroidism (e.g., overdose) resulted in greater adverse effects on ventricular remodeling and function in normal animals than in cardiomyopathic hamsters. Although the exact reason for this is not completely clear, it may be related to the presence of thyroid dysfunction in TO2 hamsters. Also, TH treatment of TO2 hamsters exerted a beneficial effect on myocardial fibronecrosis, a condition that was not present in normal animals. Therefore, a potential treatment strategy might be to retain the beneficial effects of TH without the undesirable side-effects. The TH analog DITPA may be a safer alternative since it appears to promote increased inotropy with reduced risk of tachycardia (22, 23). Clinical trials in Veterans' Affairs heart failure patients are currently being conducted with DITPA. Although preliminary studies in humans treated with DITPA appear promising (21), many important questions remain about the potential effects of TH and analogs in treatment of heart failure.

Limitation of the study. Although excessive TH treatment of TO2 hamsters did not appear to adversely affect chamber remodeling and function, six TO2-Tx hamsters died during the final week of the study, whereas only two F1B-Tx hamsters died. This suggests an increase in mortality in the TO2-Tx group. However, most of the deaths occurred during or shortly after transportation from the animal facility to our laboratory. Additionally, a renovation project was initiated on the building housing the animals just before this time, so increased stress may also have been a contributing factor. Indeed, hyperthyroidism is known to produce stress in the absence of other mitigating circumstances. Although we do not know whether there were any important differences in the TO2-Tx and F1B-Tx animals that died during the final week of the study, we believe data presented here provide a reliable understanding of the effects of excessive TH in these animals. Nonetheless, we also felt it was important to disclose this information.

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