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ORIGINAL ARTICLE

Hyperthyroidism Associated Congestive Heart Failure: A Case-Control Study

Papi G[a], Chesi G[b], Corsello SA[c], Di Donato C[a], Milite MT[a], Vittoria Ciardullo AV[a], Pontecorvia A[c], Roti E[d]

[a]Department of Internal Medicine, Azienda USL Modena, [b]Department of Internal Medicine, Azienda USL Reggio Emilia, [c]Chair of Endocrinology, Catholic University of Rome, and [d]Internal Medicine Unit, Suzzara Hospital SpA HSS, Suzzara (MN), Italy

Hyperthyroidism has been associated with cardiomyopathy and heart failure (HF). This study aims to evaluate clinical, laboratory and echocardiographic parameters, at admission and 12 months following euthyroidism restoration, in patients with hyperthyroidism-associated HF. Mechanisms underlying hyperthyroidism-associated HF and the outcomes of echocardiographic parameters along the study period are both discussed.

Materials & Methods: Patients with newly diagnosed overt hyperthyroidism and HF (Group 1), age and sex-matched euthyroid HF subjects (Group 2), and a control group were enrolled.

Results: In the 38-month study period, 56 patients were admitted for hyperthyroidism-associated HF, of whom 71% had a pre-existing, mainly hypertensive, cardiomyopathy vs 68% of Group 2 subjects. Mean heart rate was significantly higher in Group 1 than Group 2 (127±38 vs 110±17bpm; P <0.02); 30 Group 1 (54%) and 16 (29%) Group 2 patients presented with atrial fibrillation. At admission, left ventricular ejection fraction (LVEF), end diastolic (LVEDD) and end systolic (LVESD) diameters were lower, whilst LV mass (LVM), interventricular septum thickness (IVST) and LV posterior wall thickness (LVPWT) were increased in both Groups compared to controls. At the end of the study, despite achievement of euthyroidism in all hyperthyroid patients, mean LVEF was not significantly different in Group 2 but was significantly lower in Group 1 patients compared to controls; LVM, IVST and LVPWT did not change in both study groups.

Conclusion: In our series, newly diagnosed hyperthyroidism-associated HF had 2.4% prevalence. At the end of the study, LVEF significantly improved in euthyroid, but not in hyperthyroidism-associated HF patients compared to controls.

Correspondence: Dr. Giampaolo Papi, Dipartimento di Medicina Interna Azienda USL Modena, Ospedale "Ramazzini", Via S. Giacomo, 2
E-mail: papigiampaolo@hotmail.com

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Introduction

Thyroid hormones exert their action ubiquitously throughout the body. The effects of thyroid hormones, particularly tri-iodothyronine (T3), on the heart have been extensively studied, and consist of several genomic and non-genomic actions, ultimately leading to an increase in heart rate, cardiac contractility, and cardiac output.[1] Thyrotoxicosis, both overt[2,3] and subclinical,[4] is a well-defined entity characterized by serum thyroid hormone concentrations exceeding the body's physiological demand.

Several studies[5-10] have been conducted in patients with both exogenous (e.g. induced by L-thyroxine TSH-suppressive therapy) and endo-

genous thyrotoxicosis, to investigate the adverse effects of thyroid hormone excess on the cardiovascular system. Tachycardia and atrial arrhytmias are frequently observed in the thyrotoxic state.[8] Nonetheless, in patients with long-lasting hyperthyroidism, both an increased left ventricular mass and a diastolic dysfunction have been demonstrated by echocardiography.[11,12] Thyrotoxicosis may even precipitate myocardial infarction and heart failure (HF) in individuals suffering from ischemic heart disease or other preexisting cardiomyopathies, increasing myocardial oxygen demand and contractility.[13-17]

To our knowledge, few studies have been performed so far, assessing the prevalence of hyperthyroidism in patients hospitalized because of HF;[18] in most cases, available data on the clinical, biochemical and echocardiographic features of subjects with hyperthyroidism-induced HF derive from case reports.[19-22]

The present multicenter study was designed to assess retrospectively the clinical, laboratory, and echocardiographic parameters in a series of patients presenting with HF and newly diagnosed endogenous hyperthyroidism, compared to subjects with HF, not associated to hyperthyroidism and a control group by: 1. Assessing the prevalence and clinical, biochemical and ecochardiographic features in patients admitted to hospital for HF and newly diagnosed endogenous hyperthyroidism; 2. Evaluating differences in echocardiographic parameters 12 months following the restoration of the euthyroid state; 3. Comparing data with age, sex, and BMI-matched patients with HF and normal thyroid function.

Materials and Methods

All patients referred for newly-diagnosed heart failure (HF) to Policlinico (Polyclinic)"A. Gemelli" of Rome, Ramazzini Hospital of Carpi (Modena) and Civil Hospital of Scandiano (Reggio Emilia), Italy, between October 2003 and December 2006, were assessed for measurement of serum thyrotropin (TSH), free-thyroxine (FT4) and free-triiodothyronine (FT3) concentrations. Individuals with overt thyrotoxicosis, defined by serum TSH concentrations less than 0.1 mIU/l and serum FT4 and/or FT3 concentrations above the upper limit of normal range were included in the study. Subjects with previous history of hyperthyroidism, as well as those on L-thyroxine therapy, were excluded from the study.

During the 38-month period of the study, a total of 108 subjects were admitted for HF associated with overt thyrotoxicosis. Of these 108 subjects, 52 were excluded from the study, because of the following reasons: Eleven patients were on L-thyroxine replacement and TSH-suppressive therapy for hypothyroidism and thyroid nodules, respectively; 27 had previously been diagnosed as hyperthyroid; data obtained from 14 individuals were incomplete and unsatisfactory. Therefore, only 56 hyperthyroid subjects (Group 1) were definitively included in the study. Fifty-six age and sex-matched euthyroid patients admitted for HF (Group 2) and 56 age, sex, and BMI-matched healthy controls were also included in the study.

Beside thyroid function tests, the following data were also obtained on admission in patients of Groups 1 and 2: Patient's age and sex; signs and symptoms of HF; heart rate; systolic (SBP) and diastolic (DBP) blood pressure; serum haemoglobin, creatinine, transaminase, glucose, and total cholesterol concentrations; electrocardiography (ECG) and echocardiography. In Group 1 subjects, serum TSH, FT4 and FT3 concentrations were also measured 1 and 3 months after discharge from the hospital and 12 months after the restoration of the euthyroid state. In both Group 1 and Group 2 patients, ECG and echocardiography were repeated 12 months following the restoration of euthyroidism and 12 months after discharge from the hospital, respectively. Control group subjects were recruited in both the outpatient clinics of Endocrinology, where they were referred for euthyroid nodular goiter. Inclusion criteria were

the following: No previous history of thyroid and heart diseases, diabetes, dyslipidemia and hypertension. Control subjects were submitted to the measurement of serum TSH, FT4, FT3, haemoglobin, creatinine, transaminase, glucose, and total cholesterol concentrations, and ECG; echocardiography. All subjects were alive at the end of the study.

Serum TSH (normal range: 0.4-4 mIU/L; sensitivity: 0.005 mIU/l), FT4 (normal range: 8-18 pg/mL) and FT3 (normal range: 2-4.5 pg/mL) concentrations were measured using an electrochemiluminescence immunoassay. Serum haemoglobin (normal range: 12-16 g/dL), glucose (normal range: 70-110 mg/dL), creatinine (0.6-1.4 mg/dL) and total cholesterol (<250 mg/dL) concentrations were determined by routine assays. The diagnosis of Graves' Disease (GD) was established if hyperthyroidism was associated with diffuse radionuclide uptake at a thyroid scan performed with either 99mTechnetium or 131Iodine and/or elevated serum TSH-receptor autoantibodies. A diagnosis of Toxic Nodular Goiter (TNG) was associated with detection of hot nodule(s) at thyroid scan performed with either 99mTechnetium or 131Iodine. Body mass index (BMI) was calculated using the following formula: BMI=weight (Kg)/height squared (m2). The standard 12-lead ECG was performed by Archimed 4220, Esaote Biomedica, electrocardiograph. Electrocardiographic left ventricular (LV) hypertrophy was defined according to the chest lead score systems described by Romhilt and Estes[23] and Casale et al.[24] Complete M-mode and two-dimensional Doppler echocardiographic analysis was performed through a 3.5-MHz transducer utilizing the commercially available ultrasound mechanical system Sonos 1000 (Hewlett Packard). The following parameters were assessed: LV end-diastolic (LVEDD) and end-systolic (LVESD) diameters, LV posterior wall thickness (LVPWT), interventricular septum thickness (IVST). LV mass (LVM) was calculated using the following formula: LVM=1.04[(IVST+LVEDD+LVPWT)3–(LVEDD) 3]-14 g.[25] The LV ejection fraction (LVEF) was calculated by the Simpson's method, i. e., the percent difference between the diastolic and the systolic volume of the LV, both derived from the measurement of LV's area and length.

Statistical analysis

Results are reported as mean±standard deviation (SD) for continuous variables and as number plus percentage for categorical variables. Laboratory and ecochardiographic data were compared using paired and unpaired (two-tailed) Student's t-test. Statistical significance was taken as $P < 0.05$. All statistics were conducted using the STATA package, release 9.0.

Results

During the 38-month period of the study, 2368 patients were admitted to hospital for the first time, due to HF. Of them, 56 (2.4%) had newly diagnosed hyperthyroidism (Group 1), 8 were (14%) males and 48 (86%) females (male to female ratio of 1:6), with a mean age of 66±10.9 yrs (range 48-82 yrs, median 66 years). Twenty-six patients had GD and 30 TNG. Of these patients, 40 (71%) had a history of cardiomyopathy, consequent to hypertension in 36 cases, and idiopathic in the remaining 4 cases. Six individuals were smokers; 12 had type 2 diabetes mellitus treated with sulphanylureas. Of group 2 patients, 38 (68%) had a previous diagnosis of cardiomyopathy, hypertensive in 32 cases, idiopathic in 6 cases; 8 subjects were smokers and 10 were taking sulphanylureas for type 2 diabetes mellitus. Table 1 summarizes anthropometric data and laboratory results at admission in patients of groups 1 and 2, compared to control subjects. Table 2 shows the presenting signs and symptoms of HF at admission in both patient groups. Mean heart rate was significantly higher in group 1 (127±38 bpm) than in group 2 (110±17bpm, $P<0.02$).

Table 1. Clinical characteristics and laboratory results at admission in patients with HF associated (Group 1) or not associated (Group 2) to hyperthyroidism, compared to controls.

	Group 1	Group 2	P	Controls
Age (yrs)	66±10	67±12	NS	66±9*
Sex	48F, 8 M	48 F, 8 M	-	48 F, 8M
BMI	28±4	31±5	<0.05	29±3*
SBP (mmHg)	164±19	159±20	<0.05	130±11†
DBP (mmHg)	88±11	96±12	<0.05	77±4†
HR (bpm)	127±38	110±17	<0.02	76±6†
NYHA class	2.6±0.8	2.5±0.7	NS	-
TSH (mIU/L)	<0.1	2.4±0.9	<0.001	2.2±1.0‡
FT4 (pg/mL)	28.2±8	12.3±2.4	<0.001	12.0±2.2‡
FT3 (pg/mL)	6.7±1.9	2.1±0.5	<0.001	2.3±0.4‡
Hb (g/dL)	13.8±0.9	13.0±0.8	NS	14.0±0.6*
Glycemia (mg/dL)	130±22	127±18	NS	92±8†
Creatinine (mg/dL)	0.9±0.3	1.5±0.4	<0.05	0.9±0.4*
Cholesterol (mg/dL)	218±30	216±25	NS	204±18*

BMI: body mass index; DBP: diastolic blood pressure; FT3: free-tri-iodothyronine; FT4: free-thyroxine; Hb: haemoglobin; HR: heart rate; NYHA: New York Heart Association; SBP: systolic blood pressure; TSH: thyrotropin. *P=NS vs Group 1 and Group 2; †P<0.001 vs Group 1 and Group 2; ‡ P<0.001 vs Group 1, NS vs Group 2.

Table 2. Frequency of clinical features in patients admitted for HF associated (Group 1) or not associated (Group 2) to hyperthyroidism, at admission.

Sign/symptom	Group 1	Group 2
Dyspnea	56 (100)	56 (100)
Weight loss	28 (50)	0 (0)
Weight gain	20 (36)	56 (100)
Edema	26 (46)	34 (61)
Proptosis	16 (29)	0 (0)
Tremors	14 (25)	8 (14)
Gastrointestinal symptoms*	10 (18)	2 (4)

* Abdominal discomfort or pain, meteorism, diarrhea.

Thirty group 1 (54%, 16 with TNG and 14 with GD) and 16 (29%) group 2 subjects presented with atrial fibrillation. ECG signs of LV hypertrophy were disclosed in 34 (61%) group 1 and 30 (54%) group 2 patients. Ischemic heart disease was diagnosed by bicycle ergometry stress test and coronarography in 8 (14%) group 1 and 10 (18%) group 2 patients. Results of echocardiographic examination at admission in both study groups compared to control subjects are reported in Table 3. A dilated cardiomyopathy was found in 26 (46%) group 1 and 20 (36%) group 2 patients; LVEF was lower than 40% in 40 (71%) group 1 (22 with TNG and 18 with GD) and 38 (68%) group 2 subjects. Twenty group 1 and 19 group 2 patients; presented with severely depressed systolic function. At admission, all patients were given enalapril, bisoprolol, and anti-aggregation agents (acetiyl-salicilic acid or ticlopidin); Group 1 patients were also given anti-thyroid agents (methimazole or propylthiouracile). Two months later, 42 (75%) subjects, of whom 12 with TNG refused treatments different from methimazole, were still continuing with anti-thyroid agents, whilst 14 (25%) were submitted to radioiodine (131I) therapy. Three months following discharge, all group 1 and group 2 patients, except for 2 showed sinus rhythm; in subjects with atrial fibrillation, sinus rhythm recovered spontaneously in 12 patients (10-group 1, 2-group 2), after antiarrhythmia agents (i. e., propafenone or amiodarone) in 12 group 2 patients and after

electric countershock following anticoagulant plus digoxin therapy in 20 patients (18-group 1, 2-group 2). Both GD and TNG patients had normal serum FT3 (3.7±1.5pg/mL; P <0.001 vs. admission) and FT4 concentrations (13±2 pg/mL; P <0.001 vs. admission); serum TSH concentrations were in the normal range in 26 patients, undetectable in 24 patients, and above the upper limit of normal range in 6 patients. At the end of follow-up, all Group 1 and Group 2 subjects were euthyroid; only 2 (1-group 1, 1-group 2) subjects still had atrial fibrillation. LVEF exceeded 50% in only 4 (all affected by GD) out of 20 group 1 and in 10 out of 19 group 2 patients with severely depressed systolic function at admission. Results of echocardiographic study at the end of follow-up in patients of groups 1 and 2, compared to control subjects, are reported in Table 3.

Table 3. Results of echocardiography, at admission and at the end of the study, in patients admitted for HF either associated to hyperthyroidism (Group 1) or in euthyroid state (Group 2), compared to Controls

	Group 1		Controls	Group 2	
	Admission	12 months		Admission	12 months
LVEF (%)	39±9	46±10 (P<0.001)	67±7*	40±9	56±9 (P<0.001)†
LVM (gr)	150±11	151±11 (P=NS)	132±12‡	150±10	149±8 (P=NS)
LVEDD (mm)	46±4	50±4 (P<0.02)	50±3§	48±4	51±4 (P<0.02)†
LVESD (mm)	30±4	33±3 (P<0.001)	32±3¶	33±3	32±2 (P=NS)†
IVST (mm)	10±2	9.9±2 (P<0.05)	9.2±2‖	9.8±2	9.6±1 (P=NS)
LVPWT (mm)	10±1	9.4±1 (P=NS)	8.7±1**	9.2±1	9.2±1 (P=NS)†

IVST: interventricular septum thickness; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: left ventricular end systolic diameter; LVM: left ventricular mass; LVPWT: left ventricular posterior wall thickness. *P<0.001 vs Group 1 at admission and at end of study, and vs Group 2 at admission; P=NS vs Group 2 at end of study. †P<0.05 vs Group 1. ‡P<0.001 vs both Groups 1 and 2, at admission and end of study. §P<0.001 vs Group 1 at admission; P<0.02 vs Group 2 at admission; P=NS vs Groups 1 and 2 at end of study. ¶P<0.001 vs Group 1 at admission; P<0.02 vs Group 2 at admission; P=NS vs Groups 1 and 2 at end of study. ‖P<0.001 vs Group 1 at admission and end of study; P<0.003 vs Group 2 at admission, P<0.05 vs Group 2 at the end of the study. **P<0.001 vs Group 1 at admission; P<0.05 vs Group 1 at end of study; P<0.02 vs Group 2 at admission and end of study.

Discussion

This work reports the clinical and echocardiographic features of patients admitted for newly diagnosed endogenous hyperthyroidism and HF, compared to age- and sex-matched euthyroid HF patients and to healthy subjects.

In the present study, a previously unknown endogenous thyrotoxicosis was diagnosed in 2.4% of patients admitted to hospital for the first time because of HF. It should be highlighted that our series included only patients with GD and TNG.

Clinical and biochemical data

Contrary to the clinical picture peculiar to HF, i. e., dyspnea and edema associated with weight gain, a weight loss was recorded in half the patients of group 1 of our series. As a result, group 1 subjects had a lower BMI than those of group 2; this feature, which may be explained by thyroid hormone-related increase in basal metabolism and waste of

muscles and fat,[26] may help to distinguish hyperthyroid-associated from thyroid-independent HF. Further clinical characteristics of hyperthyroid-associated HF are represented by tremors and proptosis, which are not usually present in euthyroid subjects admitted for HF.

In both group 1 and group 2 patients of our series, both the mean plasma glucose concentrations and the mean blood pressure values were significantly higher compared to control subjects. Diabetes is a well-defined cardiovascular risk factor causing cardiac changes known as "diabetic cardiomyopathy", characterized by systolic and, mostly, diastolic dysfunction.[27] Chronic arterial hypertension and the consequent cardiac hypertrophy finally induce the fibrotic degeneration of the heart.[28] It might be hypothesized that both high plasma glucose concentrations and elevated blood pressure values contributed to the development of pathological changes in the myocardium, finally precipitating HF in both patient groups of our series. Overall, more than two-thirds of HF patients of our series had a pre-existing cardiomyopathy, mainly consequent to arterial hypertension. Persistently elevated values of systolic and diastolic blood pressure invariably lead to myocardial hypertrophy and increased heart weight.[29] In group 1 patients, hyperthyroidism intervened in such a compromised cardiocirculatory state with major pathophysiological implications. Cardiac changes in patients with thyrotoxicosis have been extensively described.[30-34] Thyroid hormones stimulate the beta-receptors located on myocyte surface inducing an increase in heart rate and myocardial contractility and, consequently, in minute stroke work. Tachycardia, deriving from both a direct chronotropic and an indirect adrenergic effect of thyroid hormones on the heart,[32-34] is one of the most common symptoms of thyrotoxicosis. This hyperdynamic heart, on the one hand, augments arterial pressure through addition of the reflected pressure wave (altered in time for the reduction of systole time) to forward pressure wave;[13] on the other hand, it implicates a reduced pre-load, in that elevated heart rate reduces diastolic filling time. The final result of these pathophysiological events is that the performance of hyperthyroid heart strongly depends on the atrial systole. In patients with pre-existing cardiomyopathy, in particular diastolic dysfunction, as most group 1 individuals of our series, the development of thyrotoxicosis increases the heart rate and overcomes the possibility of compromised myocardium of responding to an increased oxygen demand and contractility; as a consequence, HF manifests. Indeed, at admission, group 1 patients presented with a mean heart significantly higher than both group 2 and control subjects; more importantly, the majority of them (54%) had an atrial fibrillation, that was present in only 29% of group 2 subjects. Previous studies.[8,33] demonstrated a higher incidence of atrial fibrillation in elderly people with hyperthyroidism, even in patients with TSH suppression per se.[3] In their series of hyperthyroid patients with HF, Siu et al[18] reported up to 94% incidence of atrial fibrillation. We conclude that, contrary to euthyroid group 2 subjects, in our group 1 patients, HF was most likely triggered by elevated heart rate in the context of pre-existing compromised myocardium.

Echocardiographic features

Echocardiographic parameters obtained in our study displayed intriguing differences between patients with hyperthyroid-associated HF compared to euthyroid HF subjects and control individuals. In particular, the following results are of special interest.

As highlighted by decreased values of LVEF, LVEDD and LVESD, a left ventricular systolic and diastolic dysfunction was present either in patients with hyperthyroid-associated HF and in euthyroid HF subjects at admission. However, despite similar initial LVEF, group 1 patients presented with LVEDD and LVESD significantly lower than group 2 individuals. Such features may be caused by the impaired left ventricular diastolic filling due to elevated heart rate consequent to thyroid hormone excess.[13] On the

contrary, in subjects with thyrotoxicosis, in the absence of clinical signs and symptoms of HF, LVEF is usually elevated,[7,13] as the result of increased myocardial contractility related to the regulation of calcium concentrations in the myocytes by thyroid hormones.[35] Nonetheless, in the hyperthyroid heart, both an early ventricular filling and a faster diastolic relaxation independent of heart rate have been observed, leading to a more efficient (i. e., energy-sparing) diastolic function.[7,13] Interestingly - although normal thyroid hormone concentrations were finally achieved in all group 1 subjects after treatment of hyperthyroidism, appropriate therapy for HF was administered in both study groups, and sinus rhythm recovered in all cases - at the end of the study, compared to controls, mean LVEF was not significantly different in group 2 but was still significantly lower in Group 1 patients. Persistently impaired left ventricular systolic function in group 1 might derive from concurrent thyroid hormone and arterial hypertension action on myocyte pathophysiology. Initially, both improve cardiac performance, the former by increasing myocardial contractility through direct inotropic effect,[36,37] the latter by increasing afterload through augmented systemic vascular resistance.[38] Subsequently, down-regulation and reduced affinity of beta-receptors, as well as fibrotic involution of myocardium, occur both in long-lasting arterial hypertension and in persistent thyrotoxicosis (e. g., by toxic nodular goiter).[39] It might be speculated that thyroid hormone excess worsens, and in most cases renders, non-reversible myocyte damage caused by high blood pressure levels.

As demonstrated by elevated mean LVM, LVPWT and IVST indices, cardiac mass was significantly higher in group 1 and group 2 patients than in control individuals, and did not improve at the end of follow-up. Again, these features reflect the sustained increase in cardiac workload due to persistent arterial hypertension and, in group 1, also to hyperthyroidism.[13] A peculiar characteristic of our group 1 patients was a significantly higher hyperthyroid-related LVPWT index than that of group 2 individuals at admission that was reverted by achievement of euthyroidism.

In conclusion, the present study has investigated clinical and imaging data, at admission and 12 months after restoration of euthyroidism, in patients admitted for both HF and newly diagnosed thyrotoxicosis, compared to euthyroid HF subjects. In our series, HF associated to hyperthyroidism had a prevalence of 2.4%. Compared to euthyroid HF subjects, at admission hyperthyroid HF patients typically manifested higher heart rate, mostly due to atrial fibrillation, and weight loss rather than weight gain as well. Similar to euthyroid HF individuals, most hyperthyroid HF patients presented with severely depressed LVEF, which in a few cases, eventually improved at the end of the study, whereas this did not happen in the euthyroid group.

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References

1. Klein I, Ojama K. Thyroid hormone and the cardiovascular system. N Engl J Med 2001; 344: 501-8.
2. Larsen PR, Davies TF. Thyrotoxicosis. In: Larsen PR, Kronenberg HM, Melmed S, editors. Williams' textbook of endocrinology. 10th edition. Philadelphia: WB Saunders Co; 2002. p. 374-421.
3. Nayak B, Hodak SP. Hyperthyroidism. Endocrinol Metab Clin North Am 2007; 36: 617-56.
4. Papi G, Pearce EN, Braverman LE, Betterle C, Roti E. A clinical and therapeutic approach to thyrotoxicosis with thyroid-stimulating hormone suppression only. Am J Med 2005; 118: 349-61.

5. Klein I, Ojama K. Thyrotoxicosis and the heart. Endocrinol Metab Clin North Am 1998; 27: 51-62.
6. Osman F, Gammage MD, Sheppard MC, Franklyn JA. Clinical review 142: cardiac dysrythmias and thyroid dysfunction: the hidden menace? J Clin Endocrinol Metab 2002; 87: 963-7.
7. Biondi B, Palmieri EA, Lombardi G, Fazio S. Effects of subclinical thyroid dysfunction on the heart. Ann Int Med 2002; 137: 904-14.
8. Auer J, Sheibner P, Mische T, Langsteger W, Eber O, Eber B. Subclinical hyperthyroidism as a risk factor for atrial fibrillation. Am Heart J 2001; 142: 838-42.
9. Donatelli M, Assennato P, Abbadi V, Bucalo ML, Compagno V, Lo Vecchio S, et al. Cardiac changes in subclinical and overt hyperthyroid women: retrospective study. Int J Cardiol 2003; 90: 159-64.
10. Walsh JP, Bremner AP, Bulsara MK, O'Leary P, Leedman PJ, Feddema P, et al. Subclinical thyroid dysfunction as a risk factor for cardiovascular disease. Arch Inter Med 2005; 165: 2467-72.
11. Mercuro G, Panzuto MG, Bina A, Leo M, Cabula R, Petrini L, et al. Cardiac function, physical exercise capacity, and quality of life during long-term thyrotropin-suppressive therapy with levothyroxine: effect of individual dose tailoring. J Clin Endocrinol Metab 2000; 85: 159-64.
12. Biondi B, Palmieri EA, Fazio S, Cosco C, Nocera M, Saccà L, et al. Endogenous subclinical hyperthyroidism affects quality of life and cardiac morphology and function in young and middle-aged patients. J Clin Endocrinol Metab 2000; 85: 4701-5.
13. Biondi B, Palmieri EA, Lombardi G, Fazio S. Effects of thyroid hormone on cardiac function: the relative importance of heart rate, loading conditions, and myocardial contractility in the regulation of cardiac performance in human hyperthyroidism. J Clin Endocrinol Metab 2002; 87: 968-74.
14. Pingitore A, Iervasi G. Triiodothyronine (T3) effects on cardiovascular system in patients with heart failure. Recent Pat Cardiovasc Drug Discov 2008; 3: 19-27.
15. Conen D, Melly L, Kaufmann C, Bilz S, Ammann P, Schaer B, et al. Amiodarone-induced thyrotoxicosis: clinical course and predictors of outcome. J Am Coll Cardiol 2007; 49: 2350-5.
16. Klein I, Danzi S. Thyroid disease and the heart. Circulation 2007; 116: 1725-35.
17. Ngo AS, Lung Tan DC. Thyrotoxic heart disease. Resuscitation 2006; 70: 287-90.
18. Siu CW, Yeung CY, Lau CP, Kung AW, Tse HF. Incidence, clinical characteristics and outcome of congestive heart failure as the initial presentation in patients with primary hyperthyroidism. Heart 2007; 93: 483-7.
19. Boccaladro C, Boccalandro F, Orlander P, Wei CF. Severe reversible dilated cardiomyopathy and hyperthyroidism: case report and review of the literature. Endocr Pract 2003; 9: 140-6.
20. Kalelioglu IH, Has R, Cigerli E, Kalelioglu IH, Has R, Cigerli E, et al. Heart failure caused by thyrotoxicosis in pregnancy pregnancy--case report. Clin Exp Obstet Gynecol 2007; 34: 117-9.
21. Park JH, Shong M, Lee JH, Choi SW, Jeong JO, Seong IW. Reversible severe tricuspid regurgitation with right heart failure associated with thyrotoxicosis. Thyroid 2006; 16: 813-4.
22. Syriou V, Plastiras SC, Paterakis T, Moyssakis I, Vlachoyiannopoulos P. Severe reversible right heart failure in a patient with hyperthyroidism. Int J Clin Pract 2008; 62: 334-6.
23. Romhilt DW, Estes EH. A point-score system for the ECG diagnosis of left ventricular hypertrophy. Am Heart J 1986; 75: 752-8.
24. Casale PN, Devereux RB, Kligfield P, Eisenberg RR, Miller DH, Chaudhary BS, et al. Electrocardiographic detection of left ventricular hypertrophy: development and prospective validation of improved criteria. J Am Coll Cardiol 1985; 6: 572-80.
25. Devereux RB. Detection of left ventricular hypertrophy by M-mode echocardiography: anatomic validation, standardization and comparison to other methods. Hypertension 1987; 9 Suppl 2: 19-26.
26. Botella-Carretero JI, Alvarez-Blasco F, Sancho J, Escobar-Morreale HF. Effects of thyroid hormones on serum levels of adipokines as studied in patients with differentiated thyroid carcinoma during thyroxine withdrawal. Thyroid 2006; 16: 397-402.
27. Aneja A, Tang WH, Bansilal S, Garcia MJ, Farkouh ME. Diabetic cardiomyopathy: insights into pathogenesis, diagnostic challenges, and therapeutic options. Am J Med 2008; 121: 748-57.
28. Dìez J, Gonzàlez A, Lòpez B, Querejeta R. Mechanisms of disease: pathologic structural remodeling is more than adaptive hypertrophy in hypertensive heart disease. Nat Clin Pract Cardiovasc Med 2005; 2: 209-16.
29. Vitti P, Rago T, Tonacchera M, Pinchera A. Toxic multinodular goiter in the elderly. J Endocrinol Invest 2002; 25: 16-8.
30. Dörr M, Wolff B, Robinson DM, John U, Lüdemann J, Meng W, et al. The association of thyroid function with cardiac mass and left ventricular hypertrophy. J Clin Endocrinol Metab 2005; 90: 673-7.
31. von Olshausen K, Bischoff S, Kahaly G, Mohr-Kahaly S, Erbel R, Beyer J, et al. Cardiac arrhythmias and heart rate in hyperthyroidism. Am J Cardiol 1989; 63: 930-3.
32. Cacciatori V, Bellavere F, Pezzarossa A, Dellera A, Gemma ML, Thomaseth K, et al. Power spec-

tral analysis of heart rate in hyperthyroidism. J Clin Endocrinol Metab 1996; 81: 2828-35.
33. Sawin CT, Geller A, Wolf PA, Belanger AJ, Baker E, Bacharach P, et al. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. N Engl J Med 1994; 331: 1249-52.
34. Dillmann WH. Biochemical basis of thyroid hormone action in the heart. Am J Med 1990; 88: 626-30.
35. Klein I. Endocrine disorders and cardiovascular disease. In: Zipes DP, Libby P, Bonow R, Braunwald E, editors. Braunwald's Heart Disease: A Textbook of cardiovascular Medicine. 7th ed. Philadelphia: W.B. Saunders; 2005. P. 2051-65.
36. Meìllon JP, Passa P, Chastre J, Wolf A, Gourgon R. Left ventricular function and hyperthyroidism. Br Heart J 1981; 46: 137-43.
37. Feldman T, Borow KM, Sarne DH, Neumann A, Lang RM. Myocardial mechanics in hyperthyroidism: importance of left ventricular loading conditions, heart rate and contractile state. J Am Coll Cardiol 1986; 7: 967-4.
38. Borlaug BA, Melenovsky V, Redfield MM, Kessler K, Chang HJ, Abraham TP, et al. Impact of arterial load and loading sequence on left ventricular tissue velocities in humans. J Am Coll Cardiol 2007, 50: 1570-7.
39. Swynghedaw B. Molecular mechanisms of myocardial remodeling. Physiol Rev 1999, 79: 215-62.