Basic Science and Experimental Studies

Thyroid Hormone Replacement Therapy Attenuates Atrial Remodeling and Reduces Atrial Fibrillation Inducibility in a Rat Myocardial Infarction–Heart Failure Model

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ABSTRACT

Background: Heart failure (HF) is associated with increased atrial fibrillation (AF) risk. Accumulating evidence suggests the presence of myocardial tissue hypothyroidism in HF, which may contribute to HF development. In a recent report we demonstrated that hypothyroidism, like hyperthyroidism, leads to increased AF inducibility. The present study was designed to investigate the effect of thyroid hormone (TH) replacement therapy on AF arrhythmogenesis in HF.

Methods and Results: Myocardial infarction (MI) was produced in rats by means of coronary artery ligation. Rats with large MIs (>40%) were randomized into L-thyroxine (T_4; n = 14) and placebo (n = 15) groups 2 weeks after MI. Rats received 3.3 mg T_4 (in 60-day release form) or placebo pellets for 2 months. Compared with the placebo, T_4 treatment improved cardiac function and decreased left ventricular internal diameters as well as left atrial diameter. T_4 treatment attenuated atrial effective refractory period prolongation (45 ± 1.5 ms in placebo group vs 37 ± 1.6 ms in T_4 group; $P < .01$) and reduced AF inducibility (AF/atrial flutter/tachycardia were inducible in 11/15 rats [73%] in the placebo- vs 4/14 rats [29%] in the T_4-treated group; $P < .05$). Arrhythmia reduction was associated with decreased atrial fibrosis but was not associated with connexin 43 changes.

Conclusions: To our knowledge this is the first study demonstrating that TH replacement therapy in HF attenuates atrial remodeling and reduces AF inducibility after MI-HF. Clinical studies are needed to confirm such benefits in human patients. (*J Cardiac Fail 2014;20:1012–1019*)

Key Words: Atrial fibrillation, heart failure, thyroid hormone, arrhythmogenesis.

Heart Failure (HF) and atrial fibrillation (AF) are 2 cardiac diseases of epidemic proportion.[1,2] The number of people who are affected by HF and AF are >5 million and >2.2 million, respectively, in the United States.[3–6] AF has a very complex pathophysiology that depends strongly on underlying cardiovascular diseases, particularly HF. The relationship between HF and AF has been described as "HF begets AF, and AF begets HF."[7,8] AF prevalence increases with the severity of HF. Risk of AF reaches ~50% in patients with New York Heart Association functional class IV HF.[3] On the other hand, development of AF in HF patients is one of the leading causes of clinical deterioration.[9] Although the causative relationship between the 2 conditions has not been fully determined; their coexistence can be explained by many risk factors that are shared among them.

Accumulating evidence has shown the presence of myocardial tissue hypothyroidism (low myocardial T_3) in various cardiac diseases,[10,11] which may contribute to HF development.[11,12] Importantly, thyroid hormone (TH) replacement therapy has been shown to improve left ventricular (LV) function and structural remodeling in

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HF.[11,13−16] However, TH replacement therapy has not been adopted clinically in HF treatment. One of the major concerns in applying TH therapy in HF is that TH treatment might increase cardiac arrhythmias. The reason behind this concern is that hyperthyroidism can lead to increased atrial arrhythmogenesis,[6] and potential TH overdosing and its associated arrhythmogenesis constitute a common fear.

Recently we demonstrated that both hypothyroidism and hyperthyroidism can increase AF arrhythmogenesis.[17] Based on this finding and evidence that myocardial tissue hypothyroidism is a common pathology in HF,[11] we hypothesized that myocardial tissue hypothyroidism may contribute to increased AF arrhythmogenesis in HF. Therefore, correcting myocardial tissue hypothyroidism with TH replacement therapy may reduce, rather than increase, AF risk in HF. The present study was designed to investigate the effect of TH replacement therapy on atrial remodeling and AF inducibility in a rat myocardial infarction (MI) −HF model.

Materials and Methods

This study was approved by the Institutional Animal Care and Use Committee at New York Institute of Technology College of Osteopathic Medicine and is in compliance with the ''Guide for the Care and Use of Laboratory Animals'' (National Institutes of Health publication no. 85-23, revised 1996).

Animal Model and Study Design

Adult (12-wk-old) female Sprague-Dawley rats (Harlan Laboratories, Indianapolis, Indiana) were used in this study. MI was produced by means of ligation of the left descending coronary artery, as described in our previous reports.[14,15] Two weeks after MI surgery, echocardiography was performed to determine MI size in all of the surviving animals. Based on our own experience and literature reports, a large MI is needed to develop HF and increase AF inducibility.[18,19] Therefore, we enrolled only rats with large MI (>40% of LV circumference in short-axis view) in this study. Eligible rats (~80%) were randomly assigned into the following 2 groups: MI control group (treated with placebo; n = 15) and L-thyroxine (T_4)−treated group (MI + T_4; n = 14). Immediately after enrollment, T_4 pellets (3.3 mg, 60-day sustained release form; Innovative Research of America, Sarasota, Florida) were implanted subcutaneously in MI + T_4 group rats, as previously reported.[15,17] Placebo pellets were implanted in the MI control rats. The dosages of T_4 pellets were chosen based on our previous studies in that the 3.3-mg T_4 pellets improved LV function and ventricular remodeling in MI rats.[14,15] After 2 months of treatment, cardiac chamber dimensions and function were assessed by echocardiography and LV catheterization. In vivo atrial electrophysiology and AF inducibility test using a catheter approach were performed for each animal at the end of the study. Animals were housed in our institutional animal facility and kept on a 12:12-hour light-dark cycle and given standard rat chow and water ad libitum.

Echocardiographic Measurements

As previously described,[17] a GE Vivid 7 Dimension System (GE Vingmed Ultrasound, Horten, Norway) coupled with a M12 L linear (Matrix) array ultrasound transducer probe (5−13 MHz) was used to acquire echocardiographic data. Briefly, rats were anesthetized with the use of 1.5% isofluorane. After the chest was shaved, the animals were placed on an isothermal pad maintained at ~40°C. Two-dimensional echocardiograms were obtained from short-axis and long-axis views of the LV. MI size was determined from the short-axis view by measuring the length of the MI as a percentage of the LV circumference. Two-dimensionally targeted M-mode echocardiograms were used to measure the LV dimensions in systole and diastole. The following parameters were measured: anterior wall thickness in end-diastole and -systole, LV diastolic and systolic internal diameters, posterior wall thickness in end-diastole and -systole, and LV fractional shortening. Left atrial diameter at the aortic valve level also was measured to estimate the atrial size.

Cardiac Hemodynamic Measurements

LV hemodynamics were obtained by catheterization of the right carotid artery with the use of a Scisense pressure-volume catheter (Transonic Scisense, London, Ontario, Canada), as previously described.[17] Briefly, the right carotid artery was isolated and cannulated with a 1.9-F Scisense pressure-volume catheter under isofluorane anesthesia. The tip of the catheter was advanced through the aorta into the LV. The following parameters were measured: heart rate, LV peak systolic pressure (LVSP), LV end-diastolic pressure (LVEDP), and positive/negative change in pressure over time (±dP/dt). The data were acquired and analyzed with the use of Labscribe software (iWorx Systems, Dover, New Hampshire).

Electrophysiology Study and AF Inducibility Test

In vivo cardiac electrophysiology was assessed with the use of a 1.6-F octopolar Millar electrophysiology catheter (EPR-802; Millar Instruments, Houston, Texas) as previously described.[17] Briefly, the catheter was inserted through the right jugular vein and advanced into the right atrium with 8 poles recording atrial electrograms. Standard surface electrocardiographic lead II and 3 right atrial electrocardiograms from 3 pairs of electrodes were displayed and recorded with the use of Powerlab data acquisition systems (ADInstruments, Colorado Springs, Colorado). The purpose of recording 3 atrial electrograms from distal, middle, and proximal pairs was to facilitate determination of atrial capturing and AF pattern.

Regular pacing and standard S1S2 programmed pacing protocols were used to determine sinus node recovery time and atrial effective refractory period (ERP). The atria were paced at 3× threshold at cycle length of 150 ms or 20 ms shorter than the spontaneous sinus cycle length. Atrial ERP was defined as the longest coupling intervals that did not capture the atria.

Burst pacing containing 200 impulses at 50 Hz was used to induce AF. The duration of the subsequent spontaneous arrhythmias after burst pacing was documented. For each animal, the average arrhythmia duration based on 5 such tests was calculated.

AF was defined as irregular rapid atrial activations with varying electrographic morphology lasting ≥0.5 seconds, as described previously.[17] The atrial rates in AF were typically >1,500 beats/min in rats. We noticed in some rats that the induced atrial