Impact of Resistance to Thyroid Hormone on the Cardiovascular System in Adults

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Background: The clinical manifestations of resistance to thyroid hormone (RTH) are highly variable, and the impact of RTH on the cardiovascular system has been poorly investigated.

Aim: The objective of the study was to evaluate the cardiovascular characteristics of 16 untreated and asymptomatic patients with RTH compared with 16 euthyroid healthy controls to define the cardiovascular involvement in RTH syndrome.

Patients and Methods: Sixteen untreated and asymptomatic RTH patients (eight males; aged 33 $\pm$ 12 yr, range 21–45 yr) and 16 controls (nine males; aged 33 $\pm$ 5 yr, range 24–42 yr) were enrolled. Clinical data, thyroid status, and echocardiographic results were recorded.

Results: Heart rate was comparable with that of controls, whereas arterial pressure was higher than controls. Mean interventricular septum diastolic thickness and mean left ventricular (LV) posterior wall diastolic thickness were significantly lower in RTH patients than controls with a consequent significant decrease of the mean LV mass and LV mass indexed by body surface area. Patients also had abnormalities of myocardial relaxation as indicated by a significant increase of peak A and consequent reduction of the early to late ratio. Finally, systemic vascular resistance was significantly higher in RTH patients than controls.

Conclusions: Our results suggest the presence of cardiovascular alterations in asymptomatic and untreated RTH patients similar to those reported in hypothyroid patients. Our strict selection likely created a bias in the inclusion of a particular type of RTH patients, who could represent a minority of patients with RTH. However, no correlation was found between the type of mutation and cardiovascular characteristics of RTH patients. **(*J Clin Endocrinol Metab* 94: 2812–2816, 2009)**

Resistance to thyroid hormone (RTH) is a rare (probably one per 50,000 live births), dominantly inherited condition of altered tissue responsiveness to thyroid hormone (TH), biochemically characterized by elevated serum free T_4 (FT_4) and free T_3 (FT_3) concentrations, in the presence of nonsuppressed levels of TSH (1–7). Most patients with RTH are heterozygous for a point mutation in the ligand-binding domain of the thyroid hormone receptor (TR)-β gene. The mutations may cause either reduced affinity for T_3 or impaired interaction with one of the cofactors (coactivators and corepressors) that mediate TH actions (8). As a result, the mutant TR interferes with the function of normal TRs (dominant negative effect), which explains the dominant mode of inheritance of this syndrome.

In the past, subjects with RTH who clinically appeared to be euthyroid were formerly classified as having generalized resistance to TH. On the contrary, subjects who clinically appeared to be hyperthyroid were classified as having selective pituitary resistance to TH, regardless of the TH level (6, 7). Currently this

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Abbreviations: dCVF, Derived collagen volume fraction; E/A, early to late peak flow velocity ratio; FT_3, free T_3; FT_4, free T_4; LV, left ventricular; RTH, resistance to thyroid hormone; TH, thyroid hormone; TR, thyroid hormone receptor.

subclassification does not have a logical basis (9). Indeed, the clinical manifestations of RTH are highly variable across RTH families and within the same family, probably because of the heterogeneity of the many factors that modulate the receptor-dependent action of TH (8, 9). Therefore, RTH syndrome is characterized by a variable clinical phenotype (7) as well as the paucity of specific clinical manifestations (1, 9).

Different isoforms of TR (TRα1, TRα2, and TRβ1) are expressed in the heart; they regulate the expression of different genes and encode both structural and regulatory proteins (8). The effects of mutant TRβ on the cardiovascular system have been widely studied in animal models (10–16). However, few studies have evaluated the cardiovascular system in patients with RTH (17, 18). Ciulla *et al.* (17) evaluated the derived collagen volume fraction (dCVF) (an echocardiographic index of the collagen) in patients with RTH and thyroid dysfunctions identified by videodensitometry. They showed that dCVF was lower in hyperthyroid patients and higher in hypothyroid patients than in controls. The RTH patients had a pattern intermediate between those of hypothyroid patients and euthyroid controls, *i.e.* the dCVF was slightly increased, which suggests that mutant TR exerts an inhibitory effect on wild-type TR in the heart of these patients. Kahaly *et al.* (18) evaluated cardiovascular involvement in a large RTH group with a wide age range and heterogeneous clinical manifestations (with and without thyrotoxic cardiovascular symptoms) by Doppler echocardiography and compared their results with those of hypothyroid, hyperthyroid, and euthyroid subjects. RTH patients showed alterations of cardiovascular parameters, resembling those found in hyperthyroid patients (cardiac output and stroke volume, isovolumic relaxation, and deceleration times), whereas other parameters [diastolic and systolic diameters of left ventricular (LV), shortening and ejection fractions] were comparable with those of controls. This study was the first to highlight the heterogeneous cardiovascular phenotype in RTH patients, suggesting an incomplete cardiac response to TH in RTH syndrome (18–20).

On this basis, the aim of our study was to select a homogeneous RTH group without thyrotoxic cardiovascular symptoms, untreated with thyroid or cardiovascular drugs, in an attempt to clarify the cardiovascular characteristics of asymptomatic RTH patients.

Patients and Methods

Sixteen nonsmoking, sedentary, patients with RTH (eight men and eight females; aged 33 ± 12 yr, range 21–45 yr) and 16 nonsmoking, sedentary, and healthy euthyroid controls (nine men and seven females; aged 33 ± 5 yr, range: 24–42 yr) entered the study after having given informed consent. The diagnosis of RTH was based on the coexistence of elevated free TH levels, TSH concentrations in the normal range, no hyperthyroid manifestations, and the absence of pituitary lesions at magnetic resonance imaging (1–4). Six RTH patients had a goiter. None of the RTH subjects showed cardiovascular symptoms or used cardiovascular drugs. None of the RTH patients was submitted to thyroidectomy or received thyroid hormone or antithyroid drugs. In these patients, the genetic analyses were performed at the University of Milan (Italy). Exons 9 and 10 of the TRβ gene, including splicing signals and the flanking intronic regions of each intron, were amplified by PCRs (21). DNA sequences from each amplified fragment were analyzed with the *Taq* polymerase-based chain terminator method, using the specific TRβ forward and reverse primers (12). Seven mutations were found: R243Q (two patients), A317T (one patient), R338W (two patients), G344E (two patients), V349L (four patients), R438C (one patient), E445K (one patient). No mutations were found in three RTH subjects. Healthy euthyroid volunteers recruited among the staff and their relatives of our departments served as controls.

On the morning of the study day, participants reported to the laboratory after an overnight fast. Height and weight were measured, and venous blood was sampled for assessment of thyroid status by using a commercially available kit (Axsym System; Abbott Laboratories Diagnostics Division, Abbott Park, CA), according to the following reference ranges: serum TSH, 0.26–4.2 mU/liter; serum FT_4, 9–20 pmol/liter; serum FT_3, 3.8–8 pmol/liter). Participants then underwent cardiac assessment.

Doppler echocardiography

The same investigator, blinded to the subject's clinical data, evaluated echocardiographic traces, and two blinded experienced echocardiographists read the echocardiographic records. Echocardiographic examinations were carried out with patients in a partial left decubitus position by a Vivid Seven AB Sound machine (GE, Horten, Norway) equipped with a 2.5-MHz phased-array transducer with harmonic capability, according to the American Society of Echocardiography recommendations (22). Three cardiac cycles were averaged for measurements. Mean blood pressure and pulse pressure were calculated from systolic and diastolic blood pressure, which were measured three times in the left arm by indirect cuff sphygmomanometry after the echocardiographic study, with subjects in supine decubitus (22).

A standard 12-lead electrocardiogram was obtained in each patient. Evidence of LV hypertrophy and conduction and repolarization abnormalities was sought (23). LV M-mode measurements of wall thickness and end-diastolic and end-systolic diameters were obtained according to the Penn convention (24) and used to calculate relative wall thickness and LV mass and to estimate LV end-diastolic and end-systolic volumes with the formula of Teichholz *et al.* (25). The latter estimates were used to derive LV stroke volume and ejection fraction and to compute cardiac output and systemic vascular resistance according to standard formulae (26). LV diastolic function was assessed in the apical four-chamber view. Early and late transmitral peak flow velocities from pulsed-wave Doppler imaging were measured as previously reported (27). The ratio of pulse pressure to stroke volume was used to estimate total arterial stiffness (28).

Statistical analysis

The statistical analysis was performed using SPSS (version 9.0.1 for Windows; Chicago, IL). Data in the text and tables are expressed as mean value and SD. The two-tailed unpaired Student's *t* test was used to compare continuous variables in RTH patients and control subjects. $P < 0.05$ was considered statistically significant.

Results

Patients with RTH (19, 20, 29, 30) and controls were matched by sex, age, and anthropometry, although body weight and body surface area were slightly lower in the former. As expected, RTH patients had significantly higher serum levels of FT_4 and FT_3 associated with mean TSH values in the normal range (Table 1). No correlation was found between cardiovascular features and type of mutation.

At rest, heart rate was similar in RTH patients and controls. However, RTH patients had higher systolic, diastolic and mean arterial pressure than controls but similar pulse pressure. In particular, five patients (31%) had arterial blood pressure in the

TABLE 1. Demographics and thyroid status of RTH patients and control subjects

	Control subjects (n = 16)	RTH patients (n = 16)	*P* value
Sex (male/female)	8/8	9/7	NS
Age (yr)	33 ± 5	33 ± 12	NS
Height (cm)	167 ± 7	165 ± 5	NS
Weight (kg)	66 ± 11	60 ± 10	NS
BMI (kg/m^2)	23 ± 3	22 ± 2	NS
BSA (m^2)	1.73 ± 0.17	1.65 ± 0.17	NS
TSH (mU/liter)	1.7 ± 0.9	2.3 ± 2.2	NS
FT_4 (pmol/liter)	15 ± 3	39 ± 22	<0.05
FT_3 (pmol/liter)	6 ± 1	16 ± 12	<0.05

Data are mean ± SD. BMI, Body mass index; BSA, body surface area; NS, not statistically significant.

hypertensive range (>140/90 mm Hg) (Table 2). The LV end-diastolic diameter index was marginally higher in RTH patients than controls, whereas the LV end-diastolic wall thickness index (evaluated as the mean value of interventricular septum and posterior wall) was lower. Accordingly, the LV mass index and relative wall thickness were slightly but significantly lower in RTH patients (Table 2). Although in normal range, the level of global LV systolic function was lower in RTH patients than in controls, as indicated by the higher LV end-systolic diameter index and the lower LV ejection fraction. Nevertheless, the global LV performance, as expressed by the stroke index, did not differ between the two groups (Table 2).

TABLE 2. Cardiovascular characteristics of RTH patients and control subjects

	Control subjects (n = 16)	RTH patients (n = 16)	*P* value
HR (bpm)	78 ± 7	80 ± 15	NS
SBP (mm Hg)	**117 ± 7**	**124 ± 9**	**<0.05**
DBP (mm Hg)	**73 ± 8**	**81 ± 9**	**<0.01**
MAP (mm Hg)	**87 ± 7**	**95 ± 8**	**<0.01**
PP (mm Hg)	44 ± 7	43 ± 8	NS
LVEDDi (mm/m^2)	27.7 ± 3.4	28.7 ± 3.0	NS
LVESDi (mm/m^2)	**16.9 ± 2.4**	**18.7 ± 2.3**	**<0.05**
LVEDWTi (mm/m^2)	**5.2 ± 0.6**	**4.6 ± 0.6**	**<0.01**
LVMi (g/m^2)	**85 ± 12**	**69 ± 14**	**<0.01**
RWT	**0.38 ± 0.05**	**0.32 ± 0.04**	**<0.001**
LVEF (%)	**69 ± 6**	**63 ± 7**	**<0.05**
SI (%)	42 ± 8	40 ± 8	NS
E (cm/sec)	77 ± 11	70 ± 18	NS
A (cm/sec)	**48 ± 8**	**58 ± 15**	**<0.05**
E/A (kg)	**1.6 ± 0.2**	**1.3 ± 0.4**	**<0.01**
E-dt (msec)	**144 ± 19**	**123 ± 14**	**<0.01**
CI (liters/m^2)	1.73 ± 0.17	1.65 ± 0.17	NS
SVRi (dyne · sec/cm^{-5} · m^2)	**744 ± 160**	**949 ± 253**	**<0.05**
PP/SI (mm Hg/ml · m^2)	1.09 ± 0.32	1.12 ± 0.26	NS

Data are mean ± SD. The *bold* numbers indicate the parameters that are statistically significant between the two groups studied. HR, Heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; LVEDDi, left ventricular end-diastolic diameter index; LVESDi, left ventricular end-systolic diameter index; LVEDWTi, left ventricular end-diastolic wall thickness index (as mean value of interventricular septum and posterior wall); LVMi, left ventricular mass index; RWT, relative wall thickness; LVEF, left ventricular ejection fraction; SI, stroke index; E, early transmitral peak inflow velocity from pulsed-wave Doppler imaging; A, late transmitral peak inflow velocity from pulsed-wave Doppler imaging; E-dt, deceleration time of the early transmitral inflow from pulsed-wave Doppler imaging; CI, cardiac index; SVRi, systemic vascular resistance index; PP/SI, pulse pressure/stroke index (total arterial stiffness); NS, not statistically significant.

The transmitral in flow pattern was normal in both RTH patients and controls, although the early to late peak flow velocity ratio (E/A) of the former was significantly lower, mostly due to a consistent increase in the late component. Indeed, the deceleration time of the early transmitral inflow was shorter in RTH patients, thereby suggesting a mild to moderate global LV diastolic dysfunction (pseudonormalization) in these patients (Table 2). Finally, although the cardiac index and total arterial stiffness (estimated by the pulse pressure to stroke index ratio) were similar in the two groups, the systemic vascular resistance index was higher in RTH patients than in controls (Table 2).

Discussion

In this case-control study, we assessed cardiac morphology and function in 16 patients with RTH compared with euthyroid healthy controls. We selected a homogeneous RTH group of patients without cardiovascular symptoms and untreated with thyroid or cardiovascular drugs to assess the cardiovascular response to TH in RTH syndrome. Our results indicate that this dominantly inherited condition of altered tissue responsiveness to TH is associated with measurable alterations of LV characteristics and circulatory function. These findings reinforce the concept that TH plays an important physiologic role in the cardiovascular system.

Our RTH patients did not have cardiovascular symptoms (palpitations, dyspnea at rest and after exercise), and their heart rate was comparable with control group; this could possibly be a consequence of our inclusion criteria. The percentage of RTH patients showing tachycardia is highly variable in various reports. We found that 75–94% of RTH patients had tachycardia in a previous article (7), whereas Brucker-Davis *et al.* (6) found a comparable resting heart rate between RTH patients and controls. Moreover, resting tachycardia was found in 16% of RTH patients with a percentage similar to that of controls (6); these results could be explained by the complex direct and indirect actions of TH on the heart. In particular, this seems to coincide with the report of a normal heart rate linked to expression of different ion channels in the heart in animal models. In particular, TRβ^{PV} mouse, an animal model of RTH, showed decreased myocardial contractility and heart rate accompanied by decreased expression of the pacemaker-related gene hyperpolarization-activated cyclic nucleotide-gated 4 (15). This gene encodes channels responsible for the slow component of hyperpolarization-activated current, which contributes to pacemaker activity (30). Moreover, the expression of the pacemaker channel hyperpolarization-activated cyclic nucleotide-gated 2 was low in hypothyroid mice but normal in transgenic mice resistant to TH (16). However, it must be underlined that the TRβ^{PV} mouse is homozygous, whereas RTH patients are heterozygous. To clarify the influence of TRβ on cardiac function, another study evaluated the cardiovascular parameters in TRδ

337T, a transgenic mouse model with heterozygous cardiac-specific expression of mutant TRβ. TRδ 337T mice showed a reduced heart rate and a prolongation of electrocardiogram intervals comparable with the results found in hypothyroid mice and a decreased myocardial contractility, suggesting an impairment of cardiac-specific genes regulated by TH. In particular, the TRδ 337T mice showed a hypothyroid pattern of myosin heavy chain gene expression (14).

However, we found that mean interventricular septum diastolic thickness and mean LV posterior wall diastolic thickness were significantly lower in RTH patients than controls. Consequently, the mean LV mass and LV mass index were significantly decreased, suggesting the presence of reduced TH effects during heart development. Indeed, TH can stimulate myocardial growth (32, 33), and an increase of LV mass has been reported in hyperthyroid patients (20, 34–36). However, the effect of TH on myocardial growth/gene expression is result of the complementary and antagonistic actions of the three TR isoforms found in the heart. TRβ seems to inhibit activation of p38 (37), which is frequently associated with cardiac hypertrophy, whereas prolonged TH absence significantly reduces cardiomyocyte diameter (38). In animal models of RTH, mutant TRβ prevented TH-induced cardiac hypertrophy (39, 40), suggesting that it interfered with the function of normal TR and induced hypothyroidism in the heart of the transgenic mice. Finally, studies of the genomic effects of TH on the cardiovascular system showed that RTH and hyperthyroid hearts were molecularly different. Indeed, RTH mice had a discordant cardiac expression of the T_3-responsive gene compared with the wild-type, which suggests inappropriate regulation of T_3-modulated genes in RTH syndrome (41).

Furthermore, myocardial relaxation was deranged in our RTH patients. In fact, they had a significant increase of peak A and consequent reduction of the E/A ratio, like patients with overt and subclinical thyroid hormone deficiency (27). These abnormalities in subclinical and overt hypothyroidism result from impaired diastolic function related to the reduced sarcoplasmic reticulum calcium-ATPase activity with consequent impairment of ventricular diastolic function caused by low circulating levels of TH (19, 20).

Finally, systemic vascular resistance was significantly higher in our RTH patients than in the control group, which indicates a reduced action of TH in the vascular system. Indeed, TH directly affects arterial smooth muscle relaxation, which leads to a reduction in systemic vascular resistance (29, 42–44). Furthermore, endothelium-dependent vasodilatation and nitric oxide availability were reduced hypothyroid rats and humans (30).

Our results are apparently different from a previous study by Kahaly *et al.* (18) in which an heterogeneous RTH group showed some cardiovascular alterations similar to those found in hyperthyroid subjects, whereas other cardiovascular parameters were comparable with controls. In fact, it is difficult to compare our patients with the RTH group evaluated by Kahaly *et al.* because we used different selection criteria. Indeed, the RTH group by Kahaly *et al.* included patients with and without thyrotoxic cardiovascular symptoms, some patients treated with levothyroxine or antithyroid drugs and patients with a wide age range, including children. Furthermore, Kahaly *et al.* only compared the data of two distinct RTH groups (with and without thyrotoxic cardiovascular symptoms) without comparing them to euthyroid subjects; they compared the results of the entire RTH group only with those of euthyroid, hypothyroid, and hyperthyroid subjects. Interestingly, this study led us to try to clarify the cardiovascular characteristics of asymptomatic RTH patients compared with a group of well-matched euthyroid controls. Therefore, we selected a homogeneous RTH group of young and middle-aged patients (age range 21–45 yr), without thyrotoxic cardiovascular symptoms and untreated with thyroid or cardiovascular drugs. Our strict selection criteria likely created a bias in the inclusion of a particular type of RTH patients, who could represent a minority of patients with RTH. In fact, the type of mutations in our patients are different from those reported by Kahaly *et al.*; indeed, 10 of our subjects with RTH had R243Q, A317T, G344E, V394L, and E445K mutations, which were not present in any of the patients of Kahaly *et al.* Only three of our patients shared the same mutations as those reported by Kahaly (R338W and R438C). However, interestingly, in accordance with the results reported by Kahaly *et al.*, we found no correlation between the type of mutation and cardiovascular characteristics of RTH patients.

These results could be the consequence of the characteristic phenotypic variability of RTH syndrome, which is related to aspects different from the TR mutations. Moreover, clinical features of RTH can differ among affected individuals of a kindred harboring the same mutation (1, 2, 4). Furthermore, genetic analyses have demonstrated different mutations in patients with the same clinical phenotype (21). There is a significant temporal variation in clinical signs and in parameters of TH action in the same individuals (7). Therefore, the difference of results in two studies seems to confirm the absence of specific and diagnostic clinical characteristic and the extreme variability and heterogeneity of clinical manifestations in RTH syndrome.

In conclusion, our results support the concept that TH plays an important physiological role in the development of the cardiovascular system and suggest the presence of cardiovascular alterations in untreated and asymptomatic RTH patients similar to those reported in hypothyroid patients.

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