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Changes in left ventricular function and remodeling after myocardial infarction in hypothyroid rats

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Chen Y, Redetzke RA, Said S, Beyer AJ, Gerdes AM. Changes in left ventricular function and remodeling after myocardial infarction in hypothyroid rats. *Am J Physiol Heart Circ Physiol* 298: H259–H262, 2010. First published November 20, 2009; doi:10.1152/ajpheart.00755.2009.—It has been shown that hypothyroidism may lead to delayed wound healing after experimental myocardial infarction (MI) in rats and increased infarct size in dogs. However, the long-term effect of hypothyroidism on left ventricular (LV) remodeling after MI has not been determined. Adult female Sprague-Dawley rats with and without surgical thyroidectomy (TX) were used in the study. Four weeks after TX, MI or sham MI was performed on TX and non-TX rats. Rats from all groups were examined 4 wk later. Four weeks after TX, hypothyroid-induced LV dysfunction was confirmed by echocardiography. In terminal experiments 4 wk after MI, TX sham-MI rats showed smaller hearts and impaired LV function compared with non-TX sham-MI controls. TX + MI rats showed smaller hearts with bigger infarct areas, higher LV end-diastolic pressures, and greater impairment of relaxation ($-dP/dt$) compared with non-TX MI rats. Relative changes after MI between TX and non-TX rats for most other hemodynamic and echocardiographic indexes were similar. These results suggest that preexisting hypothyroidism exaggerates post-MI remodeling and worsens LV function, particularly diastolic function.

low thyroid function; cardiac ischemia; heart failure

HYPOTHYROIDISM IS A common condition in the general population. The prevalence rate is 4.6% in the United States population (0.3% clinical, 4.3% subclinical), is higher in females than in males, and increases with age (4). Hypothyroidism has been found to be associated with an increased risk of cardiovascular diseases such as atherosclerosis and myocardial infarction (MI) (3, 19). Hypothyroidism has also been shown to delay wound healing in experimental MI rats (9) and causes increased MI size in dogs (7). However, the long-term effect of preexisting hypothyroidism on post-MI left ventricular (LV) remodeling is unknown.

In this study, thyroidectomized (TX) rats were used to investigate the influence of hypothyroidism on LV remodeling after MI. We found that hypothyroid rats developed cardiac atrophy and had less LV chamber dilatation but more severe LV dysfunction 4 wk after MI.

MATERIALS AND METHODS

Experimental design. Adult female euthyroid (non-TX) and TX Sprague-Dawley rats weighing between 209 and 257 g were purchased from Charles River Laboratories (Wilmington, MA). MI surgery was performed 4 wk after TX. Animals from non-TX or TX groups were randomly assigned to MI or sham-MI surgery, respectively. MI was produced by a ligation of the left descending coronary artery as described in previous publications; sham MI was produced with a similar procedure, except the ligature was loosely tied (1, 15). Survivors were placed into the following groups: *1*) TX + MI ($n = 8$), *2*) TX + sham-MI ($n = 10$), *3*) non-TX + MI (MI, $n = 11$), and *4*) non-TX sham-MI group (S, $n = 10$). Animals were housed two per cage and kept on a 12-h:12-h light-dark cycle with food and water provided ad libitum. Pre-MI surgery echocardiographic data were collected 4 wk after TX. In terminal experiments 4 wk later, cardiac function was assessed by echocardiography and LV catheterization for each animal in the study. All experiments and protocols were performed in accordance with the *Guide for the Care and Use of Laboratory Animals* (NIH Publication No. 85-23, Revised 1996) and approved by the University of South Dakota Animal Care and Use Committee.

Echocardiographic measurements. Echocardiography was performed in each animal before it was euthanized using a Visualsonics 660 imaging system (20-MHz transducer; Toronto, Canada) as described previously (1, 16). Briefly, rats were anesthetized using isoflurane (1.5%). Two-dimensional echocardiograms were obtained from short-axis views of the LV at the level of the papillary muscle tips. Two-dimensionally targeted M-mode echocardiograms were used to measure the LV dimensions in systole and diastole.

Cardiac hemodynamic measurements. LV hemodynamics were obtained by catheterization of the right carotid artery using a Millar Micro-tip catheter (Millar Instruments; Houston, TX) as described previously (1, 22). Data were recorded using a Digi-Med Heart Performance Analyzer system (model HPA 410a; MicroMed; Louisville, KY). The following data were collected: heart rate, LV peak systolic pressure (LVSP), LV end-diastolic pressure (LVEDP), and positive/negative change in pressure over time ($\pm dP/dt$).

Tissue collection. After hemodynamic data were collected, the chest was opened and the hearts were arrested in diastole by an intravenous injection of saturated potassium chloride solution via inferior vena cava, quickly removed, and immediately placed in ice-cold PBS. The hearts were cannulated with an 18-gauge gavage needle through the aorta, perfused with ice-cold PBS, and subsequently trimmed, blotted, and weighed. The LV plus septum and the right ventricle (RV) were dissected and weighed. The LV was then cut into three pieces transversely, perpendicular to the LV long axis. The middle slice, which was cut 1 mm below the suture, was fixed in 4% paraformaldehyde overnight, then transferred to PBS, embedded in optimum cutting temperature compound (Sakura Finetek; Torrance, CA), and cryosectioned at 5 μm thickness for histology.

Infarct size measurement. Paraformaldehyde-fixed transverse tissue sections were obtained by cryosection, stained with hematoxylin and eosin, and viewed under a microscope with a color video camera to identify infarcted and noninfarcted areas and the border between these areas. Infarct length = (infarcted tissue outer length + infarcted tissue inner length)/2. Infarct size was estimated by measuring the percentage of endocardial and epicardial circumferences replaced by infarcted tissue using the following formula: infarct size (in %) = [(infarcted tissue outer length + infarcted tissue inner length)/(LV transversal epicardial circumference + LV transversal endocardial circumference)] × 100% (10, 14). MI animals with small infarct size

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Table 1. *Serum thyroid hormone levels*

Groups	*n*	TSH, μIU/ml	Total T3, ng/ml
Non-TX sham	10	0.53 (SD 0.48)	1.25 (SD 0.03)
TX	18	10.85 (SD 9.67)*	0.43 (SD 0.18)*

Values are means (SD); *n*, number of animals. TSH, thyroid-stimulating hormone; T3, triiodothyronine; TX, thyroidectomized. $*P < 0.01$ vs. non-TX sham (2-tailed Student's *t*-test).

Table 3. *Infarct size*

Groups	*n*	Infarct Length, mm	Infarct Size, %
Non-TX MI	11	14.3 (SD 2.1)	41.3 (SD 5.0)
TX MI	8	16.7 (SD 3.3)	53.6 (SD 9.2)*

Values are means (SD); *n*, number of animals. $*P < 0.05$ vs. non-TX MI (2-tailed Student's *t*-test).

(e.g., <20%; generally only 1 or 2 animals per group) were excluded from this study.

Serum thyroid hormone measurements. In terminal experiments, blood samples were collected from inferior vena cava after the chest was opened and separated into serum aliquots by centrifugation and stored at −80°C until assayed. Thyroid-stimulating hormone (TSH) and total triiodothyronine (T3) levels were measured using ELISA kits according to the manufacturers' specification. TSH kits were obtained from Calbiotech (Spring Valley, CA), and T3 kits were from Alpha Diagnostic (San Antonio, TX). Both kits are human but have been shown to produce excellent results in rats in our laboratory.

Statistical analysis. All data are expressed as means (SD) and were compared using two-tailed Student's *t*-test or one-way ANOVA. In addition, a Student-Newman-Keuls post hoc test was used to examine significant differences between groups. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Serum thyroid hormone levels. Table 1 shows the serum TSH and total T3 levels in terminal experiments. TX rats (with or without MI) had significantly increased TSH and decreased total T3 levels compared with non-TX sham-MI rats, confirming the success of TX surgery. Although the serum TSH levels showed some variability, all TX rats had higher TSH levels and lower total T3 levels than non-TX rats. There was no difference in thyroid levels between TX sham-MI and TX MI rats, so the data were pooled for statistical analysis.

Changes in body weight and heart weight. Table 2 shows that 4 wk after TX surgery, there were no significant differences in body weight between TX and non-TX rats, but TX MI rats showed less post-MI weight gain. In non-TX animals, 4 wk MI led to increased heart weight, heart weight-to-body weight ratio, and ventricular weight (particularly RV weight), suggesting LV dysfunction. TX animals from both MI and sham-operated groups had significantly smaller heart weights and ventricular weights than non-TX animals. After 4 wk, MI tended to increase heart weight and ventricular weight in TX animals, but this did not reach statistical significance compared with TX sham-MI animals, and the hypertrophic response was attenuated compared with that in non-TX MI rats. Although infarct length was 17% larger in TX-MI rats compared with non-TX MI rats, this did not reach statistical significance ($P = 0.16$) (Table 3). However, when compared with non-TX MI rats, TX MI rats had a significantly larger increase in percent infarct size because of their smaller hearts.

Echocardiographic changes. Four weeks after TX surgery, TX rats had smaller hearts with impaired LV function compared with age-matched non-TX rats. TX rats were characterized by smaller LV end-diastolic chamber dimensions but larger LV end-systolic chamber dimensions, thinner walls, and reduced heart rate, with decreased fractional shortening (Table 4). Table 5 shows that MI led to increased chamber dimensions and reduced fractional shortening in both TX and non-TX groups. In general, percent changes in these parameters tended to be less in TX rats with preexisting adverse remodeling before the infarction.

Hemodynamic changes after MI. Hemodynamic changes are shown in Table 6. Eight weeks after surgical TX, TX rats had decreased LVSP and decreased ±dP/d*t* compared with non-TX rats. In non-TX rats, MI led to an increase in LVEDP and decreases in LVSP, +dP/d*t,* and −dP/d*t.* In TX rats, MI led to a more pronounced increase in LVEDP and decrease in −dP/d*t* (e.g., greater percent change than in non-TX rats).

DISCUSSION

This study shows that 4 wk of hypothyroidism led to reduced heart size, decreased LV chamber dimension and wall thickness, and impaired LV systolic and diastolic function as indicated by decreased fractional shortening and ±dP/d*t.* This is consistent with previous reports (17, 20). However, chamber dilatation was not yet observed 4 wk after TX as was noted after 6 wk propylthiouracil treatment in a previous study from our laboratory (17). This may be related to the extent of

Table 2. *Body weight and heart weight data*

Groups	*n*	Body Wt1, g	Body Wt2, g	Heart Wt, mg	HW/BW2	Ventricular Wt, mg	LV Wt, mg	RV Wt, mg
Non-TX								
Sham	10	229 (SD 5)	251 (SD 12)	872 (SD 79)	3.5 (SD 0.3)	772 (SD 66)	625 (SD 53)	147 (SD 18)
MI	11	229 (SD 6)	253 (SD 10)	1,040 (SD 132)†	4.1 (SD 0.6)*	863 (SD 100)*	655 (SD 64)	208 (SD 62)*
%Difference		0	1	19	17	12	5	41
TX								
Sham	10	239 (SD 16)	243 (SD 22)	621 (SD 66)†§	2.6 (SD 0.2)†§	554 (SD 63)†§	432 (SD 56)†§	122 (SD 21)§
MI	8	224 (SD 14)	226 (SD 25)†§	670 (SD 88)†§	3.0 (SD 0.4)§	597 (SD 75)†§	466 (SD 53)†§	131 (SD 40)‡
%Difference		−6	−7	8	15	8	8	7

Values are means (SD); *n*, number of animals. Body Wt1, body weight before myocardial infarction (MI) surgery; Body Wt2, body weight at terminal study; Heart Wt, heart weight; HW/BW2, heart weight-to-body weight2 ratio; Ventricular Wt, ventricular weight; LV Wt, left ventricular weight; RV Wt, right ventricular weight. $*P < 0.05$ and $†P < 0.01$ vs. non-TX sham; $‡P < 0.05$ and $§P < 0.01$ vs. non-TX MI (ANOVA with Student-Newman-Keuls multiple comparison test between groups).

Table 4. *Pre-MI surgery echocardiographic data*

Groups	*n*	HR, beats/min	IVSd, mm	IVSs, mm	LVIDd, mm	LVIDs, mm	LVPWTd, mm	LVPWTs, mm	FS, %
Non-TX	6	372 (SD 47)	1.5 (SD 0.4)	2.6 (SD 0.2)	7.4 (SD 0.4)	4.0 (SD 0.9)	1.6 (SD 0.3)	2.8 (SD 0.5)	46 (SD 11)
TX	12	266 (SD 25)†	1.2 (SD 0.4)	1.8 (SD 0.5)†	6.6 (SD 0.5)†	4.8 (SD 0.6)*	1.2 (SD 0.2)*	1.6 (SD 0.3)†	27 (SD 6)†

Values are means (SD); *n*, number of animals. HR, heart rate; IVSd and IVSs, interventricular septal thickness in end diastole and systole, respectively; LVIDd and LVIDs, left ventricular diastolic and systolic internal diameter, respectively; LVPWTd and LVPWTs, left ventricular diastolic and systolic posterior wall thickness, respectively; FS, fractional shortening. $*P < 0.05$ and $†P < 0.01$ vs. non-TX (2-tailed Student's *t*-test).

hypothyroidism induced and/or the earlier observation time point in the current study. We have previously reported that the reduction of heart size in hypothyroidism of 4 wk duration was caused by myocyte atrophy, mainly by reduced myocyte cross-sectional area that was responsible for changes in wall thickness (12).

In response to MI, euthyroid rats showed increased heart weight, especially RV weight, with LV chamber dilatation; increased LVEDP; and decreased ±dP/d*t*. It appears that TX had an adverse effect on the infarct scar as evidenced by a tendency for increased infarct length and a significant increase in percent infarct size. There was a blunted hypertrophic response in TX rats after MI as evidenced by an attenuation of the increases in heart weight (8% vs. 19% in euthyroid rats) and LV diastolic chamber dimension (19% vs. 36% in euthyroid rats). Importantly, there was a more pronounced increase in LVEDP (206% vs. 93% in non-TX rats) and decline in −dP/d*t* (45% vs. 27% in non-TX rats) in TX rats after MI. These data suggest that hypothyroidism may exacerbate post-MI LV remodeling with further impairment of LV function, particularly diastolic function. These changes may be of particular significance since increased diastolic dysfunction post-MI has been shown to predict a worse outcome (8, 13).

In euthyroid rats 4 wk after MI, the LV chamber dimension increased and the wall thickness tended to decrease, suggesting a volume overload effect due to the loss of cardiac muscle mass. In TX rats, MI also caused an increased LV chamber dimension but with a preserved wall thickness, although these rats had a thinner wall thickness to begin with. We cannot exclude the possibility of coexisting cardiac myxedema and interstitial collagen deposition as reports have shown that hypothyroidism can cause cardiac myxedema (18) and is associated with an increased collagen deposition in the heart (21). The increased LV dimension-to-wall thickness ratio in MI rats will lead to an increase in LV wall stress and stretch, resulting in an increase in LV diastolic pressure. However, as the LV in MI rat is nonspherical, with varying wall thickness, anisotropic and nonhomogeneous material properties, the use of the law of Laplace to predict LV pressure-volume and pressure-wall stress behavior is limited. A finite element analysis has been used by others in larger models (5, 6, 11) but is beyond the scope of the present study.

In this study, infarct size was measured 4 wk after MI, when scar formation was complete. Increased percent infarct size was observed in hypothyroid rats. This is consistent with a study by Karlsberg et al. (7) where it was reported that hypothyroidism caused increased infarct size in dogs after acute MI. In that study, increased infarct size was suggested by increased serum creatine kinase levels rather than anatomical measurements as done here. The cause of infarct size increase is unclear but may relate to the reduction in arteriolar density present in hypothyroidism as reported previously by our group (17). This anatomical impairment in vascular density and the associated state of chronic vasoconstriction in hypothyroidism may adversely affect myocyte survival, particularly in the border zone. Other factors such as mitochondria loss may also contribute (7).

The presence of preexisting hypothyroidism followed by MI has been documented rarely in the clinical setting. Comtois et al. (2) reported a 0.3% (17 of 5,695 patients) incidence of this condition at their institution. They also reported a trend for higher creatine kinase peak levels and an increased incidence of residual ischemia in these patients. However, other methods were used to measure the infarct size in their study. In addition, there was no increase in residual heart failure and mortality rate in these patients. Unlike these patients, hypothyroid MI rats in the current study showed further impairment of LV function, possibly related to the presence of preexisting LV dysfunction from hypothyroidism. The greater increase in LVEDP in hypothyroid MI rats may be due to increased wall stiffness, since hypothyroid-induced cardiac myxedema (18) and collagen deposition (21) may worsen after MI. Unlike these rats, which have profound hypothyroidism after thyroidectomy, subclinical hypothyroidism is more common in the general population, especially in the elderly. It would be important to determine

Table 5. *Post-MI surgery echocardiographic data*

Groups	*n*	HR, beats/min	IVSd, mm	IVSs, mm	LVIDd, mm	LVIDs, mm	LVPWTd, mm	LVPWTs, mm	FS, %
Non-TX									
Sham	10	311 (SD 36)	1.8 (SD 0.3)	2.9 (SD 0.3)	7.2 (SD 0.4)	4.0 (SD 0.4)	1.7 (SD 0.8)	2.9 (SD 1.1)	45 (SD 5.2)
MI	11	337 (SD 49)	1.7 (SD 0.2)	2.3 (SD 0.8)	9.8 (SD 0.8)[b]	8.0 (SD 1.4)[b]	1.5 (SD 0.4)	1.9 (SD 0.5)	19 (SD 8.6)[b]
%Difference		8	−6	−21	36	100	−12	−34	−58
TX									
Sham	10	244 (SD 32)[b,d]	1.4 (SD 0.3)[b,d]	2.2 (SD 0.3)[b]	6.2 (SD 0.6)[b,d]	4.1 (SD 0.4)[d]	1.5 (SD 0.4)	2.0 (SD 0.4)	33.8 (SD 5.6)[b,d]
MI	7	254 (SD 38)[b,d]	1.4 (SD 0.2)[a,c]	2.1 (SD 0.3)[b]	7.4 (SD 0.9)[d,e]	5.7 (SD 1.2)[a]	1.6 (SD 0.4)	2.0 (SD 0.5)	23.6 (SD 8.2)[b,e]
%Difference		4	0	−5	19	39	7	0	−30

Values are means (SD); *n*, number of animals. $^aP < 0.05$ and $^bP < 0.01$ vs. non-TX sham; $^cP < 0.05$ and $^dP < 0.01$ vs. non-TX MI; $^eP < 0.01$ vs. TX sham (ANOVA with Student-Newman-Keuls multiple comparison test between groups).

Table 6. *Hemodynamic data*

Groups	*n*	HR, beats/min	LVSP, mmHg	LVEDP, mmHg	+dP/d*t*, mmHg/s	−dP/d*t*, mmHg/s
Non-TX						
Sham	8	343 (SD 38)	123 (SD 12)	5.7 (SD 1.2)	7,916 (SD 1,731)	6,535 (SD 1,207)
MI	11	332 (SD 41)	110 (SD 14)[a]	11.0 (SD 4.8)[a]	6,253 (SD 1,373)[b]	4,756 (SD 1,001)[b]
%Difference		−3	−11	93	−21	−27
TX						
Sham	10	217 (SD 21)[b,c]	108 (SD 9)[a]	6.7 (SD 2.5)	4,676 (SD 583)[b,c]	4,558 (SD 960)[b]
MI	8	205 (SD 23)[b,c]	102 (SD 9)[b]	20.5 (SD 8.7)[a,d]	3,655 (SD 1,084)[b,c]	2,493 (SD 1,056)[b,c,e]
%Difference		−6	−6	206	−22	−45

Values are means (SD); *n*, number of animals. LVSP and LVEDP, left ventricular end-systolic and end-diastolic pressure, respectively; +dP/d*t* and −dP/d*t*, maximal rate of pressure development and decline, respectively. [a]$P < 0.05$ and [b]$P < 0.01$ vs. non-TX sham; [c]$P < 0.01$ vs. non-TX MI; [d]$P < 0.05$ and [e]$P < 0.01$ vs. TX sham (ANOVA with Student-Newman-Keuls multiple comparison test between groups).

whether the findings from the present study are present in milder forms of low thyroid function.

Conclusion. Our study demonstrates that preexisting hypothyroidism may exacerbate post-MI LV remodeling with further impairment of LV function, particularly diastolic function.

DISCLOSURES

No conflicts of interest are declared by the author(s).

REFERENCES

1. **Chen YF, Kobayashi S, Chen J, Redetzke RA, Said S, Liang Q, Gerdes AM.** Short term triiodo-L-thyronine treatment inhibits cardiac myocyte apoptosis in border area after myocardial infarction in rats. *J Mol Cell Cardiol* 44: 180–187, 2008.
2. **Comtois R, Lemay C, Laliberte A.** Coexistence of hypothyroidism and myocardial infarction. *Can J Cardiol* 11: 37–42, 1995.
3. **Hak AE, Pols HA, Visser TJ, Drexhage HA, Hofman A, Witteman JC.** Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam Study. *Ann Intern Med* 132: 270–278, 2000.
4. **Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, Braverman LE.** Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab* 87: 489–499, 2002.
5. **Holmes JW, Yamashita H, Waldman LK, Covell JW.** Scar remodeling and transmural deformation after infarction in the pig. *Circulation* 90: 411–420, 1994.
6. **Janz RF, Grimm AF.** Finite-element model for the mechanical behavior of the left ventricle. Prediction of deformation in the potassium-arrested rat heart. *Circ Res* 30: 244–252, 1972.
7. **Karlsberg RP, Friscia DA, Aronow WS, Sekhon SS.** Deleterious influence of hypothyroidism on evolving myocardial infarction in conscious dogs. *J Clin Invest* 67: 1024–1034, 1981.
8. **Khumri TM, Reid KJ, Kosiborod M, Spertus JA, Main ML.** Usefulness of left ventricular diastolic dysfunction as a predictor of one-year rehospitalization in survivors of acute myocardial infarction. *Am J Cardiol* 103: 17–21, 2009.
9. **Kranz D, Hecht A, Fuhrmann I.** The influence of hyperthyroidism and hypothyroidism on the wound healing of experimental myocardial infarction in the rat. *Exp Pathol (Jena)* 12: 129–136, 1976.
10. **Litwin SE, Katz SE, Morgan JP, Douglas PS.** Long-term captopril treatment improves diastolic filling more than systolic performance in rats with large myocardial infarction. *J Am Coll Cardiol* 28: 773–781, 1996.
11. **Litwin SE, Litwin CM, Raya TE, Warner AL, Goldman S.** Contractility and stiffness of noninfarcted myocardium after coronary ligation in rats. Effects of chronic angiotensin converting enzyme inhibition. *Circulation* 83: 1028–1037, 1991.
12. **Liu Z, Gerdes AM.** Influence of hypothyroidism and the reversal of hypothyroidism on hemodynamics and cell size in the adult rat heart. *J Mol Cell Cardiol* 22: 1339–1348, 1990.
13. **Moller JE, Whalley GA, Dini FL, Doughty RN, Gamble GD, Klein AL, Quintana M, Yu CM.** Independent prognostic importance of a restrictive left ventricular filling pattern after myocardial infarction: an individual patient meta-analysis: Meta-Analysis Research Group in Echocardiography acute myocardial infarction. *Circulation* 117: 2591–2598, 2008.
14. **Pfeffer JM, Pfeffer MA, Braunwald E.** Influence of chronic captopril therapy on the infarcted left ventricle of the rat. *Circ Res* 57: 84–95, 1985.
15. **Selye H, Bajusz E, Grasso S, Mendell P.** Simple techniques for the surgical occlusion of coronary vessels in the rat. *Angiology* 11: 398–407, 1960.
16. **Tamura T, Said S, Harris J, Lu W, Gerdes AM.** Reverse remodeling of cardiac myocyte hypertrophy in hypertension and failure by targeting of the renin-angiotensin system. *Circulation* 102: 253–259, 2000.
17. **Tang YD, Kuzman JA, Said S, Anderson BE, Wang X, Gerdes AM.** Low thyroid function leads to cardiac atrophy with chamber dilatation, impaired myocardial blood flow, loss of arterioles, and severe systolic dysfunction. *Circulation* 112: 3122–3130, 2005.
18. **Thomas J, Mills KB, Grisham DW.** Primary myxedema heart disease. *J Natl Med Assoc* 70: 833–836, 1978.
19. **Vanhaelst L, Neve P, Chailly P, Bastenie PA.** Coronary-artery disease in hypothyroidism. Observations in clinical myxoedema. *Lancet* 2: 800–802, 1967.
20. **Wieshammer S, Keck FS, Waitzinger J, Henze E, Loos U, Hombach V, Pfeiffer EF.** Acute hypothyroidism slows the rate of left ventricular diastolic relaxation. *Can J Physiol Pharmacol* 67: 1007–1010, 1989.
21. **Wu Y, Peng J, Campbell KB, Labeit S, Granzier H.** Hypothyroidism leads to increased collagen-based stiffness and re-expression of large cardiac titin isoforms with high compliance. *J Mol Cell Cardiol* 42: 186–195, 2007.
22. **Zimmer HG, Gerdes AM, Lortet S, Mall G.** Changes in heart function and cardiac cell size in rats with chronic myocardial infarction. *J Mol Cell Cardiol* 22: 1231–1243, 1990.