CLINICAL STUDY

Diagnosis of subclinical central hypothyroidism in patients with hypothalamic–pituitary disease by Doppler echocardiography

Fabio Casanova Doin¹, Mariana Rosa-Borges², Manoel R A Martins², Valdir A Moisés¹ and Julio Abucham²

¹Cardiology Division, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, Brazil and ²Neuroendocrine Unit, Endocrinology Division, Escola Paulista de Medicina, Universidade Federal de São Paulo, Rua Pedro de Toledo 910, 04039-002 São Paulo, Brazil

(Correspondence should be addressed to J Abucham; Email: julioabucham@uol.com.br)

Abstract

Objective: The diagnosis of subclinical central hypothyroidism in hypothalamic–pituitary patients cannot be established by serum markers of thyroid hormone action. Myocardial function by echocardiography has been shown to reflect thyroid hormone action in primary thyroid dysfunction. We evaluated the performance of echocardiography in diagnosing subclinical central hypothyroidism.

Design: Cross-sectional and before and after.

Methods: Echocardiography and serum thyroid hormones were assessed in overt primary ($n=20$) and central ($n=10$) hypothyroidism, subclinical primary hypothyroidism ($n=10$), hypothalamic–pituitary disease with normal free thyroxine (FT_4 ; $n=25$), and controls ($n=28$). Receiver operating characteristic (ROC) curves were generated using overt hypothyroidism patients and selected cut-off values were applied to detect both primary and central subclinical hypothyroidism. After levothyroxine ($L-T_4$) intervention, patients were echocardiographically reevaluated at predefined targets: normal thyrotropin (TSH) in primary hypothyroidism, normal FT_4 in overt central hypothyroidism, and higher than pretreatment FT_4 in echo-defined subclinical central hypothyroidism.

Results: Parameters with highest areas under the ROC curves (area under the curve (AUC) ≥ 0.94) were as follows: isovolumic contraction time (ICT), ICT/ejection time (ET), and myocardial performance index. Highest diagnostic accuracy (93%) was obtained when at least one parameter was increased (positive and negative predictive values: 93%). Hypothyroidism was echocardiographically diagnosed in eight of ten patients with subclinical primary hypothyroidism and in 14 of 25 patients (56%) with hypothalamic–pituitary disease and normal serum FT_4 . Echocardiographic abnormalities improved significantly after $L-T_4$ and correlated ($0.05 < P < 0.001$) with changes in FT_4 ($-0.62 < r < -0.55$) and TSH ($0.63 < r < 0.68$) in primary hypothyroidism and with FT_4 in central hypothyroidism ($-0.72 < r < -0.50$).

Conclusion: Echocardiography can be useful in diagnosing subclinical central hypothyroidism in patients with hypothalamic–pituitary disease.

European Journal of Endocrinology 166 631–640

Introduction

Central hypothyroidism is a frequent disorder in patients with hypothalamic–pituitary disease. It results from decreased stimulation of an otherwise normal thyroid gland by a decreased and/or biologically less active thyrotropin (TSH) (1, 2). Risk factors for central hypothyroidism include large sellar lesions, previous surgery, radiotherapy, and other pituitary hormone deficiencies. In practice, the diagnosis of central hypothyroidism relies on a low serum free thyroxine (FT_4) with decreased, normal, or slightly elevated serum TSH (3). However, a low serum FT_4 is a highly specific but insensitive marker of hypothyroidism, whereas several serum markers of thyroid hormone action and the response of TSH to its releasing hormone have shown low diagnostic sensitivity (4, 5).

The cardiovascular system is a major target of thyroid hormone, which influences cardiac function both directly and indirectly via changes in peripheral vascular resistance and circulating volume (6). Noninvasive evaluation of myocardial function, both in animals and humans, has shown opposite abnormalities in systolic time intervals in primary hypothyroidism and hyperthyroidism that can be reversed by appropriate therapy (7, 8, 9). In primary hypothyroidism, systolic time intervals are typically lengthened and decreased after T_4 replacement in correlation with changes in thyroid hormones (10).

Formerly, assessment of systolic intervals was cumbersome, involving simultaneous recordings of electrocardiogram, phonocardiogram, and carotid pulse tracing (11). Currently, Doppler echocardiography is a simple and widely available method that allows

Table 1 Baseline clinical and hormonal characteristics of controls and patients with overt primary hypothyroidism, overt central hypothyroidism, subclinical primary hypothyroidism, and hypothalamic–pituitary disease with normal FT₄ levels. Plus–minus values are means $\pm$ s.d.

	Controls (n=28)	Overt primary hypothyroidism (n=20)	Overt central hypothyroidism (n=10)	Subclinical primary hypothyroidism (n=10)	Hypothalamic– pituitary normal FT ₄ (n=25)	P value ^a
Age (years)	35.8 $\pm$ 8.8	40.7 $\pm$ 13.8	31.0 $\pm$ 9.8	35.7 $\pm$ 8.8	33.0 $\pm$ 11.0	0.11
Female sex (no.)	16	16	5	8	13	0.13
Heart rate (bpm)	67 $\pm$ 9	66 $\pm$ 11	62 $\pm$ 8	70 $\pm$ 13	65 $\pm$ 11	0.74
Systolic BP (mmHg)	118 $\pm$ 11	117 $\pm$ 12	121 $\pm$ 9	115 $\pm$ 8	117 $\pm$ 12	0.80
Diastolic BP (mmHg)	77 $\pm$ 10	78 $\pm$ 10	81 $\pm$ 9	75 $\pm$ 7	78 $\pm$ 9	0.67
Serum FT ₄ (ng/dl) ^b	1.02 $\pm$ 0.15	0.29 $\pm$ 0.13 ^c	0.45 $\pm$ 0.14 ^c	0.94 $\pm$ 0.24	0.95 $\pm$ 0.14	<0.001
Serum TSH (mU/l)	1.70 $\pm$ 1.03	97.17 $\pm$ 53.75 ^c	3.26 $\pm$ 3.35	14.28 $\pm$ 5.59 ^c	0.99 $\pm$ 1.08	<0.001

BP, blood pressure; FT₄, free thyroxine; TSH, thyrotropin.^aP values are for the comparisons between all groups by ANOVA, except for sex distribution (χ^2 test).^bTo convert serum FT₄ from nanograms per deciliter to picomole per liter multiply by 12.87.^cP value <0.05 for comparisons between patients and controls (Dunnett's or Dunn's multiple comparison test).

reliable evaluation of cardiac structure and function (12). Previous echocardiographic studies have demonstrated alterations in systolic and diastolic parameters in both overt and subclinical primary hypothyroidism (13, 14, 15, 16, 17). In this study, we tested the hypothesis that selected parameters of myocardial function by echocardiography could be useful in diagnosing subclinical central hypothyroidism in patients with hypothalamic–pituitary disease and normal serum FT₄ levels.

Materials and methods

Patients and controls

The study included 35 patients with hypothalamic–pituitary disease (ten macroprolactinomas, six craniopharyngiomas, six idiopathic hypopituitarism, five Sheehan's syndrome, five nonfunctioning pituitary macroadenomas, one sarcoidosis, one Langerhans cell histiocytosis, and one brain traumatic injury), irrespective of previous surgery, radiotherapy, pharmacological treatment, or hormone replacement therapy (including T₄), and 30 patients with primary hypothyroidism, diagnosed by high serum TSH, due to Hashimoto's thyroiditis (n=28) or previous thyroidectomy. Patients were carefully evaluated to

exclude hypertension or coexisting primary cardiac disease which could interfere with the echocardiographic results; patients with acromegaly or Cushing's disease were not included due to the frequent association with hypertension and/or cardiac hypertrophy.

Patients with hypothalamic–pituitary disease and low serum FT₄ were classified as overt central hypothyroidism; patients with primary thyroid disease, high serum TSH, and low serum FT₄ as overt primary hypothyroidism; and patients with primary thyroid disease, high TSH, and normal serum FT₄ as subclinical primary hypothyroidism. Patients with hypothalamic–pituitary disease and normal serum FT₄ were further classified as subclinical central hypothyroidism or euthyroidism according to echocardiography.

Twenty-eight healthy subjects were included as controls. Patients and controls were studied after informed consent and study approval by the Ethic Committee.

Study design

Baseline assessment Patients were submitted to physical exam and baseline hormonal and echocardiographic assessment. Fasting morning blood collection for hormone measurements and echocardiographic evaluation were performed on the same day.

Table 2 Baseline echocardiographic parameters in patients with overt primary hypothyroidism, overt central hypothyroidism, and controls. Plus–minus values are means $\pm$ s.d.

	Controls (n=28)	Overt primary hypothyroidism (n=20)	Overt central hypothyroidism (n=10)	P value ^a
Left ventricle ejection fraction	0.67 $\pm$ 0.04	0.63 $\pm$ 0.05 ^b	0.61 $\pm$ 0.05 ^b	0.003
MPI	0.40 $\pm$ 0.05	0.65 $\pm$ 0.15 ^b	0.51 $\pm$ 0.10 ^b	<0.001
ICT (ms)	39 $\pm$ 10	74 $\pm$ 23 ^b	75 $\pm$ 24 ^b	<0.001
ICT/ET ratio	0.13 $\pm$ 0.03	0.28 $\pm$ 0.11 ^b	0.25 $\pm$ 0.08 ^b	<0.001
ET (ms)	298 $\pm$ 16	271 $\pm$ 24 ^b	298 $\pm$ 25	<0.001
Isovolumic relaxation time (ms)	80 $\pm$ 13	99 $\pm$ 23 ^b	77 $\pm$ 16	<0.001

ICT, isovolumic contraction time; ICT/ET, ICT/ejection time; MPI, myocardial performance index.

^aP values are for the comparisons between all groups by ANOVA.^bP value <0.05 for comparisons between patients and controls (Dunnett's multiple comparison test).

T₄ intervention Patients with overt primary hypothyroidism, overt central hypothyroidism, subclinical primary hypothyroidism, and hypothalamic–pituitary disease with normal serum FT₄ and echocardiographically defined hypothyroidism (subclinical central hypothyroidism) were started on levothyroxine (L-T₄; 1.0–1.7 µg/kg of body weight per day) and/or increased by 25 µg every 4–6 weeks until reaching the following: normal serum TSH in overt and subclinical primary hypothyroidism; normal serum FT₄ in overt central hypothyroidism (mid-range/high-normal); and a higher than baseline serum FT₄ (mid-range/high-normal) in subclinical central hypothyroidism. Patients were monitored for signs and symptoms of thyrotoxicosis; patients with hypothalamic–pituitary disease were also monitored through serum triiodothyronine (T₃) measurements. Echocardiography was repeated when hormonal targets were reached. Replacement of other hormone deficiencies was kept constant for at least 6 months before and during the study.

Hormone assays

Serum TSH was measured in duplicate by an in-house sensitive third-generation immunofluorometric assay (intra- and interassay coefficients of variation (CV), 4 and 6% respectively; sensitivity, 0.03 mU/l; and normal reference values: 0.4–5.0 mU/l). Serum FT₄ was measured in duplicate by an immunofluorometric assay (Delfia; Wallac Oy, Turku, Finland; intra- and interassay CV, 4.4 and 6.1% respectively; sensitivity, 0.16 ng/dl; and normal reference values: 0.7–1.54 ng/dl). Serum T₃ (total) was measured by an immunofluorometric assay (Delfia; Wallac Oy; intra- and interassay CV, 3.0%; sensitivity, 20 ng/dl; and normal reference values, 80–210 ng/dl).

Echocardiographic assessment

A complete two-dimensional Doppler echocardiographic examination was performed using an ATL-5000 ultrasound machine (Philips, Andover, MA, USA) with a 2.0–2.5 MHz transducer according to standard technique (12). Left ventricle ejection fraction was obtained by Teichholz method (18). Assessment of the myocardial performance index (MPI) (19), defined as the sum of isovolumic contraction time (ICT) and isovolumic relaxation time divided by left ventricle ejection time (ET), was carried out by sequential recording of the mitral inflow (from the apical four-chamber view with the pulsed wave Doppler sample volume positioned at the tips of the mitral leaflets during diastole) and of the left ventricle outflow tract (from the apical long axis view with the sample volume positioned just below the aortic valve). Measurements of Doppler tracings were performed with simultaneous electrocardiogram recording in five consecutive heart beats and expressed as the mean value as previously described

Figure 1 ROC curves and the corresponding AUC for (A) the isovolumic contraction time (ICT), (B) the ratio between ICT and ejection time, and (C) the myocardial performance index (MPI) as markers of hypothyroidism in patients with overt primary and central hypothyroidism. An AUC value of 0.5 is no better than expected by chance and a value of 1.0 indicates a perfect diagnostic marker. Arrows indicate the chosen diagnostic cut-off values.

(20). Measurements were made by a single observer (FCD) uninformed of patients' data.

Statistical analysis

Comparisons between more than two groups were made by ANOVA, followed by paired or unpaired parametric or nonparametric post hoc tests. Correlations were calculated using Pearson's (r) or Spearman's (r_s) coefficients. Comparison between frequencies were calculated by χ^2 or Fisher's exact test. Receiver operating characteristic (ROC) curves were generated using selected echocardiographic parameters from controls and patients with biochemical overt hypothyroidism according to currently accepted diagnostic gold standards: low serum FT₄ with low, normal, or slightly increased TSH in patients with hypothalamic–pituitary disease for central hypothyroidism; and low serum FT₄ with high TSH in patients with primary thyroid disease. Echocardiographic parameters from patients with subclinical primary hypothyroidism or hypothalamic–pituitary disease with normal serum FT₄ were not used to generate the ROC curves and served as application groups. P values <0.05 were considered significant. Statistical analyses were performed using GraphPad Prism version 5.00 for Windows (GraphPad Software Inc., San Diego, CA, USA, www.graphpad.com). Data were expressed as mean $\pm$ s.d.

Results

No significant differences were found in age, sex distribution, heart rate, or blood pressure between patients with overt primary hypothyroidism, overt central hypothyroidism, subclinical primary hypothyroidism, hypothalamic–pituitary disease with normal serum FT₄, and controls (Table 1).

Baseline assessment in overt hypothyroidism

As expected, serum FT₄ was significantly lower in both overt primary and overt central hypothyroidism as compared with controls, and serum TSH was significantly higher in overt primary hypothyroidism

but not in overt central hypothyroidism as compared with controls (Table 1).

As shown in Table 2, left ventricle ejection fraction, MPI, ICT, and ICT/ET ratio were significantly different from controls in both overt primary and overt central hypothyroidism. Left ventricle ET and isovolumic relaxation time were significantly different only in overt primary hypothyroidism. No significant differences in ventricular dimensions and left ventricle mass index were observed (data not shown). One patient with primary hypothyroidism presented mild pericardial effusion.

ROC curves analysis of echocardiographic parameters in the diagnosis of hypothyroidism

Figure 1 shows the echocardiographic parameters with the highest areas under the ROC curves. The chosen cut-off values for the diagnosis of hypothyroidism were the following: ICT > 53 ms (sensitivity, 83%; confidence interval (CI), 65–94%; specificity, 96%; CI, 82–100%); ICT/ET ratio > 0.18 (sensitivity, 83%; CI, 65–94%; specificity, 96%; CI, 82–100%); and MPI > 0.46 (sensitivity, 90%; CI, 74–98%; specificity, 93%; CI, 77–99%). For ICT and ICT/ET ratio, cut-off values showed identical accuracy, positive, and negative predictive values of 90, 96, and 84% respectively. For MPI, accuracy, positive, and negative predictive values were 91, 93, and 90% respectively. A highest diagnostic accuracy of 93% was obtained when at least one parameter was increased (positive and negative predictive values, 93%). Intra- and interobserver variability (percent of mean value) for MPI, ICT, and ICT/ET ratio were 2.7 ± 2.2 , 5.9 ± 5.9 , 4.1 ± 2.9 , 6.3 ± 7 , and 9.1 ± 5.6 , $9.4 \pm 4\%$ respectively.

Echocardiographic diagnosis of hypothyroidism in patients with normal serum FT₄

Serum FT₄ levels in patients with subclinical primary hypothyroidism and in patients with hypothalamic–pituitary disease with normal FT₄ were not significantly different from controls. As expected, serum TSH levels

Table 3 Baseline echocardiographic parameters in patients with subclinical primary hypothyroidism, hypothalamic–pituitary disease with normal serum FT₄ and controls. Plus–minus values are means $\pm$ s.d.

	Controls ($n=28$)	Subclinical primary hypothyroidism ($n=10$)	Hypothalamic–pituitary normal FT ₄ ($n=25$)	P value ^a
Left ventricle ejection fraction	0.67 ± 0.04	0.67 ± 0.04	0.62 ± 0.03^b	<0.001
MPI	0.40 ± 0.05	0.48 ± 0.09^b	0.43 ± 0.07	0.005
ICT (ms)	39 ± 10	53 ± 11^b	55 ± 17^b	<0.001
ICT/ET ratio	0.13 ± 0.03	0.19 ± 0.04^b	0.18 ± 0.06^b	<0.001
ET (ms)	298 ± 16	288 ± 27	302 ± 16	0.12
Isovolumic relaxation time (ms)	80 ± 13	84 ± 16	78 ± 16	0.50

FT₄, free thyroxine; ICT, isovolumic contraction time; ICT/ET, ICT/ejection time; MPI, myocardial performance index.

^a P values are for the comparisons between all groups by ANOVA.

^b P value <0.05 for comparisons between patients and controls (Dunnnett's multiple comparison test).

were significantly higher in subclinical primary hypothyroidism, but not in hypothalamic–pituitary disease with normal FT_4 , as compared with controls (Table 1). No significant differences in ventricular dimensions and left ventricle mass indexes were observed among these groups (data not shown).

Subclinical primary hypothyroidism

As shown in Table 3, all three diagnostic echocardiographic parameters were significantly increased in subclinical primary hypothyroidism. Eight of ten patients with subclinical primary hypothyroidism were also diagnosed as hypothyroid by echocardiography (Fig. 2).

Hypothalamic–pituitary disease with normal serum FT_4

As shown in Table 3, both ICT and ICT/ET ratio were significantly increased, and left ventricle ejection fraction was significantly decreased in hypothalamic–pituitary disease with normal serum FT_4 .

Hypothyroidism was diagnosed by echocardiography in 14 of 25 patients (56%) with hypothalamic–pituitary disease and normal serum FT_4 (Fig. 2). These patients were younger than patients echocardiographically defined as euthyroid (28 ± 8 vs 40 ± 11 years, $P=0.004$, t -test), but no significant differences were found in sex, heart rate, blood pressure, serum FT_4 and

Figure 2 Selected diagnostic echocardiographic parameters in patients with overt and subclinical primary hypothyroidism, overt central hypothyroidism, hypothalamic–pituitary disease with normal serum free thyroxine (FT_4), and controls. Each circle represents one patient. Dashed horizontal lines indicate the chosen cut-off values: 53 ms for the ICT, 0.18 for the ratio between ICT and ET, and 0.46 for the MPI. Patients with hypothalamic–pituitary disease and normal FT_4 that had at least one of the three parameters above the cut-off value were diagnosed as subclinical central hypothyroidism and are represented by solid circles.

Table 4 Clinical and hormonal parameters in patients with or without echocardiographically defined subclinical central hypothyroidism. Plus-minus values are means $\pm$ s.d.

	Subclinical central hypothyroidism		<i>P</i> value ^a
	Yes (<i>n</i> =14)	No (<i>n</i> =11)	
Age (years)	28 $\pm$ 8	40 $\pm$ 11	0.004
Female sex (no.)	6	7	0.43
Heart rate (bpm)	65 $\pm$ 9	64 $\pm$ 9	0.79
Systolic blood pressure (mmHg)	118 $\pm$ 14	117 $\pm$ 11	0.85
Diastolic blood pressure (mmHg)	79 $\pm$ 8	76 $\pm$ 10	0.41
Serum FT ₄ (ng/dl) ^b	0.96 $\pm$ 0.14	0.95 $\pm$ 0.15	0.87
Serum T ₃ (ng/dl) ^c	114 $\pm$ 25	105 $\pm$ 9	0.27
Untreated GH deficiency (no.)	9	9	0.41
Hypogonadism (no.)	5	7	1
Glucocorticoid deficiency (no.)	3	6	1

FT₄, free thyroxine; T₃, triiodothyronine.

^a*P* values for comparisons between groups by unpaired *t*-test (age, heart rate, blood pressure, serum FT₄, and T₃) or Fisher's exact test (sex, untreated GH deficiency, hypogonadism, and glucocorticoid deficiency).

^bTo convert serum FT₄ from nanograms per deciliter to picomole per liter multiply by 12.87.

^cTo convert serum T₃ from nanograms per deciliter to nanomole per liter multiply by 0.0154.

T₃, prevalence of untreated GH deficiency, or other pituitary hormone deficiencies (Table 4).

Baseline echocardiographic and hormonal correlations

In primary hypothyroidism, as expected, the highest correlation was found between serum TSH and serum FT₄ ($r_s = -0.70$, $P < 0.001$); serum TSH was also correlated with ICT ($r_s = 0.53$, $P = 0.003$), ICT/ET ratio ($r_s = 0.54$, $P = 0.002$), and MPI ($r_s = 0.55$, $P = 0.002$). FT₄ correlated with ICT ($r_s = -0.54$, $P = 0.002$), ICT/ET ratio ($r_s = -0.55$, $P = 0.002$), and MPI ($r_s = -0.62$, $P < 0.001$).

In central hypothyroidism, diagnosed either biochemically or echocardiographically, the highest correlation was between serum FT₄ and the MPI ($r = -0.79$, $P < 0.001$); serum FT₄ also correlated with ICT ($r = -0.52$, $P = 0.02$) and ICT/ET ratio ($r = -0.60$, $P = 0.006$).

Changes after T₄ intervention

Fifty-four patients met the criteria for T₄ intervention; 43 completed the study (Fig. 3 and Table 5). Two thyroidectomized patients were not included because TSH levels were suppressed after L-T₄ and four patients were not available on recall. Five patients were excluded due to poor compliance. No patient developed clinical signs and/or symptoms of excessive T₄ replacement.

L-T₄ significantly increased serum FT₄ in all groups, but did not significantly change heart rate and blood pressure. Mean serum TSH decreased to the normal range in primary hypothyroidism and serum T₃ increased within the normal range in all patients with hypothalamic-pituitary disease.

Overt hypothyroidism

After treatment, all diagnostic echocardiographic parameters decreased significantly in overt hypothyroidism. In overt primary hypothyroidism, these three

Figure 3 Diagnostic parameters before and after thyroxine (T₄) intervention in patients with overt primary, overt central, subclinical primary, and subclinical central hypothyroidism. Box and whisker plots show the 10th, 25th, 50th (median), 75th, and 90th percentile values for the isovolumic contraction time (ICT), the ratio between ICT and ejection time (ET), and the myocardial performance index, before (gray boxes) and after (white boxes) T₄ intervention in patients with primary and central overt and subclinical hypothyroidism. **P* < 0.05, paired *t*-test. Black dots represent outliers. Values in parentheses are the numbers of patients in each group.

Table 5 Clinical, hormonal, and echocardiographic parameters before and after T₄ intervention in patients with overt primary hypothyroidism, overt central hypothyroidism, subclinical primary hypothyroidism, and echocardiographically defined subclinical central hypothyroidism. Plus-minus values are means $\pm$ s.d.

T ₄ intervention	Overt primary hypothyroidism (n=15)		Overt central hypothyroidism (n=9)		Subclinical primary hypothyroidism (n=9)		Subclinical central hypothyroidism (n=10)	
	Before	After	Before	After	Before	After	Before	After
Heart rate (bpm)	67 $\pm$ 11	69 $\pm$ 11	62 $\pm$ 8	68 $\pm$ 9	67 $\pm$ 14	72 $\pm$ 11	65 $\pm$ 11	72 $\pm$ 9.6
Systolic BP (mmHg)	117 $\pm$ 11	117 $\pm$ 12	122 $\pm$ 10	118 $\pm$ 19	117 $\pm$ 7	114 $\pm$ 11	121 $\pm$ 15	128 $\pm$ 10
Diastolic BP (mmHg)	77 $\pm$ 10	77 $\pm$ 7	82 $\pm$ 9	78 $\pm$ 13	77 $\pm$ 5	77 $\pm$ 6	81 $\pm$ 8	88 $\pm$ 4
Serum FT ₄ (ng/dl) ^a	0.29 $\pm$ 0.12	1.14 $\pm$ 0.18 ^b	0.45 $\pm$ 0.15	1.22 $\pm$ 0.43 ^b	0.96 $\pm$ 0.24	1.14 $\pm$ 0.18 ^b	0.96 $\pm$ 0.15	1.38 $\pm$ 0.22 ^b
Serum T ₃ (ng/dl) ^c	NA	NA	82 $\pm$ 26	127 $\pm$ 29 ^b	NA	NA	103 $\pm$ 21	140 $\pm$ 31 ^b
Serum TSH (mU/l)	100.30 $\pm$ 59.10	2.43 $\pm$ 1.34 ^b	3.61 $\pm$ 3.34	NA	13.0 $\pm$ 4.13	2.28 $\pm$ 1.54 ^b	0.89 $\pm$ 1.17	NA
Left ventricle ejection fraction	0.62 $\pm$ 0.05	0.66 $\pm$ 0.04 ^b	0.61 $\pm$ 0.05	0.63 $\pm$ 0.04	0.67 $\pm$ 0.04	0.67 $\pm$ 0.05	0.64 $\pm$ 0.03	0.64 $\pm$ 0.05
MPI	0.67 $\pm$ 0.05	0.44 $\pm$ 0.10 ^b	0.53 $\pm$ 0.08	0.38 $\pm$ 0.08 ^b	0.48 $\pm$ 0.09	0.40 $\pm$ 0.07	0.48 $\pm$ 0.06	0.39 $\pm$ 0.09 ^b
ICT (ms)	76 $\pm$ 21	45 $\pm$ 23 ^b	79 $\pm$ 21	38 $\pm$ 13 ^b	51 $\pm$ 8	40 $\pm$ 13 ^b	72 $\pm$ 8	52 $\pm$ 19 ^b
ICT/ET ratio	0.30 $\pm$ 0.12	0.16 $\pm$ 0.10 ^b	0.27 $\pm$ 0.07	0.13 $\pm$ 0.04 ^b	0.18 $\pm$ 0.03	0.14 $\pm$ 0.04 ^b	0.23 $\pm$ 0.03	0.17 $\pm$ 0.06 ^b
ET (ms)	266 $\pm$ 24	285 $\pm$ 26 ^b	296 $\pm$ 26	293 $\pm$ 20	288 $\pm$ 28	287 $\pm$ 18	305 $\pm$ 0	302 $\pm$ 17
Isovolumic relaxation time (ms)	99 $\pm$ 23	81 $\pm$ 20 ^b	78 $\pm$ 16	73 $\pm$ 16	85 $\pm$ 16	75 $\pm$ 17 ^b	73 $\pm$ 15	67 $\pm$ 18

BP, blood pressure; FT₄, free thyroxine; T₃, triiodothyronine; TSH, thyrotropin; NA, not applicable; ICT, isovolumic contraction time; ICT/ET, ICT/ejection time; MPI, myocardial performance index.

^aTo convert serum FT₄ from nanograms per deciliter to picomole per liter multiply by 12.87.

^bP value < 0.05 for comparisons between parameters before and after thyroxine intervention (paired *t*-test).

^cTo convert serum T₃ from nanograms per deciliter to nanomole per liter multiply by 0.0154.

parameters decreased in all 15 patients and each one reached values lower than the mean + 2 s.d. of control subjects in 73–77% of patients. In overt central hypothyroidism, these parameters also decreased in all nine patients, and all but one of each diagnostic parameter decreased below mean + 2 s.d. of controls. After T₄, echocardiographic measurements below the mean – 2 s.d. were observed in four of 24 patients.

Subclinical hypothyroidism

T₄ intervention significantly decreased all diagnostic echocardiographic parameters in both subclinical primary and subclinical central hypothyroidism, and corrected 28 of 29 (97%) abnormal parameters in subclinical primary hypothyroidism, and 21 of 29 (72%) in subclinical central hypothyroidism. Low echocardiographic measurements (<mean – 2 s.d.) were observed in two of 18 patients.

Echocardiographic and hormonal correlations after T₄

Significant correlations were found between changes (Δ = posttreatment minus pretreatment values) in serum thyroid hormones and changes in diagnostic echocardiographic parameters in patients with primary and central hypothyroidism (overt and subclinical).

In primary hypothyroidism, Δ TSH correlated ($0.01 < P < 0.001$) with Δ FT₄ ($r_s = -0.67$), Δ ICT ($r_s = 0.63$), Δ ICT/ET ratio ($r_s = 0.68$), and Δ MPI ($r_s = 0.66$); Δ FT₄ correlated ($0.01 < P < 0.001$) with Δ ICT ($r = -0.60$), Δ ICT/ET ratio ($r_s = -0.55$), and Δ MPI ($r_s = -0.62$).

In central hypothyroidism, Δ FT₄ correlated ($0.05 < P < 0.01$) with Δ ICT ($r = -0.51$), Δ ICT/ET ratio ($r = -0.50$), and Δ MPI ($r_s = -0.72$).

As shown in Fig. 4, when all patients with both primary and central overt and subclinical hypothyroidism were analyzed together, Δ FT₄ correlated significantly with Δ ICT ($r = -0.54$), Δ ICT/ET ratio ($r = -0.64$), and Δ MPI ($r_s = -0.70$).

Discussion

In this study, we have shown that echocardiography is a simple and accurate method to detect tissue hypothyroidism, which was especially useful in diagnosing subclinical central hypothyroidism in patients with hypothalamic–pituitary disease and normal serum FT₄. As opposed to subclinical primary hypothyroidism, which is easily diagnosed by increased serum TSH with normal serum FT₄ levels, the diagnosis of subclinical central hypothyroidism has been elusive in clinical practice. Selected myocardial function parameters including the systolic time intervals – ICT and ICT/ET ratio – and the MPI, which are largely independent of heart rate (11, 21), have shown high diagnostic accuracy as demonstrated by ROC curve analysis using only patients with overt central and primary hypothyroidism and controls. When applied to patients with subclinical primary hypothyroidism, these markers were in diagnostic agreement with serum TSH levels in 80% of cases. In patients with hypothalamic–pituitary disease and normal serum FT₄ who were considered at risk for subclinical central hypothyroidism, these markers indicated tissue hypothyroidism in 56% of patients. The specificity of these measurements to detect

Figure 4 Correlations between changes (Δ = posttreatment minus pretreatment values) in serum FT₄ and each echocardiographic diagnostic parameter after levothyroxine in patients with primary (solid circles) and central (open circles) overt and subclinical hypothyroidism ($n = 42$). Slanting lines represent linear regression lines between parameters. FT₄, free thyroxine; ICT, isovolumic contraction time; ICT/ET, ICT/ejection time ratio; MPI, myocardial performance index.

tissue thyroid hormone deficiency was further supported by their reversal or improvement after T₄, without any clinical or biochemical sign of excessive T₄ replacement, in both biochemical and echocardiographically defined hypothyroidism.

The pathophysiology of disturbed myocardial performance in hypothyroidism, as reflected by alterations in several echocardiographic parameters, involves both direct and indirect effects of thyroid hormone in the heart. At the molecular level, these disturbances have been shown to result from both genomic and non-genomic effects of thyroid hormone in the cardiovascular system (6). Thyroid hormone regulates the expression of structural proteins, like α - and β -myosin heavy chains in cardiac myocytes, and of key regulatory proteins through binding of T₃ to nuclear receptors that activate or repress transcription of several specific genes. Intracellular calcium cycling via sarcoplasmic reticulum calcium-activated ATPase and its inhibitor, phospholamban, which are regulated by thyroid hormone in opposite ways, is thought to be largely responsible for enhanced contractile function and diastolic relaxation (22). These mechanisms underlie the reduced velocity of shortening and rate of tension development observed in papillary muscle from hypothyroid animals (23). Hypothyroidism, at any end-diastolic volume, blunts the development of myocardial force in early systole, which lengthens the time required for the intraventricular pressure to reach the arterial diastolic pressure and initiate the ejective phase.

Impaired development of myocardial force plays a major role in the abnormalities found in ICT and ICT/ET ratio, both in primary and central hypothyroidism, which improved after T₄ replacement in correlation with changes in serum thyroid hormone levels. In addition, left ventricle ejection fraction, a much less sensitive marker of tissue hypothyroidism, was significantly decreased in overt hypothyroidism and also improved after treatment. Although diastolic function, as reflected by the isovolumic relaxation time, was significantly impaired only in overt primary hypothyroidism, it was improved by T₄ replacement in both overt and subclinical primary hypothyroidism. MPI, an index that combines both systolic (ICT and ET) and diastolic (isovolumic relaxation time) time intervals, was also increased in hypothyroidism and improved in correlation with changes in serum thyroid hormones.

Although other pituitary hormone deficiencies like GH, glucocorticoid, and sex steroids were highly prevalent in our patients with hypothalamic–pituitary disease, they are unlikely to have had a major influence in the echocardiographic diagnosis of subclinical central hypothyroidism. First, these deficiencies, either treated or untreated, were equally distributed between patients with and without echocardiographically defined hypothyroidism. Second, similar abnormalities were also found in subclinical primary hypothyroidism with similar serum FT₄ levels, which also improved after

T₄ replacement. Third, these echocardiographic abnormalities in patients with hypothalamic–pituitary disease and low serum FT₄ were not more severe than in overt primary hypothyroidism.

A role for GH in heart morphology and function has been supported by clinical and experimental evidence (24, 25, 26, 27). Echocardiographic assessment of patients with GH deficiency has shown reduced cardiac mass, especially in childhood-onset deficiency, but the functional abnormalities have been reportedly subtle and best shown by radionuclide angiography (27). A meta-analysis of the echocardiographic effects of GH replacement in adults has shown improvement in left ventricle mass and stroke volume, but not in fractional shortening (28). However, none of these reports assessed the echocardiographic parameters selected in our study. Notwithstanding, the interaction between GH and thyroid hormones has relevant diagnostic and therapeutic implications in patients with hypothalamic–pituitary disease (29). Accordingly, GH replacement has been shown to decrease serum FT₄ and reverse T₃ and to increase serum T₃ by improving peripheral T₄ to T₃ conversion (30). In practice, the T₄-lowering effect of GH has been shown to unmask biochemical hypothyroidism in 36–47% of patients with hypothalamic–pituitary disease (31, 32). On the other hand, since untreated GH deficiency is a state of decreased T₃ generation and GH improves T₄ biological effects, thyroid status can be influenced by GH replacement or withdrawal. In fact, we have shown that biologically appropriate target levels of serum FT₄ during L-T₄ replacement should be higher in untreated GH deficiency (33).

The main limitation to the use of echocardiographic parameters in the diagnosis of hypothyroidism is the coexistence of cardiac disease. Accordingly, patients with positive clinical history of cardiac disease, hypertension, acromegaly, and Cushing's disease were not included and those with structural echocardiographic abnormalities were excluded by our study protocol. Nevertheless, further studies are necessary to elucidate whether these exclusion criteria could be less stringent in order to include hypertensive, acromegalic, and Cushing's disease patients with controlled hypertension who do not show any structural abnormalities in the echocardiographic evaluation. Another potential limitation is the use of drugs that could influence the diagnostic echocardiographic parameters via changes in circulating volume and/or peripheral vascular resistance, such as diuretics and some antihypertensive drugs, although their effects are reportedly small (34). Another potential, albeit limited influence is the age-related physiological impairment of myocardial relaxation that may increase MPI, but not ICT, especially after the sixth decade (35).

Patients with hypopituitarism have increased all-cause mortality with cardiovascular disease as the leading etiology (36). Analysis of mortality in hypopituitary cohorts has been challenging due to diversity of underlying etiologies, treatment modalities, hormone

deficiencies, and hormone replacements (37). Subclinical primary hypothyroidism, on the other hand, has been associated with increased risk of coronary heart disease events and mortality (38). In this context, our results indicate that echocardiography should have a major role in assessing thyroid status in patients with hypothalamic–pituitary disease and normal serum FT₄ levels.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

The study was partially supported by the research grant of Centro de Estudos de Endocrinologia da Escola Paulista de Medicina (CENEPAM). The funding organization had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgements

The authors are grateful for the support from Erika Barbosa Ribeiro on the patients' selection work.

References

- 1 Beck-Peccoz P, Amr S, Menezes-Ferreira MM, Faglia G & Weintraub BD. Decreased receptor binding of biologically inactive thyrotropin in central hypothyroidism. Effect of treatment with thyrotropin-releasing hormone. *New England Journal of Medicine* 1985 **312** 1085–1090. (doi:10.1056/NEJM198504253121703)
- 2 Oliveira JH, Persani L, Beck-Peccoz P & Abucham J. Investigating the paradox of hypothyroidism and increased serum thyrotropin (TSH) levels in Sheehan's syndrome: characterization of TSH carbohydrate content and bioactivity. *Journal of Clinical Endocrinology and Metabolism* 2001 **86** 1694–1699. (doi:10.1210/jc.86.4.1694)
- 3 Shimon I, Cohen O, Lubetsky A & Olchovsky D. Thyrotropin suppression by thyroid hormone replacement is correlated with thyroxine level normalization in central hypothyroidism. *Thyroid* 2002 **12** 823–827. (doi:10.1089/105072502760339406)
- 4 Ferretti E, Persani L, Jaffrain-Rea ML, Giambona S, Tamburrano G & Beck-Peccoz P. Evaluation of the adequacy of levothyroxine replacement therapy in patients with central hypothyroidism. *Journal of Clinical Endocrinology and Metabolism* 1999 **84** 924–929. (doi:10.1210/jc.84.3.924)
- 5 Hartoft-Nielsen ML, Lange M, Rasmussen AK, Scherer S, Zimmermann-Belsing T & Feldt-Rasmussen U. Thyrotropin-releasing hormone stimulation test in patients with pituitary pathology. *Hormone Research* 2004 **61** 53–57. (doi:10.1159/000075239)
- 6 Klein I & Ojamaa K. Thyroid hormone and the cardiovascular system. *New England Journal of Medicine* 2001 **344** 501–509. (doi:10.1056/NEJM200105103441901)
- 7 Amidi M, Leon DF, DeGroot WJ, Kroetz FW & Leonard JJ. Effect of the thyroid state on myocardial contractility and ventricular ejection rate in man. *Circulation* 1968 **38** 229–239. (doi:10.1161/01.CIR.38.2.229)
- 8 Taylor RR, Covell JW & Ross J Jr. Influence of the thyroid state on left ventricular tension-velocity relations in the intact, sedated dog. *Journal of Clinical Investigation* 1969 **48** 775–784. (doi:10.1172/JCI106035)
- 9 Hillis WS, Bremner WF, Lawrie TD & Thomson JA. Systolic time intervals in thyroid disease. *Clinical Endocrinology* 1975 **4** 617–624. (doi:10.1111/j.1365-2265.1975.tb01931.x)

- 10 Crowley WF Jr, Ridgway EC, Bough EW, Francis GS, Daniels GH, Kourides IA, Myers GS & Maloof F. Noninvasive evaluation of cardiac function in hypothyroidism. Response to gradual thyroxine replacement. *New England Journal of Medicine* 1977 **296** 1–6. (doi:10.1056/NEJM197701062960101)
- 11 Weissler AM, Harris WS & Schoenfeld CD. Bedside technics for the evaluation of ventricular function in man. *American Journal of Cardiology* 1969 **23** 577–583. (doi:10.1016/0002-9149(69)90012-5)
- 12 Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS & Stewart WJ. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *Journal of the American Society of Echocardiography* 2005 **18** 1440–1463. (doi:10.1016/j.echo.2005.10.005)
- 13 Kahaly G, Mohr-Kahaly S, Beyer J & Meyer J. Left ventricular function analyzed by Doppler and echocardiographic methods in short-term hypothyroidism. *American Journal of Cardiology* 1995 **75** 645–648. (doi:10.1016/S0002-9149(99)80641-9)
- 14 Monzani F, Di Bello V, Caraccio N, Bertini A, Giorgi D, Giusti C & Ferrannini E. Effect of levothyroxine on cardiac function and structure in subclinical hypothyroidism: a double blind, placebo-controlled study. *Journal of Clinical Endocrinology and Metabolism* 2001 **86** 1110–1115. (doi:10.1210/jc.86.3.1110)
- 15 Vitale G, Galderisi M, Lupoli GA, Celentano A, Pietropaolo I, Parenti N, De Divitiis O & Lupoli G. Left ventricular myocardial impairment in subclinical hypothyroidism assessed by a new ultrasound tool: pulsed tissue Doppler. *Journal of Clinical Endocrinology and Metabolism* 2002 **87** 4350–4355. (doi:10.1210/jc.2002-011764)
- 16 Biondi B, Palmieri EA, Lombardi G & Fazio S. Subclinical hypothyroidism and cardiac function. *Thyroid* 2002 **12** 505–510. (doi:10.1089/105072502760143890)
- 17 Yazici M, Gorgulu S, Sertbas Y, Erbilin E, Albayrak S, Yildiz O & Uyan C. Effects of thyroxine therapy on cardiac function in patients with subclinical hypothyroidism: index of myocardial performance in the evaluation of left ventricular function. *International Journal of Cardiology* 2004 **95** 135–143. (doi:10.1016/j.ijcard.2003.05.015)
- 18 Teichholz LE, Kreulen T, Herman MV & Gorlin R. Problems in echocardiographic volume determinations: echocardiographic–angiographic correlations in the presence of absence of asynergy. *American Journal of Cardiology* 1976 **37** 7–11. (doi:10.1016/0002-9149(76)90491-4)
- 19 Tei C, Ling LH, Hodge DO, Bailey KR, Oh JK, Rodeheffer RJ, Tajik AJ & Seward JB. New index of combined systolic and diastolic myocardial performance: a simple and reproducible measure of cardiac function – a study in normals and dilated cardiomyopathy. *Journal of Cardiology* 1995 **26** 357–366.
- 20 Doin FL, Borges Mda R, Campos O, de Camargo Carvalho AC, de Paola AA, Paiva MG, Abucham J & Moises VA. Effect of central hypothyroidism on Doppler-derived myocardial performance index. *Journal of the American Society of Echocardiography* 2004 **17** 622–629. (doi:10.1016/j.echo.2004.03.010)
- 21 Lavine SJ. Effect of heart rate and preload on index of myocardial performance in the normal and abnormal left ventricle. *Journal of the American Society of Echocardiography* 2005 **18** 133–141. (doi:10.1016/j.echo.2004.08.036)
- 22 Klein I & Danzi S. Thyroid disease and the heart. *Circulation* 2007 **116** 1725–1735. (doi:10.1161/CIRCULATIONAHA.106.678326)
- 23 Buccino RA, Spann JF Jr, Pool PE, Sonnenblick EH & Braunwald E. Influence of the thyroid state on the intrinsic contractile properties and energy stores of the myocardium. *Journal of Clinical Investigation* 1967 **46** 1669–1682. (doi:10.1172/JCI105658)
- 24 Timsit J, Riou B, Bertherat J, Wisniewsky C, Kato NS, Weisberg AS, Lubetzki J, Lecarpentier Y, Winegrad S & Mercadier JJ. Effects of chronic growth hormone hypersecretion on intrinsic contractility, energetics, isomyosin pattern, and myosin adenosine triphosphatase activity of rat left ventricle. *Journal of Clinical Investigation* 1990 **86** 507–515. (doi:10.1172/JCI114737)
- 25 Ito H, Hiroe M, Hirata Y, Tsujino M, Adachi S, Shichiri M, Koike A, Nogami A & Marumo F. Insulin-like growth factor-I induces hypertrophy with enhanced expression of muscle specific genes in cultured rat cardiomyocytes. *Circulation* 1993 **87** 1715–1721. (doi:10.1161/01.CIR.87.5.1715)
- 26 Delafontaine P. Insulin-like growth factor I and its binding proteins in the cardiovascular system. *Cardiovascular Research* 1995 **30** 825–834. (doi:10.1016/S0008-6363(95)00163-8)
- 27 Colao A. The GH-IGF-I axis and the cardiovascular system: clinical implications. *Clinical Endocrinology* 2008 **69** 347–358. (doi:10.1111/j.1365-2265.2008.03292.x)
- 28 Maison P & Chanson P. Cardiac effects of growth hormone in adults with growth hormone deficiency: a meta-analysis. *Circulation* 2003 **108** 2648–2652. (doi:10.1161/01.CIR.0000100720.01867.1D)
- 29 Behan LA, Monson JP & Agha A. The interaction between growth hormone and the thyroid axis in hypopituitary patients. *Clinical Endocrinology* 2011 **74** 281–288. (doi:10.1111/j.1365-2265.2010.03815.x)
- 30 Portes ES, Oliveira JH, MacCagnan P & Abucham J. Changes in serum thyroid hormones levels and their mechanisms during long-term growth hormone (GH) replacement therapy in GH deficient children. *Clinical Endocrinology* 2000 **53** 183–189. (doi:10.1046/j.1365-2265.2000.01071.x)
- 31 Porretti S, Giavoli C, Ronchi C, Lombardi G, Zaccaria M, Valle D, Arosio M & Beck-Peccoz P. Recombinant human GH replacement therapy and thyroid function in a large group of adult GH-deficient patients: when does L-T(4) therapy become mandatory? *Journal of Clinical Endocrinology and Metabolism* 2002 **87** 2042–2045. (doi:10.1210/jc.87.5.2042)
- 32 Agha A, Walker D, Perry L, Drake WM, Chew SL, Jenkins PJ, Grossman AB & Monson JP. Unmasking of central hypothyroidism following growth hormone replacement in adult hypopituitary patients. *Clinical Endocrinology* 2007 **66** 72–77.
- 33 Martins MR, Doin FC, Komatsu WR, Barros-Neto TL, Moises VA & Abucham J. Growth hormone replacement improves thyroxine biological effects: implications for management of central hypothyroidism. *Journal of Clinical Endocrinology and Metabolism* 2007 **92** 4144–4153. (doi:10.1210/jc.2007-0941)
- 34 Moller JE, Poulsen SH & Egstrup K. Effect of preload alternations on a new Doppler echocardiographic index of combined systolic and diastolic performance. *Journal of the American Society of Echocardiography* 1999 **12** 1065–1072. (doi:10.1016/S0894-7317(99)70103-3)
- 35 Spencer KT, Kirkpatrick JN, Mor-Avi V, Decara JM & Lang RM. Age dependency of the Tei index of myocardial performance. *Journal of the American Society of Echocardiography* 2004 **17** 350–352. (doi:10.1016/j.echo.2004.01.003)
- 36 Rosen T & Bengtsson BA. Premature mortality due to cardiovascular disease in hypopituitarism. *Lancet* 1990 **336** 285–288. (doi:10.1016/0140-6736(90)91812-0)
- 37 Sherlock M, Ayuk J, Tomlinson JW, Toogood AA, Aragon-Alonso A, Sheppard MC, Bates AS & Stewart PM. Mortality in patients with pituitary disease. *Endocrine Reviews* 2010 **31** 301–342. (doi:10.1210/er.2009-0033)
- 38 Rodondi N, den Elzen WP, Bauer DC, Cappola AR, Razvi S, Walsh JP, Asvold BO, Iervasi G, Imaizumi M, Collet TH, Bremner A, Maisonneuve P, Sgarbi JA, Khaw KT, Vanderpump MP, Newman AB, Cornuz J, Franklyn JA, Westendorp RG, Vittinghoff E & Gussekloo J. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. *Journal of the American Medical Association* 2010 **304** 1365–1374. (doi:10.1001/jama.2010.1361)

Received 20 October 2011

Revised version received 21 December 2011

Accepted 20 January 2012