Gender-specific effects of thyroid hormones on cardiopulmonary function in SHHF rats

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Schlenker, E. H., T. Tamura, and A. M. Gerdes. Gender-specific effects of thyroid hormones on cardiopulmonary function in SHHF rats. J Appl Physiol 95: 2292–2298, 2003.—Spontaneously hypertensive heart failure (SHHF) rats develop hypertension and heart failure. We hypothesized that induction of hyperthyroidism should accelerate development of heart failure in male SHHF rats. Male and female SHHF rats received diets containing desiccated thyroid glands (DTG) or a control diet for 8 wk. Male and female Wistar-Kyoto rats were used as normotensive controls. DTG treatment reduced body weight in male, but not female, SHHF rats but increased body temperature and heart weight-to-body weight ratio in both genders. In DTG-treated male SHHF rats, serum triiodothyronine levels doubled relative to SHHF controls, whereas O\textsubscript{2} consumption increased in DTG-treated SHHF rats. Frequency of breathing in air increased in DTG-treated female rats, and ventilation increased in DTG-treated male rats. Ventilatory equivalents exhibited gender differences in SHHF rats, were decreased in both genders by DTG treatment, and reached levels similar to those of Wistar-Kyoto rats. DTG increased heart rate, right ventricular pressure, and contractility in both genders and increased left ventricular pressure in SHHF male rats. These results refute our hypothesis and suggest that cardiopulmonary function of SHHF male rats may be improved by DTG treatment.

Methods

Animals. Lean male and female SHHF rats were obtained from Genetic Models (Indianapolis, IN), and WKY rats were obtained from Harlan Sprague Dawley (Indianapolis, IN). The University of South Dakota Animal Care and Use Committee approved all procedures used in this study.

Rats were housed three to four per cage according to genotype and gender. Light cycles consisted of 12 h on (6 AM) and 12 h off (6 PM). SHHF rats of each gender and genotype were divided randomly into two groups: 1) those that received water and powdered Purina rat chow ad libitum (controls) and 2) those that received water and powdered Purina rat chow to which 0.6% desiccated thyroid gland (DTG; Sigma Chemical, St. Louis, MO) was added for 8 wk (treated). WKY rats received water and powdered Purina rat chow ad libitum. SHHF rats consisted of seven control and nine DTG-treated males and seven control and eight DTG-treated females, and the WKY rats consisted of eight males and eight females.
females. The method used to induce hyperthyroidism has been previously used by our group (11).

**Measurement of ventilation and O₂ consumption.** To evaluate ventilation in air and in response to a brief hypercapnic challenge (7% CO₂ in O₂), conscious rats were placed in a 19-cm-long × 9.5-cm-diameter Plexiglas cylindrical chamber. One end of the chamber contained ports to allow air or the test gases to enter. At this end, chamber temperature was monitored using a Digitec thermometer. Pressure changes associated with ventilation were measured using a low-pressure transducer (Statham, Hato Rey, Puerto Rico) coupled to a Grass polygraph recording system. With the use of Boyle’s law, the pressure changes were calibrated with a glass syringe attached to the chamber by injection of a known volume of gas into the chamber. This barometric method to evaluate ventilation has been used previously in our laboratory (33, 34). Ventilatory parameters included tidal volume, frequency of breathing, and minute ventilation.

A port was connected to a rotameter on the other side of the chamber to determine the flow rate through the chamber. A Beckman OM-14 O₂ analyzer and a Vacumed CO₂ analyzer were used to measure the fractional content of O₂ and CO₂ entering and leaving the chamber. Measurements of flow rate and the fractional contents of gases entering and exiting the chamber were used to determine O₂ consumption using the flow through system. O₂ consumption, minute ventilation, and tidal volume were corrected by body weight (BW) as follows: tidal volume × 100 · 1 BW⁻¹, minute ventilation × 100 · 1 BW⁻¹, and O₂ consumption/BW. Another parameter that was calculated from the data was the ventilatory equivalent (ventilation ÷ O₂ consumption), which was used to determine how well ventilation and O₂ consumption were matched.

**Procedures used to evaluate ventilation and O₂ consumption.** Each rat was weighed and then placed in the chamber and exposed to air for 30 min of acclimatization. Ventilation and O₂ consumption were determined. Then the rat was exposed to the hypercapnic challenge for 5 min, and its ventilation was evaluated. Subsequently, the rat was removed from the chamber, and its rectal temperature was measured using a thermometer-thermocouple system (Sensortek, Clifton, NJ). The ventilatory responses to hypercapnia were determined using a specially designed curved ultraminiature catheter containing a pressure transducer (model SPR-407, Millar, Houston, TX) was inserted into the left ventricle via the right common carotid artery. Right ventricular hemodynamic parameters were measured using a specially designed curved ultraminiature catheter (model SPR-407, curved, Millar) inserted through the right jugular vein. The catheters were connected to a Crystal Biotech DataFlow System (Hopkinton, MA) to evaluate left and right ventricular pressures (LVP and RVP, respectively), left and right end-diastolic pressures, and heart rate (HR). At the end of the experiment, the rat was euthanized with an overdose of thiopental sodium (Pentothal), and hematocrit and heart weight (HW) were evaluated.

**Serum thyroid hormone (T₃ and thyroxine) levels.** At the end of the experiments, blood was collected by cardiac puncture. The blood was spun down at 3,000 rpm, and the serum was decanted and frozen at −80°C until analyzed for thyroid hormone levels. Total thyroid hormone plasma levels were determined using RIA kits (Diagnostic Systems, Webster, TX). The procedure followed the basic principle of RIA, where there is competition between a radioactive and a nonradioactive antigen for a fixed number of antibody-binding sites. The amount of 125I-labeled T₃ or thyroxine (T₄) bound to the antibody is inversely proportional to the concentration of unlabeled T₃ or T₄.

All reagents and samples were allowed to reach room temperature (−25°C) and then thoroughly mixed by gentle inversion. Unbound materials were removed by decanting and washing the coated tubes before counting in a gamma counter (COMPAC 120). The detection limits for the assays were 4.3 ng/dl for T₃ and 0.4 μg/dl for T₄. Samples of standards, controls, and unknowns were assayed in duplicate. The intra-assay coefficient of variation was 4%.

**Data analysis.** O₂ consumption, ventilatory parameters, thyroid hormone levels, HW-to-BW ratio (HW/BW), ventilatory responses to hypercapnia, and the cardiovascular parameters were compared for effects of gender and treatment using a two-factor ANOVA. Another two-way ANOVA was used to compare genotype and gender in the untreated controls. If the ANOVA was significant (P < 0.05), a post hoc unpaired Student’s t-test with Bonferroni’s correction was used. Values are means ± SE.

**RESULTS**

**Thyroid hormone levels.** There was a gender effect of DTG treatment on T₄ levels (Table 1) in the SHHF rats [F(1,27) = 4.62, P = 0.044]. There was no difference in T₄ levels between untreated WKY and SHHF male rats, but T₄ levels were higher in untreated SHHF female than in untreated WKY rats (P < 0.003).

In the SHHF rats, there was a borderline trend toward an interaction (P = 0.056), but gender [F(1,7) = 12.94, P < 0.001] and treatment [F(1,27) = 8.96, P < 0.006] were significant for serum T₃ levels (Table 1). DTG treatment increased T₃ levels in male, but not female, SHHF rats. There was no difference in baseline T₃ levels between untreated WKY and SHHF male rats.

**BW, body temperature, and O₂ consumption.** SHHF rats were significantly heavier than WKY rats (Table 1, SHHF female, SHHF male rats. There was no difference in basal body temperature (T₃) in WKY and SHHF females. There was a significant effect of gender on T₄ levels, but not on T₃ levels. There was no difference in basal O₂ consumption (0.18 ± 1.89 μg/dl) in untreated WKY and SHHF rats.

| Table 1. Thyroid hormone levels in WKY and SHHF rats |
|-----------------|-----------------|-----------------|-----------------|
|                 | Males           | Females         |
|                 | Untreated       | Treated         | Untreated       | Treated         |
| T₃, μg/dl       |                 |                 |                 |                 |
| WKY             | 2.67 ± 0.18     | 1.89 ± 0.25†    | 1,128 ± 13      | 97 ± 14         |
| SHHF            | 2.72 ± 0.18     | 2.86 ± 0.15     | 3.34 ± 0.28‡    | 2.97 ± 0.22     |
| T₄, ng/dl       |                 |                 |                 |                 |
| WKY             | 54 ± 5          | 79 ± 14         | 112 ± 29       | 126 ± 10        |
| SHHF            | 64 ± 3          | 118 ± 13*       | 112 ± 9†       |

Values are means ± SE. T₃, thyroxine; T₄, triiodothyronine; WKY, Wistar-Kyoto rats. Comparisons were made within spontaneously hypertensive heart failure (SHHF) rats for gender and treatment effects using a 2-factor ANOVA and between genotypes and gender also using a 2-factor ANOVA. *Significant effect of treatment in SHHF male rats, P < 0.05. †Genotype differences, P < 0.05. ‡Gender type differences, P < 0.05.
Table 2. Effects of thyroid hormone supplementation on body weight, body temperature, and O2 consumption in WKY and SHHF male and female rats

<table>
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<th>Untreated</th>
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<tr>
<td></td>
<td>WKY</td>
<td>SHHF</td>
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<tr>
<td>BW, g</td>
<td></td>
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</tr>
<tr>
<td>Males</td>
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<tr>
<td>BW, g</td>
<td>305.1 ± 5.2</td>
<td>410 ± 9.2</td>
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<tr>
<td>Tb, °C</td>
<td>36.2 ± 0.3</td>
<td>36.4 ± 0.2</td>
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<td>VO2, ml·g⁻¹·h⁻¹</td>
<td>17.5 ± 0.8</td>
<td>12.3 ± 1.3</td>
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<tr>
<td>Females</td>
<td></td>
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<tr>
<td>BW, g</td>
<td>192.3 ± 2.8</td>
<td>229 ± 5.2</td>
</tr>
<tr>
<td>Tb, °C</td>
<td>37.0 ± 0.2</td>
<td>38.6 ± 0.4</td>
</tr>
<tr>
<td>VO2, ml·g⁻¹·h⁻¹</td>
<td>23.0 ± 1.5</td>
<td>16.6 ± 1.1</td>
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</table>

Values are means ± SE. BW, body weight; Tb, body temperature; VO2, O2 consumption corrected for body weight. *Significantly different from comparing gender-matched control SHHF rats, P < 0.05. †Significantly different from SHHF rats for each gender, P < 0.05. ‡Gender differences within a genotype, P < 0.05.

2). BW was significantly less (P < 0.01) in DTG-treated male SHHF than in control rats. Administration of DTG had no significant effect on BW in SHHF female rats. Body temperature was significantly higher in male and female SHHF than in gender-matched WKY rats (P < 0.05 for each). Body temperatures were elevated in male DTG-treated SHHF rats relative to genotype control rats body (P = 0.015) but not DTG-treated SHHF females relative to controls. There were genotype differences in weight-corrected O2 consumption in male [F(1,27) = 29.4, P < 0.00003] and female [F(1,27) = 14.6, P = 0.00817] rats. In general, weight-corrected O2 consumption was higher in WKY than in SHHF rats. DTG treatment increased O2 consumption in male and female SHHF rats (P < 0.001 for each). Thus treatment with DTG had different effects on BW in male and female SHHF rats but similar effects on O2 consumption in both genders.

Control of breathing. Weight-corrected minute ventilation (Table 3) exhibited a genotype difference [F(1,27) = 5.42, P = 0.029]. There were no differences between untreated SHHF and WKY female rats in this parameter, but weight-corrected ventilation was greater in WKY male than in SHHF male rats (P = 0.01). A significant treatment effect was noted in weight-corrected minute ventilation [F(1,27) = 148.9, P = 0.0093], with an increase noted in DTG-treated SHHF male (P = 0.019), but not female, rats.

The increase in minute ventilation in DTG-treated SHHF male rats was due to a significant increase in weight-corrected tidal volume (P = 0.05; Table 3). This parameter was not significantly elevated in DTG-treated SHHF female rats. In contrast, frequency of breathing was increased significantly by DTG treatment in SHHF female (P < 0.01), but not SHHF male, rats. Thus the increase in weight-corrected minute ventilation in DTG-treated SHHF male rats was due to small significant increases of tidal volume, whereas in SHHF female rats the major response to

DTG treatment was an increase in breathing frequency.

To determine whether ventilation and O2 consumption were affected in a parallel manner by DTG treatment, the ventilatory equivalent (ventilation ÷ O2 consumption) was evaluated (Fig. 1). When untreated SHHF and WKY rats are compared, a genotype [F(1,27) = 9.97, P = 0.0043] and gender difference [F(1,27) = 4.59, P = 0.043] become apparent. SHHF rats have higher ventilatory equivalents than WKY rats, and this parameter is higher in male than in female rats (Fig. 1). In male and female SHHF rats, the ventilatory equivalent was significantly decreased by DTG treatment [F(1,23) = 6.07, P = 0.02] relative to the untreated gender-matched controls. DTG treatment caused the ventilatory equivalents of SHHF rats
to reach levels noted in WKY male rats and eliminated the gender difference noted in the untreated SHHF rats.

The ventilatory responses to hypercapnia (Fig. 2) in SHHF rats exhibited a significant gender difference \([F(1,27) = 12.28, P = 0.002]\) and a treatment effect \([F(1,27) = 4.78, P = 0.04]\). In SHHF male and female rats individually, the ventilatory response to hypercapnia was maintained with DTG administration. The ventilatory response to hypercapnia was greater in untreated WKY than in SHHF rats \((P < 0.04)\).

**Cardiovascular parameters.** HW/BW (Table 4) exhibited a significant gender and genotype interaction in the untreated groups \([F(1,27) = 5.76, P = 0.0245]\). HW/BW was higher in untreated SHHF rats of both genders than in WKY rats \((P < 0.001\) for each) and higher in female than in male rats. DTG treatment increased HW/BW further in SHHF rats \((P < 0.00001)\).

There was no significant genotype difference in HR (Table 4). Male and female SHHF rats exhibited a treatment effect \([F(1,15) = 52.6, P < 0.001]\), with a marked elevation of HR after DTG.

DTG-treated SHHF animals showed an interaction between gender and treatment \([F(1,15) = 11.07, P = 0.0034]\), with an increase in LVP in female, but not male, rats (Fig. 3A). LVP was higher in untreated male and female SHHF than in untreated WKY rats \((P < 0.001\) for both). Thus DTG did not increase LVP further in SHHF male rats but did increase LVP in female rats. To evaluate left ventricular contractility, the first derivative of LVP \((dP/dt)\) was determined (Fig. 3B). In SHHF rats, DTG had no significant effect. Untreated WKY male and female rats exhibited a higher \(dP/dt\) than gender-matched SHHF rats \((P < 0.004\) for each gender).

RVP (Fig. 4A) was elevated by DTG treatment in SHHF rats \([F(1,15) = 36.2, P < 0.0001]\). RVP was higher in untreated male WKY male than in untreated SHHF male rats \((P < 0.02)\), whereas no differences were noted in RVP between untreated female WKY and SHHF rats. Right ventricular contractility (Fig. 4B) was increased by DTG treatment in SHHF rats \([F(1,15) = 21.93, P = 0.00014]\). Right

Table 4. Effects of thyroid hormone supplementation on heart weight-to-body weight ratio and heart rate in SHHF and WKY male and female rats

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<th>Unreated</th>
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<tr>
<td></td>
<td>WKY</td>
<td>SHHF</td>
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<tr>
<td><strong>Males</strong></td>
<td></td>
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<tr>
<td>HW/BW</td>
<td>3.25 ± 0.08†</td>
<td>3.79 ± 0.08</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>229 ±8</td>
<td>240 ± 6</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td></td>
<td></td>
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<tr>
<td>HW/BW</td>
<td>3.80 ± 0.10†</td>
<td>4.79 ± 0.11</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>244 ± 7</td>
<td>238 ± 8</td>
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</table>

Values are means ± SE. HW, heart weight. †Significantly different from gender-matched untreated SHHF rats, \(P < 0.05\). ‡Significantly different from untreated SHHF rats for each gender, \(P < 0.05\).
contraction, RVP, and right ventricular contractility relative to controls. In contrast, LVP was elevated in DTG-treated SHHF male, but not female, rats. Potential mechanisms for these findings are discussed below.

**BW and DTG treatment.** SHHF female rats maintained BW relative to untreated controls, although BW was lower in WKY BW than in SHHF rats (28, 40). In contrast, DTG-treated SHHF male rats lost weight. These results suggest an interaction between gender and thyroid hormone effects in rats (32, 40). Maintenance of BW necessitates that the amount of food intake balances use of food for energy, such as activities, growth, and maintenance of body temperature. In DTG-treated SHHF female rats, body temperature was similar to that in control female SHHF rats, but O$_2$ consumption was increased. Thus DTG-treated SHHF female rats needed to eat more and/or lose less heat to maintain BW than did male rats (25).

A potential limitation in incorporating DTG in the food is that the amount consumed per animal is unknown and is linked to the amount an animal eats. A potential benefit of incorporating DTG into food is that it is administered without injections, pumps, or pellets, methods that increase stress on the animals. **Hyperthyroidism and the cardiovascular system.** Hyperthyroidism induced experimentally by administration of DTG, T$_4$, or T$_3$ has profound effects on cardiovascular function (10, 15, 28, 25, 37). Gay and coworkers (10) showed increases in HR, RVP, LVP, ventricular contractility, and mean circulatory filling pressure in male Sprague-Dawley (SD) rats treated for 8–10 days with T$_4$. Total peripheral resistance and LVP and venous compliance were decreased relative to controls. Effects on HR, left ventricular dP/dt, and LVP were similar in female SD rats treated with T$_3$ for 14 days. Increased RVP and pulmonary arterial pressure in hyperthyroid female SD rats occurred concomitantly with ventricular hypertrophy, a positive chronotropic effect, and an increased cardiac output. Many of these cardiovascular effects were also noted in the present study in SHHF rats of both genders.

Few studies have investigated the effects of hyperthyroidism in rat models of hypertension, such as the SHR. When Heckmann and Zimmer (15) administered T$_3$ to female SHR, 30% of the animals died, whereas there was no mortality in SD female rats. In the SHR that survived T$_3$ treatment, HR and HW/BW were markedly increased, but LVP, right ventricular weight, left ventricular dP/dt, cardiac output, and total peripheral resistance were not affected. These results are in contrast to those in the present study in SHHF male rats, in that their response to thyroid hormone treatment is similar to that of SD female rats. In comparison, DTG-treated SHHF female rats showed no increase in LVP. In the present study, DTG was administered for 8 wk, rather than 1–2 wk, before cardiovascular measurements. The attenuated cardiovascular responses of SHHF rats to DTG may be the result of a euthyroid sick syndrome. Potential mechanisms for development of this disorder in SHHF rats may include elevations of reverse T$_3$, cytokines such as

**Fig. 4.** Right ventricular pressure (A, RVP) and right ventricular contractility (B) in male and female untreated and DTG-treated SHHF rats and untreated WKY rats. DTG-treated SHHF rats exhibited an increase in right ventricular contractility that reached values in WKY rats. Different letters (a–c) denote significant differences among means (a minimum value of $P < 0.05$).
tumor necrosis factor-α, and stress hormones such as glucocorticoids (9, 37), all of which inhibit to various extent deiodinonases, which convert T₄ to T₃. In addition, the lack of significant increases in T₄ levels with treatment suggests that absorption of this hormone is not normal in SHHF rats. Increases in O₂ consumption in male and female SHHF rats suggest that our treatment was increasing thyroid hormone levels. Further evidence for this possibility was noted in a preliminary study using WKY rats treated with the same or lower levels of DTG, in which we found marked increases in T₄ and T₃ serum levels in this genotype (unpublished observations).

Effects of hyperthyroidism on ventilation. Hyperthyroidism can affect control of breathing through various mechanisms. These include increased metabolic demand and body temperature (37), elevated LVP (7), increased blood pressure (11), remodeling of the respiratory muscles and lungs (1, 20), increased hematocrit (25), and alteration of neurotransmitter levels in brain regions involved in control of breathing (16, 21, 38).

An increase in O₂ demand is a powerful stimulus to increase ventilation. One measure of the efficacy of the respiratory system to respond to changes in metabolism is the ventilatory equivalent (ventilation ÷ O₂ consumption). In the present study, ventilatory equivalent was significantly lower in DTG-treated SHHF male and female rats than in untreated controls. These data suggest that DTG-treated SHHF rats did not increase ventilation to match O₂ consumption. Although there was a clear gender difference in WKY ventilatory equivalent, DTG did not alter this relation or its magnitude. In support for the latter findings, Hillbom and Poso (17) rendered male rats hyperthyroid by administering T₃ for 6 days and found no effect on blood gases. This indicates that ventilation and metabolism were matched in these animals. Ianuzzo and coworkers (19) induced hyperthyroidism in male SD rats by subcutaneous injection of T₄ for 6 wk and noted no effect on tidal volume or frequency, although diaphragmatic fiber types were markedly altered and fiber diameters were smaller. These ventilatory results contrast with our findings in SHHF, but not WKY, rats and suggest that the type and length of thyroid hormone treatment and underlying factors such as strain influence control of breathing.

In hyperthyroid human subjects, ventilation is in excess of metabolic demands (20, 29). This is especially apparent when the subject exercises. However, the level of exercise that can be attained by a hyperthyroid subject is generally lower than that attained by matched euthyroid subjects (20). Ventilatory responses to hypoxic and hypercapnic gas challenges are also greater in hyperthyroid subjects (29). In the present study, the ventilatory response to hypercapnia was not altered by DTG treatment. However, untreated WKY rats exhibited higher responses to hypercapnia than did untreated SHHF rats. This was especially true in WKY compared with SHHF male rats.

Other factors that may modulate ventilation are reflexes associated with the cardiovascular system. For example, Crisp and colleagues (7) reported that elevating LVP in anesthetized dogs decreased phrenic nerve activity, an index of ventilatory drive to the diaphragm. In a separate study, Crisp and coworkers (6) noted that elevating RVP had no effect on ventilation. Thus the depressed ventilatory equivalent in DTG-treated SHHF male and female rats may be related to their elevated LVP. However, LVP is similar in untreated and DTG-treated SHHF male rats and higher than in untreated SHHF female rats, but ventilatory equivalent is higher in untreated SHHF male rats than in DTG-treated male and untreated female rats. These results suggest that not only LVP, but also gender, in SHHF rats affects control of ventilation.

Studies that investigate the interaction between hypertension, gender, and control of breathing focus on their roles in sleep apnea syndrome (cessation of airflow during sleep) (2). Male gender and hypertension are significant risk factors in humans for developing sleep apnea (26). Clinically, sleep apnea exacerbates underlying cardiovascular disease or may contribute to its etiology and may increase morbidity and mortality. Treatment with antihypertensive drugs or assisted ventilation may be helpful in some patients (29).

Animal models of hypertension have been useful to study hypertension and abnormal control of breathing. Carley and coworkers (3) reported that male SHR exhibited increased postsigh apneas (a measure of control of breathing) during sleep relative to normotensive controls. Administration of hydralazine, which normalized the blood pressure in SHR, markedly decreased sleep apnea and the number of postsigh apneas (4).

These and other studies in SHR and in hypertensive humans indicate a significant relation between hypertension and abnormalities of control of breathing (26). Except in the epidemiological studies and the present study, the role of gender has not been specifically investigated in modulating hypertensive factors that also influence control of breathing.

In summary, this study investigated how the interaction between hypertension, hyperthyroidism, and gender affects control of cardiopulmonary function. These results suggest a host of further studies cited above to understand how thyroid hormone therapy affects remodeling of the heart, lungs, and central nervous system in SHHF male and female rats. Our original hypothesis that hyperthyroidism would have a more deleterious effect on the cardiopulmonary system of SHHF male rats was not supported, but, rather, DTG actually may have a beneficial effect in this genotype. SHHF rats may serve as a good model to investigate a beneficial role of thyroid hormone abnormalities associated with heart failure.

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DISCLOSURES

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