Washington University School of Medicine
Digital Commons@Becker

Open Access Publications

2017

Myocardial induction of type 3 deiodinase in dilated cardiomyopathy

Ari J. Wassner
Boston Children's Hospital

Rebecca H. Jugo
Boston Children's Hospital

David M. Dorfman
Brigham and Women's Hospital

Robert F. Padera
Brigham and Women's Hospital

Michelle A. Maynard
Boston Children's Hospital

See next page for additional authors

Follow this and additional works at: https://digitalcommons.wustl.edu/open_access_pubs

Recommended Citation

Wassner, Ari J.; Jugo, Rebecca H.; Dorfman, David M.; Padera, Robert F.; Maynard, Michelle A.; Zavacki, Ann M.; Jay, Patrick Y.; and Huang, Stephen A., ,"Myocardial induction of type 3 deiodinase in dilated cardiomyopathy." Thyroid.27,5. 732-737. (2017).
https://digitalcommons.wustl.edu/open_access_pubs/6605

This Open Access Publication is brought to you for free and open access by Digital Commons@Becker. It has been accepted for inclusion in Open Access Publications by an authorized administrator of Digital Commons@Becker. For more information, please contact engeszer@wustl.edu.

Authors
Ari J. Wassner, Rebecca H. Jugo, David M. Dorfman, Robert F. Padera, Michelle A. Maynard, Ann M. Zavacki, Patrick Y. Jay, and Stephen A. Huang

This open access publication is available at Digital Commons@Becker: https://digitalcommons.wustl.edu/open_access_pubs/6605

THYROID
Volume 27, Number 5, 2017
© Mary Ann Liebert, Inc.
DOI: 10.1089/thy.2016.0570

Myocardial Induction of Type 3 Deiodinase in Dilated Cardiomyopathy

Ari J. Wassner,[1] Rebecca H. Jugo,[1] David M. Dorfman,[2] Robert F. Padera,[2] Michelle A. Maynard,[1] Ann M. Zavacki,[3] Patrick Y. Jay,[4] and Stephen A. Huang[1]

Downloaded by Washington Univ from www.liebertpub.com at 03/06/18. For personal use only.

Background: The thyroid hormone–inactivating enzyme type 3 deiodinase (D3) is induced during hypertrophic and ischemic cardiomyopathy, leading to a state of local cardiac hypothyroidism. Whether D3 induction occurs in dilated cardiomyopathy is unknown.
Methods: This study characterized changes in cardiac D3 and thyroid hormone signaling in a transgenic model of progressive dilated cardiomyopathy (TG9 mice).
Results: Cardiac D3 was dramatically induced 15-fold during the progression of dilated cardiomyopathy in TG9 mice. This D3 induction localized to cardiomyocytes and was associated with a decrease in myocardial thyroid hormone signaling.
Conclusions: Cardiac D3 is induced in a mouse model of dilated cardiomyopathy, indicating that D3 induction may be a general response to diverse forms of cardiomyopathy.

Keywords: heart, deiodinase, D3, heart failure, cardiomyopathy

Introduction

Heart failure affects more than five million Americans and is a major cause of morbidity and mortality (1,2). As is commonly observed in other significant noncardiac illnesses, a ''low T3 syndrome'' develops in 6–32% of chronic heart failure patients. This pattern, characterized by normal serum concentrations of thyrotropin (TSH) and free thyroxine (fT4) but low triiodothyronine (T3) is associated with poor outcome in cardiac failure (3–8). While primary hypo- and hyperthyroidism have important cardiac manifestations that improve with treatment, it is less clear whether the secondary decrease in serum T3 observed in heart failure is an adaptive or maladaptive response (9–11). While several trials of short-term T3 treatment demonstrate improvement in cardiac function in patients with chronic heart failure (3,12–15), the true functional significance of hypotriiodothyronemia in heart failure and the effect of chronic T3 therapy remain unclear.

Delineating the role of T3 in the failing heart also relies on an emerging understanding of the role of thyroid hormone activation and inactivation within specific tissues, catalyzed by the iodothyronine deiodinase family of selenoenyzmes. The thyroid gland primarily secretes the prohormone T4, which is converted in peripheral tissues into the active hormone T3 by types 1 and 2 deiodinase (D1 and D2) (16,17). In contrast, type 3 deiodinase (D3) inactivates both T4 and T3 by inner-ring deiodination to reverse T3 (rT3) and 3,5-diiodo-L-thyronine, respectively (18). Thus, all tissues are exposed to uniform levels of circulating thyroid hormone, but the differential expression of activating (D1 and D2) and inactivating (D3) deiodinases in individual tissues allows local regulation of thyroid hormone action.

Although there is negligible deiodinase expression in healthy cardiomyocytes, the induction of cardiac D3 has been demonstrated in animal models of both hypertrophic (19–22) and ischemic cardiomyopathy (23,24). These rodent studies show that failure-induced cardiac D3 dramatically decreases local T3 signaling (20,23,25), and a recent report of positive D3 immunostaining in the cardiomyocytes of patients with ischemic cardiomyopathy indicates that this physiology also extends to humans (26). Studies of D3 knockout mice show that heterozygous animals with a paternally inherited null allele have markedly reduced cardiac D3 expression due to tissue-specific *Dio3* gene imprinting. These mice develop restrictive cardiomyopathy that is characterized by myocardial fibrosis and decreased tolerance to isoproterenol-induced cardiac hypertrophy (22). While the confounder of D3

[1]Thyroid Program, Division of Endocrinology, Boston Children's Hospital, Boston, Massachusetts.
[2]Department of Pathology; [3]Thyroid Section, Division of Endocrinology, Diabetes, and Hypertension; Brigham and Women's Hospital, Boston, Massachusetts.
[4]Departments of Pediatrics and Genetics, Washington University School of Medicine, St. Louis, Missouri.

insufficiency in other paternally imprinted tissues complicates the interpretation of this model, these findings support a crucial role for D3 in cardiac function and remodeling and justify further study of D3 induction in cardiac disease.

This study investigated the hypothesis that D3 is induced in the dilated form of cardiomyopathy by studying a transgenic murine model of dilated cardiomyopathy, the TG9 mouse (27). Marked induction of D3 mRNA and activity was observed in the hearts of TG9 mice as failure advanced, confirming that myocardial D3 is induced in dilated cardiomyopathy. D3 expression was localized to cardiomyocytes by immunostaining and associated with decreased expression of T3-responsive genes. These findings support the concept that D3 induction is a general response of the cardiomyocyte to diverse forms of heart failure.

Materials and Methods

Animals

Transgenic overexpression of Cre recombinase in cardiomyocytes, as driven by the α-myosin heavy chain (αMHC) promoter, causes dilated cardiomyopathy and progressive congestive heart failure in the TG9 mouse (27). Based on the consistent finding of heart failure in seven independent founder animals, heart failure in this model is presumed to be caused by the high level of myocardial Cre expression and not by disruption of other genes by insertion of the Cre construct (27). All experiments used male TG9 mice or wild-type mice of the same strain (FVB). Tissues were flash frozen for enzyme/RNA analysis or fixed in formalin for histology. Experiments were approved by the Boston Children's Hospital Institutional Animal Care and Use Committee.

Deiodination assays and serum thyroid hormone measurements

Frozen tissues were assayed for D3 activity, as previously described (28). Serum total T4 and T3 were measured, as previously described, using a modified Coat-a-Count radioimmunoassay (Siemens) and T3 charcoal uptake to correct for serum binding and express results as fT4 index (fT4I) and free T3 index (fT3I) (29,30).

Immunohistochemistry

D3 immunohistochemistry was performed using a polyclonal rabbit anti-D3 antibody (D3-18; 1:50 dilution), as

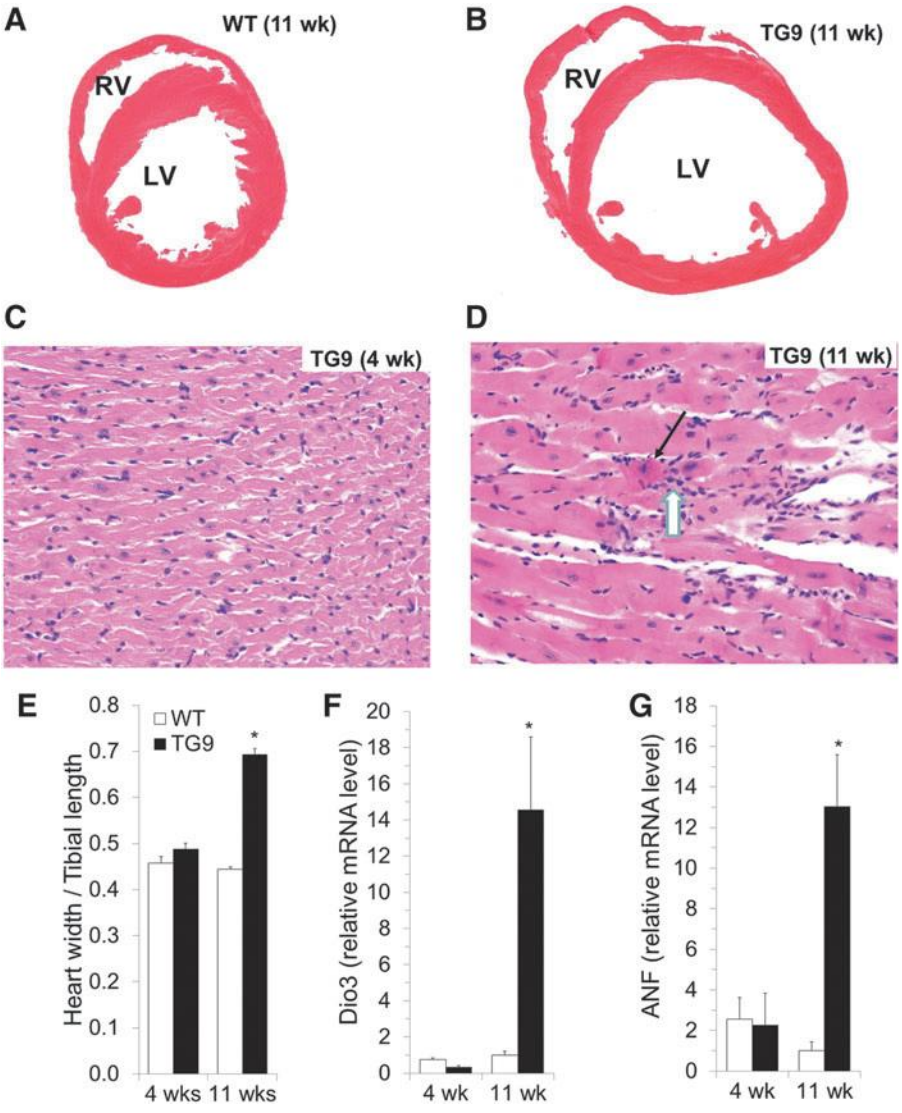

FIG. 1. Type 3 deiodinase (D3) is induced in the failing hearts of TG9 mice. Compared with nontransgenic controls (**A**), TG9 mice (**B**) develop severe, dilated cardiomyopathy at 11 weeks of age that is characterized by biventricular dilation (left ventricle [LV], right ventricle [RV]). At high magnification (400×), there is moderate cardiomyocyte hypertrophy observed in 11-week-old TG9 hearts (**D**) compared with the 4-week-old TG9 hearts (**C**) and nontransgenic hearts at the same ages. In the failing myocardium, there is myocyte cell death (black arrow) and evidence of healing manifest by a mild inflammatory infiltrate (white arrow). Heart failure is also demonstrated by increased heart size (**E**). Cardiac *Dio3* mRNA expression (**F**) in the failing heart is dramatically increased 15-fold relative to nontransgenic controls and parallels the induction the molecular marker of failure atrial natriuretic factor (**G**). $*p \leq 0.005$ (compared with all other groups).

Downloaded by Washington Univ from www.liebertpub.com at 03/06/18. For personal use only.

previously described (31,32). Isotype-negative controls were performed.

Gene expression analysis

Total RNA was extracted from tissues using Trizol (Ambion) and reverse transcribed using the iScript cDNA synthesis kit (Bio-Rad). Quantification of mRNA was performed by the iQ5 Multicolor Real-Time PCR Detection System (Bio-Rad), as previously described (33). The housekeeping gene *GAPDH* was used as an internal control. Primer sequences are available upon request.

Statistics

Data are presented as means ± standard error of the mean. Analyses were performed by two-factor analysis of variance using a test of age × group interaction to assess the differential change with age between groups. p-Values <0.05 were considered significant.

Results

D3 is induced in the cardiomyocytes of TG9 mice with dilated cardiomyopathy

TG9 mice develop ventricular dilatation that is first detectable at about six weeks of age. Left ventricular dilatation and contractile function then worsen over a highly consistent time course, with death occurring at around 12 weeks. By 11 weeks of age, TG9 mice showed signs of severe congestive heart failure, including decreased activity level, labored breathing, and poor peripheral perfusion (27). The hearts of the TG9 mice at 11 weeks demonstrated pathologic features of heart failure, including biventricular dilation (Fig. 1A and B) and occasional atrial thrombi. Histologic examination of the TG9 hearts at 11 weeks revealed chronic changes of moderate-to-severe myocyte hypertrophy when compared with either TG9 mice at 4 weeks or to nontransgenic mice at 4 or 11 weeks, and also showed occasional myocyte cell death with evidence of healing (Fig. 1C and D).

Like humans with chronic heart failure, TG9 mice developed increased heart width ($p < 0.001$; Fig. 1E). The development of heart failure in TG9 mice was accompanied by marked induction of cardiac D3 expression, with a 17-fold increase in *Dio3* mRNA compared to age-matched, nontransgenic mice ($p = 0.002$; Fig. 1F). This degree of upregulation was comparable to that of atrial natriuretic factor ($p = 0.002$; Fig. 1G), an established biomarker of heart failure and ventricular strain. Cardiac D3 activity was also increased 15-fold ($p = 0.001$; Fig. 2A). This D3 induction was tissue specific; there was no significant increase in the brains ($p = 0.24$; Fig. 2B) of TG9 mice. As expected from prior reports of hepatic D3 induction in critically ill mice (33) or humans (34), D3 activity was increased in the livers ($p = 0.007$; Fig. 2C) of TG9 mice during failure. Immunohistochemistry localized D3 expression in the failing hearts of TG9 mice to cardiomyocytes (Fig. 2D–E).

Dilated cardiomyopathy in TG9 mice leads to reductions in systemic thyroid hormone status and T3-responsive cardiac gene expression

Recapitulating the suppression of systemic thyroid status observed in chronic heart failure and other severe nonthyroidal illness (4–8,35,36), the progression of heart failure in TG9 mice was associated with significant decreases in circulating thyroid hormones, with a 68% fall in the serum fT4I and a 71% fall in the serum fT3I ($p < 0.001$; Fig. 3A and B).

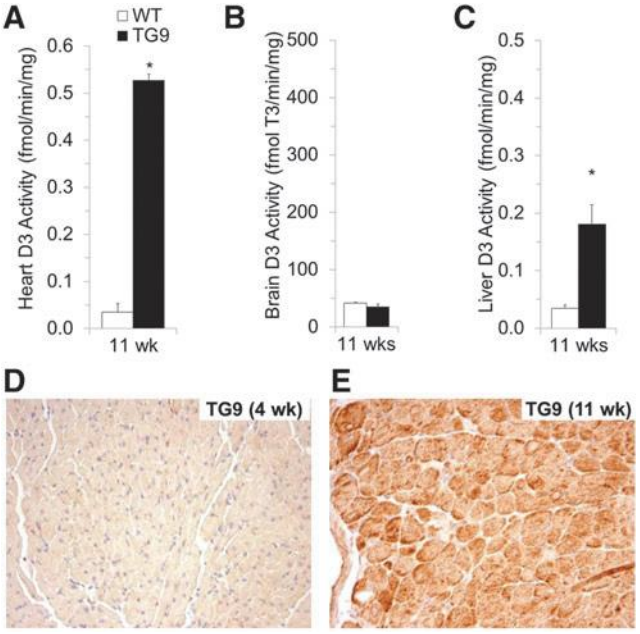

FIG. 2. D3 activity induced by dilated cardiomyopathy is tissue specific and localizes to cardiomyocytes. Paralleling the increase in cardiac *Dio3* mRNA, D3 activity is markedly induced in the failing hearts of TG9 mice (**A**) (*$p < 0.01$), but not in the brains of the same animals (**B**). Liver D3 is induced during heart failure, as expected from the nonthyroidal illness syndrome (**C**) (*$p < 0.01$). Immunohistochemistry demonstrates that D3 is expressed in cardiomyocytes in the failing hearts of 11-week-old TG9 mice (**E**). No significant D3 staining is observed in 4-week-old TG9 mice prior to the onset of heart failure (**D**).

To determine if the reduction in systemic thyroid status and the induction of cardiomyocyte D3 in TG9 mice was sufficient to decrease local thyroid hormone signaling in the failing heart, the expression of cardiac genes that are regulated by T3 was measured (Fig. 3C–F). SERCA2a (*Atp2a2*) and αMHC (*Myh6*) are positively regulated by thyroid hormone, whereas β-myosin heavy chain (βMHC, *Myh7*) is negatively regulated (37). Since αMHC and βMHC are regulated in opposite directions, the ratio of αMHC/βMHC expression is a sensitive marker of cardiac thyroid hormone signaling. Consistent with cardiac-specific hypothyroidism, there was a 56% decrease in SERCA2a mRNA ($p = 0.004$; Fig. 3C) and a dramatic 95% reduction in the αMHC/βMHC ratio ($p < 0.001$; Fig. 3F) in D3-expressing TG9 hearts. The fall in αMHC/βMHC ratio was mediated primarily by increased expression of βMHC (Fig. 3E) with little change in αMHC (Fig. 3D), similar to the expression pattern associated with myocardial D3 induction in a model of ischemic cardiomyopathy (23).

Discussion

Thyroid hormone has profound effects on cardiac function, inducing changes in heart rate, myofibril structure, intracellular

Downloaded by Washington Univ from www.liebertpub.com at 03/06/18. For personal use only.

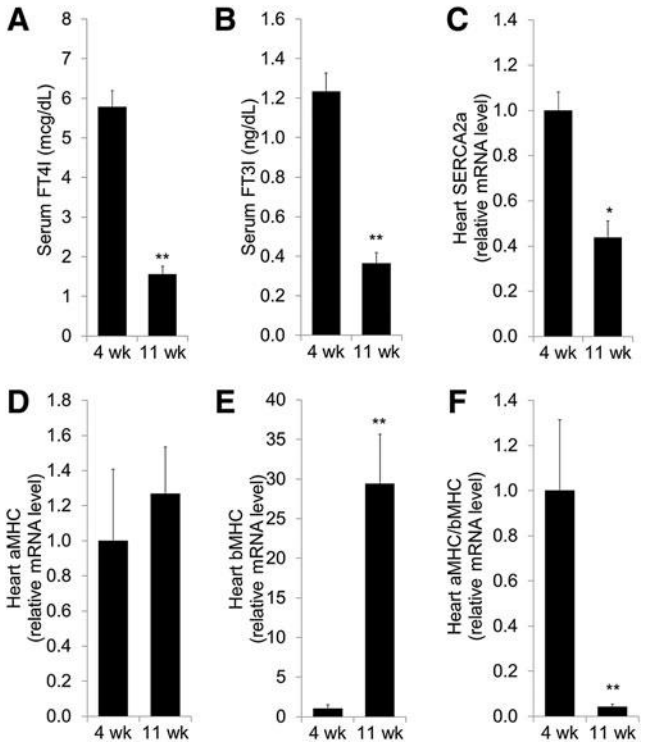

FIG. 3. Dilated cardiomyopathy in TG9 mice is associated with reductions in systemic thyroid hormone status and in the cardiac expression of thyroid hormone–responsive genes. Dilated cardiomyopathy is associated with a decrease in serum free thyroxine index (**A**) and free triiodothyronine index (**B**). Cardiac expression of α-myosin heavy chain promoter/β-myosin heavy chain promoter and SERCA2a, which are positively regulated by thyroid hormone, is decreased in the myocardium of failing hearts (**C**)–(**F**). $*p = 0.01$; $**p < 0.001$.

calcium release and reuptake, and electrical activity (37,38). These effects have long been recognized in patients with severe primary hypothyroidism who manifest decreases in heart rate, cardiac output, and myocardial efficiency that are fully reversible with thyroid hormone replacement. Illustrating that thyroid status is also regulated locally, animal studies have shown that deiodinase expression in cardiomyocytes is sufficient to alter tissue-specific T3 signaling in the heart, even in the absence of changes in systemic thyroid function. This concept was first established by studies of D2 transgenic mice that overexpress human D2 in their hearts. Due to increased local activation of T4 to T3, these mice have tachycardia and increased cardiac metabolic rate (39–41). Illustrating the impact of local deiodination on cardiac pathophysiology, these D2 transgenic mice display altered tolerance to doxorubicin-induced cardiotoxicity (41) and aortic banding (21). Because human cardiomyocytes express negligible D2, the direct relevance of these findings to patients remains unclear. However, these experiments are robust proof of the concept that cardiomyocyte deiodination is a potent mechanism to regulate T3-dependent function and injury tolerance in the heart.

In recent years, high D3 expression has been discovered in rodent models of hypertrophic and ischemic cardiomyopathy (23,25) and also in human hearts with ischemic cardiomyopathy (26). This cardiac D3 induction is sufficient to produce anatomically specific hypothyroidism (25), and one study of mice with lifelong D3 deficiency supports that myocardial D3 induction plays a protective role in hypertrophic heart failure (22). Whether D3 induction occurs in other forms of heart failure was unknown. The present study demonstrates for the first time that cardiac D3 activity is dramatically increased in a murine model of dilated cardiomyopathy. The absolute level of cardiac D3 activity induced in failing TG9 hearts is similar to that measured in other rodent models of ischemic (23,24) or hypertrophic (25) cardiomyopathy, and the localization of D3 to cardiomyocytes in TG9 hearts matches the pattern reported in ischemic cardiomyopathy (20,23,26).

Considering that dilated cardiomyopathy is pathophysiologically and histologically distinct from the hypertrophic and ischemic forms of cardiomyopathy (42,43), the data suggest that cardiac D3 induction is a general, fundamental response to myocardial injury and strain. Although the mechanisms underlying cardiomyocyte D3 induction are not fully defined, one possible stimulus shared among various forms of myocardial injury is local hypoxia, which leads to the activation of hypoxia-inducible factors (HIFs). It has previously been shown that HIF-1α is a transcriptional stimulator of the *Dio3* gene and mediates D3 induction and local cardiac hypothyroidism in a rat model of hypertrophic heart failure (25). In fact, cardiomyocyte hypoxia alone is sufficient to induce D3 in isolated primary rat cardiomyocytes (25), and studies of monocrotaline-induced right ventricular hypertrophy show robust D3 induction in hypertrophic cardiomyocytes prior to the onset of heart failure (19). The demonstration of increased HIF-1α expression in human hearts with chronic hypertrophic (44), ischemic (26), or dilated cardiomyopathy (45) suggests that HIF-1α activation may be a common mechanism for D3 induction across diverse forms of heart failure. Additional patient studies to define the patterns of D3 induction in human cardiomyopathy are warranted.

In summary, this study used a novel mouse model to show that cardiomyocyte D3 is induced during dilated cardiomyopathy. This D3 induction was associated with decreased systemic thyroid status and the altered expression of thyroid hormone responsive cardiac genes. Further study is justified to identify the key targets of thyroid hormone signaling in chronic heart failure and to define the specific role of D3 in cardiac disease. The recent precedents of conditional knockout mice with hepatocyte-specific (33) or muscle stem cell–specific (46) D3 deficiency, which have revealed important functional roles of D3 in nonthyroidal illness and tissue regeneration, warrant the creation of cardiomyocyte-specific knockout mice to dissect D3's functional roles in various forms of heart failure and the specific contribution of cardiomyocyte D3 to the low T3 syndrome.

Acknowledgments

The authors thank Dr. P. Reed Larsen for his helpful insights and comments on this manuscript and Dr. Henry A. Feldman for assistance with statistical analyses. This work was supported by the Pan-Mass Challenge Fund, the William F. Milton Foundation Award, a Research Grant from the American Thyroid Association, a donation from the Murray Family, and the National Institutes of Health grants DK076099, HL105857, DK044128, DK007699, and HD052896.

Downloaded by Washington Univ from www.liebertpub.com at 03/06/18. For personal use only.

Downloaded by Washington Univ from www.liebertpub.com at 03/06/18. For personal use only.

Author Disclosure Statement

The authors have nothing to disclose.

References

1. Krum H, Abraham WT 2009 Heart failure. Lancet **373:** 941–955.
2. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Després JP, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jiménez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Rosamond W, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Woo D, Yeh RW, Turner MB, Subcommittee AHASCaSS 2016 Executive summary: heart disease and stroke statistics—2016 update: a report from the American Heart Association. Circulation **133:**447–454.
3. Hamilton MA, Stevenson LW, Fonarow GC, Steimle A, Goldhaber JI, Child JS, Chopra IJ, Moriguchi JD, Hage A 1998 Safety and hemodynamic effects of intravenous triiodothyronine in advanced congestive heart failure. Am J Cardiol **81:**443–447.
4. Hamilton MA, Stevenson LW, Luu M, Walden JA 1990 Altered thyroid hormone metabolism in advanced heart failure. J Am Coll Cardiol **16:**91–95.
5. Opasich C, Pacini F, Ambrosino N, Riccardi PG, Febo O, Ferrari R, Cobelli F, Tavazzi L 1996 Sick euthyroid syndrome in patients with moderate-to-severe chronic heart failure. Eur Heart J **17:**1860–1866.
6. Ascheim DD, Hryniewicz K 2002 Thyroid hormone metabolism in patients with congestive heart failure: the low triiodothyronine state. Thyroid **12:**511–515.
7. Iervasi G, Pingitore A, Landi P, Raciti M, Ripoli A, Scarlattini M, L'Abbate A, Donato L 2003 Low-T3 syndrome: a strong prognostic predictor of death in patients with heart disease. Circulation **107:**708–713.
8. Wang W, Guan H, Gerdes AM, Iervasi G, Yang Y, Tang YD 2015 Thyroid status, cardiac function, and mortality in patients with idiopathic dilated cardiomyopathy. J Clin Endocrinol Metab **100:**3210–3218.
9. Utiger RD 1995 Altered thyroid function in nonthyroidal illness and surgery. To treat or not to treat? N Engl J Med **333:**1562–1563.
10. De Groot LJ 1999 Dangerous dogmas in medicine: the nonthyroidal illness syndrome. J Clin Endocrinol Metab **84:**151–164.
11. Accorroni A, Saponaro F, Zucchi R 2016 Tissue thyroid hormones and thyronamines. Heart Fail Rev **21:**373–390.
12. Moruzzi P, Doria E, Agostoni PG, Capacchione V, Sganzerla P 1994 Usefulness of L-thyroxine to improve cardiac and exercise performance in idiopathic dilated cardiomyopathy. Am J Cardiol **73:**374–378.
13. Moruzzi P, Doria E, Agostoni PG 1996 Medium-term effectiveness of L-thyroxine treatment in idiopathic dilated cardiomyopathy. Am J Med **101:**461–467.
14. Pingitore A, Galli E, Barison A, Iervasi A, Scarlattini M, Nucci D, L'Abbate A, Mariotti R, Iervasi G 2008 Acute effects of triiodothyronine (T3) replacement therapy in patients with chronic heart failure and low-T3 syndrome: a randomized, placebo-controlled study. J Clin Endocrinol Metab **93:**1351–1358.
15. Gerdes AM, Iervasi G 2010 Thyroid replacement therapy and heart failure. Circulation **122:**385–393.
16. Bianco AC, Salvatore D, Gereben B, Berry MJ, Larsen PR 2002 Biochemistry, cellular and molecular biology, and physiological roles of the iodothyronine selenodeiodinases. Endocr Rev **23:**38–89.
17. Gereben B, Zavacki AM, Ribich S, Kim BW, Huang SA, Simonides WS, Zeold A, Bianco AC 2008 Cellular and molecular basis of deiodinase-regulated thyroid hormone signaling. Endocr Rev **29:**898–938.
18. Huang SA 2005 Physiology and pathophysiology of type 3 deiodinase in humans. Thyroid **15:**875–881.
19. Wassen FW, Schiel AE, Kuiper GG, Kaptein E, Bakker O, Visser TJ, Simonides WS 2002 Induction of thyroid hormone-degrading deiodinase in cardiac hypertrophy and failure. Endocrinology **143:**2812–2815.
20. Pol CJ, Muller A, Simonides WS 2010 Cardiomyocyte-specific inactivation of thyroid hormone in pathologic ventricular hypertrophy: an adaptative response or part of the problem? Heart Fail Rev **15:**133–142.
21. Trivieri MG, Oudit GY, Sah R, Kerfant BG, Sun H, Gramolini AO, Pan Y, Wickenden AD, Croteau W, Morreale de Escobar G, Pekhletski R, St Germain D, Maclennan DH, Backx PH 2006 Cardiac-specific elevations in thyroid hormone enhance contractility and prevent pressure overload-induced cardiac dysfunction. Proc Natl Acad Sci U S A **103:**6043–6048.
22. Ueta CB, Oskouei BN, Olivares EL, Pinto JR, Correa MM, Simovic G, Simonides WS, Hare JM, Bianco AC 2012 Absence of myocardial thyroid hormone inactivating deiodinase results in restrictive cardiomyopathy in mice. Mol Endocrinol **26:**809–818.
23. Pol CJ, Muller A, Zuidwijk MJ, van Deel ED, Kaptein E, Saba A, Marchini M, Zucchi R, Visser TJ, Paulus WJ, Duncker DJ, Simonides WS 2011 Left-ventricular remodeling after myocardial infarction is associated with a cardiomyocyte-specific hypothyroid condition. Endocrinology **152:**669–679.
24. Olivares EL, Marassi MP, Fortunato RS, da Silva AC, Costa-e-Sousa RH, Araujo IG, Mattos EC, Masuda MO, Mulcahey MA, Huang SA, Bianco AC, Carvalho DP 2007 Thyroid function disturbance and type 3 iodothyronine deiodinase induction after myocardial infarction in rats a time course study. Endocrinology **148:**4786–4792.
25. Simonides WS, Mulcahey MA, Redout EM, Muller A, Zuidwijk MJ, Visser TJ, Wassen FW, Crescenzi A, da-Silva WS, Harney J, Engel FB, Obregon MJ, Larsen PR, Bianco AC, Huang SA 2008 Hypoxia-inducible factor induces local thyroid hormone inactivation during hypoxic–ischemic disease in rats. J Clin Invest **118:**975–983.
26. Pol CJ, Muller A, Janssen R, Zuidwijk MJ, dos Remedios CG, Visser TJ, Paulus WJ, Simonides WS 2011 Cardiac induction of the thyroid hormone degrading enzyme deiodinase type III in human ischemic cardiomyopathy. Abstract presented at the 93rd Annual Meeting of the Endocrine Society (ENDO 2011), Boston, Massachusetts, June 4–7. Abstract no. P1-785.
27. Buerger A, Rozhitskaya O, Sherwood MC, Dorfman AL, Bisping E, Abel ED, Pu WT, Izumo S, Jay PY 2006 Dilated cardiomyopathy resulting from high-level myocardial expression of Cre-recombinase. J Card Fail **12:**392–398.
28. Richard K, Hume R, Kaptein E, Sanders JP, van Toor H, De Herder WW, den Hollander JC, Krenning EP, Visser TJ 1998 Ontogeny of iodothyronine deiodinases in human liver. J Clin Endocrinol Metab **83:**2868–2874.

29. Zavacki AM, Ying H, Christoffolete MA, Aerts G, So E, Harney JW, Cheng SY, Larsen PR, Bianco AC 2005 Type 1 iodothyronine deiodinase is a sensitive marker of peripheral thyroid status in the mouse. Endocrinology **146:**1568–1575.
30. Bianco AC, Anderson G, Forrest D, Galton VA, Gereben B, Kim BW, Kopp PA, Liao XH, Obregon MJ, Peeters RP, Refetoff S, Sharlin DS, Simonides WS, Weiss RE, Williams GR, Action ATATFoAaStITHEa 2014 American Thyroid Association guide to investigating thyroid hormone economy and action in rodent and cell models. Thyroid **24:**88–168.
31. Huang SA, Dorfman DM, Genest DR, Salvatore D, Larsen PR 2003 Type 3 iodothyronine deiodinase is highly expressed in the human uteroplacental unit and in fetal epithelium. J Clin Endocrinol Metab **88:**1384–1388.
32. Huang SA, Fish SA, Dorfman DM, Salvatore D, Kozakewich HP, Mandel SJ, Larsen PR 2002 A 21-year-old woman with consumptive hypothyroidism due to a vascular tumor expressing type 3 iodothyronine deiodinase. J Clin Endocrinol Metab **87:**4457–4461.
33. Castroneves LA, Jugo RH, Maynard MA, Lee JS, Wassner AJ, Dorfman D, Bronson RT, Ukomadu C, Agoston AT, Ding L, Luongo C, Guo C, Song H, Demchev V, Lee NY, Feldman HA, Vella KR, Peake RW, Hartigan C, Kellogg MD, Desai A, Salvatore D, Dentice M, Huang SA 2014 Mice with hepatocyte-specific deficiency of type 3 deiodinase have intact liver regeneration and accelerated recovery from nonthyroidal illness after toxin-induced hepatonecrosis. Endocrinology **155:**4061–4068.
34. Peeters RP, Wouters PJ, Kaptein E, van Toor H, Visser TJ, Van den Berghe G 2003 Reduced activation and increased inactivation of thyroid hormone in tissues of critically ill patients. J Clin Endocrinol Metab **88:**3202–3211.
35. Huang SA, Bianco AC 2008 Reawakened interest in type III iodothyronine deiodinase in critical illness and injury. Nat Clin Pract Endocrinol Metab **4:**148–155.
36. Fruhwald FM, Ramschak-Schwarzer S, Pichler B, Watzinger N, Schumacher M, Zweiker R, Klein W, Eber B 1997 Subclinical thyroid disorders in patients with dilated cardiomyopathy. Cardiology **88:**156–159.
37. Kahaly GJ, Dillmann WH 2005 Thyroid hormone action in the heart. Endocr Rev **26:**704–728.
38. Danzi S, Klein I 2014 Thyroid disease and the cardiovascular system. Endocrinol Metab Clin North Am **43:**517–528.
39. Pachucki J, Hopkins J, Peeters R, Tu H, Carvalho SD, Kaulbach H, Abel ED, Wondisford FE, Ingwall JS, Larsen PR 2001 Type 2 iodothyronin deiodinase transgene expression in the mouse heart causes cardiac-specific thyrotoxicosis. Endocrinology **142:**13–20.
40. Carvalho-Bianco SD, Kim BW, Zhang JX, Harney JW, Ribeiro RS, Gereben B, Bianco AC, Mende U, Larsen PR 2004 Chronic cardiac-specific thyrotoxicosis increases myocardial beta-adrenergic responsiveness. Mol Endocrinol **18:**1840–1849.
41. Hong EG, Kim BW, Jung DY, Kim JH, Yu T, Seixas Da Silva W, Friedline RH, Bianco SD, Seslar SP, Wakimoto H, Berul CI, Russell KS, Lee KW, Larsen PR, Bianco AC, Kim JK 2013 Cardiac expression of human type 2 iodothyronine deiodinase increases glucose metabolism and protects against doxorubicin-induced cardiac dysfunction in male mice. Endocrinology **154:**3937–3946.
42. Kessler EL, Boulaksil M, van Rijen HV, Vos MA, van Veen TA 2014 Passive ventricular remodeling in cardiac disease: focus on heterogeneity. Front Physiol **5:**482.
43. McNally EM, Barefield DY, Puckelwartz MJ 2015 The genetic landscape of cardiomyopathy and its role in heart failure. Cell Metab **21:**174–182.
44. Krishnan J, Suter M, Windak R, Krebs T, Felley A, Montessuit C, Tokarska-Schlattner M, Aasum E, Bogdanova A, Perriard E, Perriard JC, Larsen T, Pedrazzini T, Krek W 2009 Activation of a HIF1alpha-PPARgamma axis underlies the integration of glycolytic and lipid anabolic pathways in pathologic cardiac hypertrophy. Cell Metab **9:**512–524.
45. Zolk O, Solbach TF, Eschenhagen T, Weidemann A, Fromm MF 2008 Activation of negative regulators of the hypoxia-inducible factor (HIF) pathway in human end-stage heart failure. Biochem Biophys Res Commun **376:**315–320.
46. Dentice M, Ambrosio R, Damiano V, Sibilio A, Luongo C, Guardiola O, Yennek S, Zordan P, Minchiotti G, Colao A, Marsili A, Brunelli S, Del Vecchio L, Larsen PR, Tajbakhsh S, Salvatore D 2014 Intracellular inactivation of thyroid hormone is a survival mechanism for muscle stem cell proliferation and lineage progression. Cell Metab **20:**1038–1048.

Address correspondence to:
Ari J. Wassner, MD
Division of Endocrinology
Boston Children's Hospital
300 Longwood Avenue
Boston, MA 02115

E-mail: ari.wassner@childrens.harvard.edu

Downloaded by Washington Univ from www.liebertpub.com at 03/06/18. For personal use only.