Cardiac Effect of Thyrotoxicosis in Acromegaly*

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ABSTRACT

Cardiac structure and function are affected both by acromegaly and hyperthyroidism. Whereas the former is mainly characterized by ventricular hypertrophy as well as diastolic and systolic impairment, the latter frequently leads to increased heart rate and enhancement of contractility and cardiac output.

To further investigate this issue, we designed this two-arm study. In the first cross-sectional study, we compared echocardiography and radionuclide angiography results obtained in eight hyperthyroid acromegalic patients, eight hyperthyroid nonacromegalic patients, and eight healthy subjects. All acromegalic patients were receiving treatment for acromegaly at the onset of hyperthyroidism. In the second longitudinal study, performed in the group of acromegalic patients, we compared the cardiovascular results obtained during hyperthyroidism with the retrospective data obtained at the initial diagnosis of acromegaly and after 1-yr treatment for this disease and those prospective data obtained during the remission of hyperthyroidism.

In the cross-sectional study, hyperthyroid acromegalic patients showed an increase in the left ventricular (LV) mass index (LVMi) compared to healthy and hyperthyroid controls ($P < 0.05$), with evidence of LVMi hypertrophy in five of them (62.5%). A significant correlation was found between LVMi and GH levels (r = 0.785; $P < 0.05$). The LV ejection fraction (LVEF) at rest was higher in the control hyperthyroid population than in healthy controls ($P < 0.05$), whereas the LVEF response to exercise was reduced in acromegalic patients ($P < 0.05$ vs. healthy controls). In acromegalics, the exercise-induced change in LVEF was significantly reduced compared to that in healthy controls ($P < 0.001$), but not to that in hyperthyroid controls ($P < 0.07$), being abnormal (<5% increase vs. baseline values) in six patients. Four of these six patients (66%) had elevated GH and insulin-like growth factor I levels during the treatment of acromegaly. An inverse correlation between GH and LVEF at rest (r = −0.896; $P < 0.05$) and at peak exercise (r = −0.950; $P < 0.001$) was recorded. The peak filling rate was reduced in hyperthyroid acromegalic patients compared to those in both control populations ($P < 0.05$).

In the longitudinal study, acromegalic patients showed an increased LVMi during hyperthyroidism compared to that observed after successful treatment of acromegaly ($P < 0.05$); resting LVEF was increased compared to both basal ($P < 0.001$) and posttreatment values ($P < 0.05$). However, the exercise-induced change in LVEF was reduced ($P < 0.05$ vs. previous follow-up values). Remission of hyperthyroidism led to significant reduction of LVMi ($P < 0.05$) and resting LVEF ($P < 0.05$) and an increase in exercise-induced LVEF ($P < 0.05$).

In light of these findings, hyperthyroidism produces a detrimental effect on the cardiovascular system of acromegalic patients, particularly in those with uncontrolled disease. Thus, control of GH and insulin-like growth factor I should be a major objective, as cardiovascular risk persists in patients with ineffective hormonal suppression, and constant endocrine and cardiovascular surveillance remain crucial steps in patient follow-up. (*J Clin Endocrinol Metab* **85:** 1426–1432, 2000)

ENDOCRINE-RELATED cardiovascular disorders, either structural or functional, have long been recognized in acromegaly and hyperthyroidism, and their progression has been extensively studied (1–6). In acromegaly, cardiac involvement is considered a major determinant for patients' morbidity, and it increases the mortality rate (4, 7–10). A proposed sequence of events (5) infers that, initially, low systemic vascular resistance and high diastolic capacity may enhance the cardiac output and cause concentric cardiac hypertrophy in acromegaly. Subsequently, diastolic competence impairs and gives rise to systolic complications (11–16), so that unless effective suppression of GH and insulin-like growth factor I (IGF-I) is achieved, cardiac output may grad-

ually decline and predispose to congestive heart failure (5). Furthermore, concomitant disorders, such as arterial hypertension, coronary artery disease, and ventricular arrhythmia, are able to worsen the prognosis (5, 15).

Similarly, thyrotoxicosis can play *per se* a key role in cardiac performance. The effects of thyroid hormones are prompt on both heart contractility and systemic vascular system. In these conditions, increased heart rate, reduction of systemic vascular resistance, and enhancement of diastolic function have been reported (6, 17–22). These factors contribute to increase the preload and the cardiac output (6). When prolonged, this condition may impair ventricular filling capacities and induce cardiac failure (18–25), which can be accelerated by aging and preexisting cardiovascular disorders (17, 19, 25).

Accordingly, we investigated the hypothesis that the concomitant presence of acromegaly and hyperthyroidism could enhance the risk of developing cardiovascular complications. This objective was supported by the demonstration that thyroid disorders can frequently occur in acromegalic patients;

TABLE 1. Individual patients' data at diagnosis of hyperthyroidism

Sex/age (yr)	Duration of acromegaly (yr)	GH (μg/L)	IGF-I (μg/L)	Treatment of acromegaly	Duration of hyperthyroidism (months)	Treatment of hyperthyroidism
F, 25	4	0.8	210	Surgery, radiotherapy	7	Methimazole
F, 46	7	1.7	219	Octreotide	5	Methimazole
F, 46	18	6.9	246	Octreotide	8	Methimazole
M, 50	11	4.7	291	Surgery, radiotherapy, octreotide	4	Methimazole
F, 52	19	4.2	421	Surgery, octreotide	6	Methimazole
F, 64	30	1.8	187	Surgery, octreotide	8	Methimazole
F, 67	25	2.1	250	Octreotide	10	Methimazole, radioiodine
M, 74	22	8.5	375	Octreotide	6	Methimazole, radioiodine

TABLE 2. Hormonal data in acromegalic patients evaluated at diagnosis of acromegaly, after 1 yr of treatment, at diagnosis of hyperthyroidism, and after 6–8 months of biochemical remission of hyperthyroidism

	Serum GH levels (μg/L)	Plasma IGF-I levels (μg/L)	Serum fT_3 levels (pg/mL)	Serum fT_4 levels (pg/mL)	Serum TSH levels (mIU/mL)
At diagnosis of acromegaly	32.9 ± 9	589 ± 47	2.2 ± 0.2	10 ± 0.5	1.4 ± 0.3
After 1 yr of treatment	2.4 ± 0.5[a]	283.1 ± 36.5[a]	2.6 ± 0.7	11.5 ± 1.5	1.2 ± 0.3
At diagnosis of hyperthyroidism	3.5 ± 1	274.8 ± 29.3	9.1 ± 1.2[b]	25.2 ± 2.1[b]	0.07 ± 0.01[b]
During remission of hyperthyroidism	3.8 ± 1	281 ± 37.4	2.9 ± 0.3[c]	11.5 ± 1.6[c]	1.9 ± 0.2[c]

For individual P value, see the text.

[a] Euthyroid patients in remission *vs.* baseline values.

[b] Hyperthyroid acromegalic patients *vs.* values of euthyroid acromegaly in remission.

[c] Hyperthyroid patients in remission *vs.* active hyperthyroidism.

goiter is recorded in up to 92% (7, 26–29) and hyperthyroidism in 3.5–26% of cases (7, 26, 28).

This report describes the changes in cardiac structure and function in eight patients who developed hyperthyroidism after acromegaly. The development of thyrotoxicosis represented a worsening of both cardiac hypertrophy and diastolic and systolic function.

Subjects and Methods

Patients

In 1990 we started a program of cardiological evaluation in all patients admitted to our department for pituitary tumors. Among 93 patients with acromegaly admitted between 1990 and 1999, 10 (10.7%) developed hyperthyroidism after the initial diagnosis of acromegaly, but 8 (8.6%; 6 women and 2 men; age, 53 ± 5 yr; mean ± SEM) had complete hormone, echocardiography, and gated blood pool radionuclide angiography records and constituted the study population. Disease duration was deduced by the patient's clinical history and photograph records; in this series it was 17 ± 3 yr. Hyperthyroidism was diagnosed on the basis of clinical features, elevated free thyroid hormone levels, and suppressed TSH levels. No patient had previously received thyroid hormone supplementation. No iodine had been administered for diagnostic/therapeutic procedures within the previous 6 months. All acromegalic patients developed hyperthyroidism after the diagnosis and treatment of acromegaly. The presumed interval occurring between the onset of hyperthyroidism and diagnosis was 6.7 ± 0.7 months. The study was approved by the local ethics committee, and all patients gave informed consent to participate.

Study design

To address the role of hyperthyroidism in acromegalic cardiomyopathy, the study was designed in two arms: a cross-sectional study aimed at comparing the results of the patient group with those obtained in 8 age- and sex-matched healthy controls free of thyroid disorders and in 8 nonacromegalic hyperthyroid patients. In these 24 subjects endocrine evaluation of pituitary and thyroid hormones, echocardiography, and gated blood pool radionuclide angiography were carried out. A longitudinal study was performed in the group of acromegalic patients by comparing the data obtained retrospectively in patients when they received the initial diagnosis of acromegaly (study 0) with those obtained respectively after 1 yr of treatment for this disease (study 1), when they received diagnosis of hyperthyroidism (study 2), and after 6–8 months of biochemical remission of hyperthyroidism (study 3).

Hormonal assessment and thyroid evaluation

Hormonal profiles included assay of GH (calculated as the mean of three consecutive samples drawn at 15-min intervals), ethanol-extracted IGF-I, free T_4 (fT_4) and T_3 (fT_3), and TSH levels in the basal condition and when suppressed after 200-μg iv TRH injection (TSH peak normal when >3 mIU/mL). Assay of anti-TSH receptor antibodies was performed when Graves' disease was suspected. As cure criteria for acromegaly, fasting GH values below 2.5 μg/L and/or glucose-suppressed GH levels below 1 μg/L together with normal IGF-I values for age were taken into consideration (3); biochemical remission of hyperthyroidism was considered when normalization of fT_3 and fT_4 levels as well as restoration of normal TSH secretion was obtained. All hormonal profiles were assessed by immunoradiometric assay, using commercially available kits. Normal IGF-I ranges in our laboratory in 20- to 30-, 31- to 40-, 41- to 50-, and over 50-yr-old subjects were 110–502, 100–494, 100–303, and 78–258 μg/L. Normal ranges for fT_3, fT_4, and TSH were, respectively, 1.6–3.4 pg/mL, 7.1–18.5 pg/mL, and 0.5–4.7 μU/mL. Thyroid morphology was investigated by means of ultrasonography and ^{99}Tc scintigraphy.

Cardiovascular evaluations

A preliminary exercise electrocardiogram and thallium-201 myocardial scintigraphy excluded concomitant coronary arterieal disease in patients who had experienced chest pain resembling angina pectoris. Patients received a careful physical examination at each step of the study. Assessment of the cardiovascular morphology by M- and B-mode Doppler echocardiography and of cardiac function by measuring left ventricular ejection fraction and assessment of peak filling rate by gated blood pool radionuclide angiography were performed in all subjects. Radionuclide angiography was chosen as a useful operator-independent method to study left ventricle performance, because it can provide direct and objective evaluation of ventricular function.

Echocardiography

All subjects were studied when lying in the left lateral recumbent position after a 10-min resting period, according to the recommenda-

tions provided by the American Society of Echocardiography (30). A complete M-mode, two-dimensional analysis was performed using an ultrasound mechanical system equipped with 3.5 MHz transducer (Apogee CX, Interspec, Ambler, PA), and evaluation of left ventricle mass was obtained using Devereux's formula during the M-mode measurement, according to Penn's convention (31). Left ventricle hypertrophy was considered when left ventricular myocardial mass, corrected for the body surface area (LVMi), was greater than 135 g/m² in males and 110 g/m² in females (31).

Radionuclide angiography

The study was performed at rest and after exercise and was accompanied by measurements of heart rate and blood pressure as previously reported in detail (16). The procedure of *in vivo* labeling of red blood cells

TABLE 3. Hemodynamic parameters, left ventricular functional, and morphological data for healthy controls subjects, hyperthyroid control patients, and hyperthyroid acromegalic patients

Parameters	Healthy control subjects	Hyperthyroid control patients	Hyperthyroid acromegalic patients	*P*
HR (beats/min)				
r	73.4 ± 2.6	104 ± 5.1^a	111.7 ± 6.2^a	0.001
e	139.1 ± 3.9	151.7 ± 4^a	156.3 ± 7.1^a	NS
SBP (mm Hg)				
r	118.6 ± 2	122.3 ± 3.1	131.1 ± 6.3	NS
e	148.7 ± 1.9	151 ± 4.8	153.4 ± 6	NS
DBP (mm Hg)				
r	83.6 ± 4.1	87.1 ± 2.2	$97.1 \pm 3.9^{a,b}$	0.05
e	107.3 ± 2.9	109 ± 3.2	114.1 ± 3.1	NS
LVMi (g/m²)				
r	82.5 ± 5.3	102.1 ± 7.5^a	$128.6 \pm 12^{a,b}$	0.05
LV EF (%)				
r	62.7 ± 2.4	69.1 ± 1.7^a	67.5 ± 2.5	NS
e	75.8 ± 3.2	66.1 ± 1.6^a	58 ± 4.4^a	0.05
ΔEF	20.1 ± 2.2	-4.7 ± 2.1^a	-14.5 ± 4.7^a	0.001
PER (EDV/s)				
e	3.5 ± 0.2	3.5 ± 0.1	3.4 ± 0.2	NS
PFR (EDV/s)				
r	3.3 ± 0.2	3.8 ± 0.2	$2.4 \pm 0.2^{a,b}$	0.001
PFR (SV/s)				
r	4.1 ± 0.3	4.1 ± 0.3	3 ± 0.2^a	0.05
PFR/PER				
r	0.94 ± 0.1	1.1 ± 0.1	0.74 ± 0.1	NS
EC (watts)				
e	118 ± 4.1	84.3 ± 8.1^a	$65.6 \pm 7.1^{a,b}$	0.001
ED (min)				
e	9.3 ± 0.3	7.9 ± 0.4^a	$6.3 \pm 0.2^{a,b}$	0.001

For abbreviations of cardiovascular parameters, see the text. r and e indicate resting and exercise testing, respectively. Individual *P* values are reported in the text.
[a] Significant *vs.* healthy control subjects.
[b] Significant *vs.* hyperthyroid control patients.

was performed with 555 MBq (15 mCi) of $^{99\ m}$Tc. Acquisition was performed at rest and during dynamic physical exercise in the 45° left anterior projection with a 15° craniocaudal tilt, with the patient in the supine position, using a small field of view γ-camera (Starcam 300 A/M, General Electric, Milwaukee, WI) and a low energy collimator. Data were recorded at a rate of 30 frames/cardiac cycle for the resting study and 16 frames/cardiac cycle for the exercise study on a dedicated computer system (General Electric). At least 200,000 counts/frame were acquired. Exercise studies were performed using a bicycle ergometer with a restraining harness to minimize the patient's motion under the camera. Exercise loads were increased by 25 watts every 2 min up to submaximal exercise. Radionuclide angiography studies were analyzed using a standard commercial software system (General Electric). Left ventricular regions of interests were automatically drawn for each frame, and a background region of interest was also computer delineated on the end-systolic frame. After background correction, a left ventricular time-activity curve was generated. Indexes of left ventricular function were derived by computer analysis of the background-corrected time-activity curve. The ejection fraction (EF) was computed relatively to end-diastolic and end-systolic counts. Peak left ventricular ejection and filling rates were also calculated after a Fourier expansion with four harmonics. The peak ejection rate was computed as the minimum negative peak before end-systole, and the peak filling rate (PFR) was calculated as the maximum positive peak after end-systole on the first derivative of the left ventricular time-activity curve. Both peak ejection rate and PFR were computed as left ventricular counts per s, normalized for the number of counts at end-diastole and expressed as end-diastolic volume per s; to minimize the influence of the ejection fraction, the PFR was also expressed relative to the left ventricular stroke volume and as the ratio of PFR to peak ejection rate (32). Time to peak ejection rate was determined from the R wave, and time to peak filling rate was determined relative to end systole (minimal volume on the time-activity curve).

Statistical analysis

Data are the mean ± SEM; one-way ANOVA, followed by Newman-Keuls test, was employed for comparison among acromegalic patients in hyperthyroidism with healthy and hyperthyroid controls (cross-sectional study) and with remaining follow-up evaluations (longitudinal study), applying Bonferroni's correction. Pearson's analysis was used to correlate cardiovascular results with hormonal data during the different intervals in acromegalic patients' group. $P < 0.05$ was considered statistically significant.

Results

Clinical and hormonal data

Patients' data are included in Tables 1 and 2, respectively. At the time of diagnosis of hyperthyroidism, one patient had been cured of acromegaly after surgery and radiotherapy. Of the remaining seven patients, all were subjected to chronic sc octreotide treatment, and normal GH and IGF-I levels were recorded in three of them (43%). Two patients suffered from

FIG. 1. Individual data and mean ± SEM values of LVMi in hyperthyroid acromegalic patients compared to healthy control subjects and hyperthyroid control subjects (cross-sectional study).
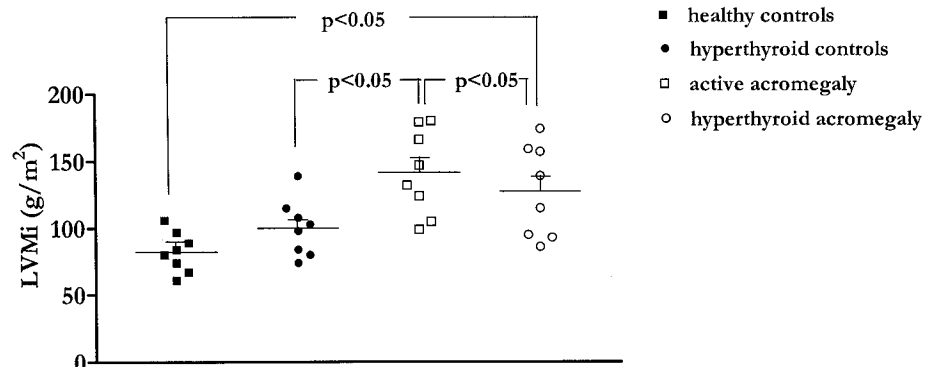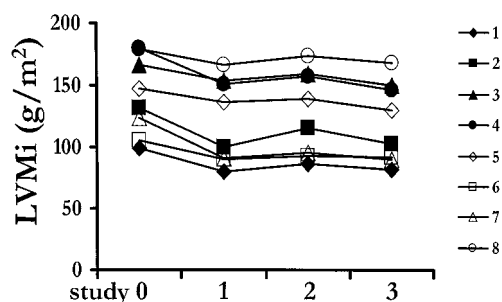
FIG. 2. Individual data of LVMi in acromegalic patients during the different follow-up evaluations (longitudinal study). Patients are numbered as described in the text.

both arterial hypertension and glucose intolerance, one from hypertension, and another from diabetes mellitus. Hyperthyroidism presented with clinical and biochemical features suggestive of Graves' disease in four patients (50%), showing elevated Tr-Ab levels (in all) or ophthalmopathy (in three patients). Multinodular goiter with elevated uptake at scintigraphy was documented in two of them and in all of the remaining patients. Diastolic blood pressure at rest was higher ($P < 0.05$) in hyperthyroid acromegalic patients than in healthy controls. Heart rate was significantly higher in hyperthyroid acromegalic than in healthy controls both at rest ($P < 0.001$) and after exercise ($P < 0.05$), due to the presence of overt tachyarrhythmia in four and atrial fibrillation in two patients, and supplementation with β-adrenergic antagonists was provided after they had completed the cardiological evaluation.

Methimazole was employed as a therapeutic approach to hyperthyroidism in six patients, followed by conventional radioiodine in the remaining two, and after 6–8 months, normal fT_3 ($P < 0.05$), fT_4 ($P < 0.05$), and TSH ($P < 0.001$) levels were found. Heart rate was significantly reduced both at rest ($P < 0.001$) and after exercise ($P < 0.05$), and it was normalized in all patients except in one of the two patients suffering from atrial fibrillation. No significant change in blood pressure was recorded.

Cardiovascular data

Cross-sectional study (Table 3). LVMi values were significantly higher in the group of the hyperthyroid acromegalic patients than in either healthy subjects or control hyperthyroid population ($P < 0.05$ in both cases; Fig. 1). During hyperthyroidism, echocardiographic evidence of LV hypertrophy was detected in five acromegalic patients (62.5%; no. 2–5 and 8; Figs. 1 and 2), four of whom (80%) showed elevated GH levels despite being subjected to chronic octreotide treatment. LVMi was higher in patients with elevated GH levels than in patients showing GH suppression (157.2 ± 7.2 *vs.* 97.2 ± 6.2 g/m^2; $P < 0.001$) at the onset of hyperthyroidism. As a consequence, a significant correlation was observed between GH levels and LVMi (r = 0.785; $P < 0.05$).

Compared to healthy subjects, resting LVEF was significantly higher in hyperthyroid controls ($P < 0.05$) and hyperthyroid acromegalic patients, although it did not reach statistical significance (Fig. 3). By contrast, an abnormal LVEF response to exercise (<5% increase *vs.* baseline values)
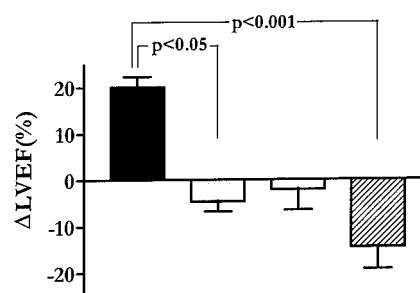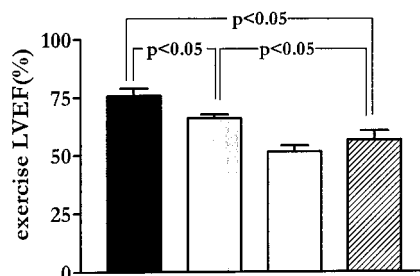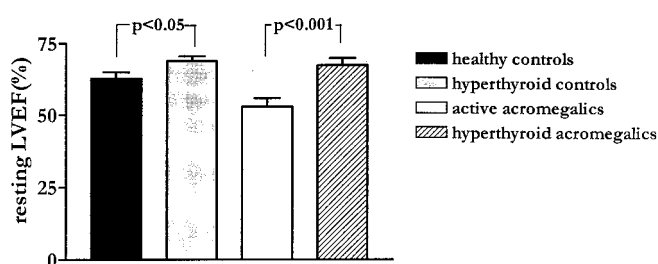

FIG. 3. Mean ± SEM values of LVEF in the resting condition (*top*), at peak exercise (*middle*), and as exercise-induced change (Δ LVEF; *bottom*) in hyperthyroid acromegalic patients compared to healthy control subjects and hyperthyroid control subjects (cross-sectional study).

was observed in six acromegalic patients, among whom four (66%) had unsuppressed GH levels. In these four patients, the LVEF response to exercise was significantly lower than that in patients with suppressed GH during therapy (49.2 ± 4.7% *vs.* 64.2 ± 3.8%; $P < 0.05$). With respect to the healthy population, the EF response to exercise was reduced in both acromegalic patients and hyperthyroid patients ($P < 0.05$ in both cases; Fig. 3). The exercise-induced change in LVEF (Δ LVEF) was significantly lower in hyperthyroid acromegalic patients than in healthy controls ($P < 0.001$), but not in hyperthyroid controls ($P < 0.07$; Fig. 3). In the group of hyperthyroid acromegalic patients, a significant correlation was found between GH values and LVEF at rest (r = -0.896; $P < 0.05$), at peak exercise (r = -0.950; $P < 0.001$), and as Δ LVEF (r = -0.888; $P < 0.05$). Δ LVEF was correlated with PFR at rest (r = 0.740; $P < 0.05$). PFR was significantly lower in the patient population compared with those in healthy and hyperthyroid controls ($P < 0.05$ and < 0.001, respectively) and inversely correlated with age (r = -0.718; $P < 0.05$) and disease duration (r = -0.745; $P < 0.05$). Hyperthyroid status exerted a precocious muscular exhaustion in acromegalic

TABLE 4. Hemodynamic parameters, left ventricular functional, and morphological data for acromegalic patients at different follow-up evaluations

Parameters	Study 0	Study 1	P	Study 2	Study 3	P
HR (beats/min)						
r	76 ± 3.1	73.9 ± 2	NS	$111.7 \pm 6.2^{a,b}$	71.1 ± 4.1	0.001
e	136.7 ± 3.9	129.6 ± 4.9	NS	$156.3 \pm 7.1^{a,b}$	124.1 ± 3.3	0.05
SBP (mm Hg)						
r	128.8 ± 4.2	124.2 ± 4.1	NS	131.1 ± 6.3	125.9 ± 4.9	NS
e	149.6 ± 6.6	146 ± 5.9	NS	153.4 ± 6	149 ± 3.7	NS
DBP (mm Hg)						
r	94.6 ± 3	90.2 ± 3	NS	97.1 ± 3.9	93.4 ± 2.1	NS
e	111.6 ± 4.1	107 ± 3.3	NS	114.1 ± 3.1	109.4 ± 3.6	NS
LVMi (g/m²)						
r	142 ± 11.2	121 ± 12.1	0.05	$128.6 \pm 12^{a,b}$	120.4 ± 11.5^{a}	0.05
LV EF (%)						
r	53.1 ± 3	60.1 ± 2.8	0.05	$67.5 \pm 2.5^{a,b}$	58.6 ± 1.6^{a}	0.05
e	51.6 ± 2.7	64.6 ± 2.2	0.05	58 ± 4.4^{b}	61.5 ± 2^{a}	0.05
ΔEF	-2.1 ± 4.4	8.1 ± 2.9	0.05	$-14.5 \pm 4.7^{a,b}$	4.8 ± 1.7^{a}	0.05
PER (EDV/s)						
e	3.6 ± 0.3	3.5 ± 0.3	NS	3.4 ± 0.2	3.2 ± 0.2	NS
PFR (EDV/s)						
r	2.7 ± 0.2	3.1 ± 0.3	NS	2.4 ± 0.2	2.9 ± 0.3	NS
PFR (SV/s)						
r	3.2 ± 0.4	3.8 ± 0.2	NS	3 ± 0.2^{b}	3.8 ± 0.1	0.05
PFR/PER						
r	0.77 ± 0.1	0.87 ± 0.1	NS	0.74 ± 0.1	0.9 ± 0.1	NS
EC (watts)						
e	84.3 ± 8.1	96.8 ± 9.9	NS	65.6 ± 7.1^{b}	93.7 ± 10.3	0.05
ED (min)						
e	7.1 ± 0.9	8.4 ± 0.6	NS	6.3 ± 0.2^{b}	8.1 ± 0.7	0.05

For abbreviations of cardiovascular parameters, see the text. r and e indicate resting and exercise testing, respectively. Study 0, Patients at diagnosis of active acromegaly; study 1, patients after treatment of acromegaly; study 2, patients at the onset of hyperthyroidism; study 3, patients after achieving hyperthyroidism remission. Individual *P* values are reported in the text.

[a] Significant *vs.* study 0.
[b] Significant *vs.* study 1.

patients, with reduced exercise capacity and duration compared with both healthy controls ($P < 0.05$ and < 0.001) and control hyperthyroid patients ($P < 0.05$). Remarkably, three acromegalic patients precociously concluded their workout due to muscular exhaustion.

Longitudinal study (Table 4). In study 2, LVMi values were higher than those in study 1 ($P < 0.05$), whereas LVMi values were lower compared to data recorded in study 0 ($P < 0.05$; Fig. 2). A direct correlation was found between LVMi values obtained in study 0 and those recorded in study 2 (r = 0.705; $P < 0.05$). Resting LVEF was significantly enhanced compared to both previous follow-up values ($P < 0.001$ and 0.05, respectively), but the response to exercise was impaired, and the Δ LVEF was lower compared to values recorded in study 1 ($P < 0.05$ and 0.001, respectively; Fig. 4). Additionally, exercise capacity and duration were reduced compared to results obtained during study 1 ($P < 0.05$ in both cases). The achievement of euthyroidism (study 3) was followed by a significant reduction of LVMi ($P < 0.05$) in all patients, and a normalization of LVMi was observed in one patient (no. 2, Fig. 2). A prompt improvement of cardiac performance at peak exercise was similarly obtained, with an increase in LVEF at peak exercise as well as in Δ LVEF ($P < 0.05$ in both cases; Fig. 4). An exercise-induced change in LVEF was correlated to PFR (r = 0.780; $P < 0.05$). Additionally, exercise capacity and duration improved ($P < 0.05$ in both cases).

Discussion

Cardiovascular disorders associated with both acromegaly and hyperthyroidism have been extensively studied, and they are known to progressively lead to structural and functional impairment of the heart (1–6). The evaluation of cardiac morphology and function in eight thyrotoxic acromegalic patients showed an increase in the left ventricular mass and a reduction of cardiac performance during physical exercise. Cardiac performance was enhanced in resting conditions, as shown in control hyperthyroid patients, but an impaired response at peak exercise and a premature muscular exhaustion were observed, probably as a result of the reduced functional reserve. Additionally, tachyarrhythmia or atrial fibrillation was observed. Hyperthyroidism exerted a detrimental effect that was more evident in patients failing to achieve GH and IGF-I suppression. These results taken together suggest an enhanced cardiovascular risk when acromegaly is complicated with hyperthyroidism, especially in patients with persistently elevated GH and IGF-I levels.

Although a limited number of investigations of the coexistence of acromegaly and hyperthyroidism currently exist (7, 26, 28), growing evidence has accumulated that the thyroid can be enlarged in up to 92% of acromegalic patients (26–29), independently of TSH levels (28, 33). Data concerning the prevalence of hyperthyroidism in the setting of acromegaly are not uniform, as it was reported to range between 3.5–26% (7, 26, 28). In our experience, 9 patients
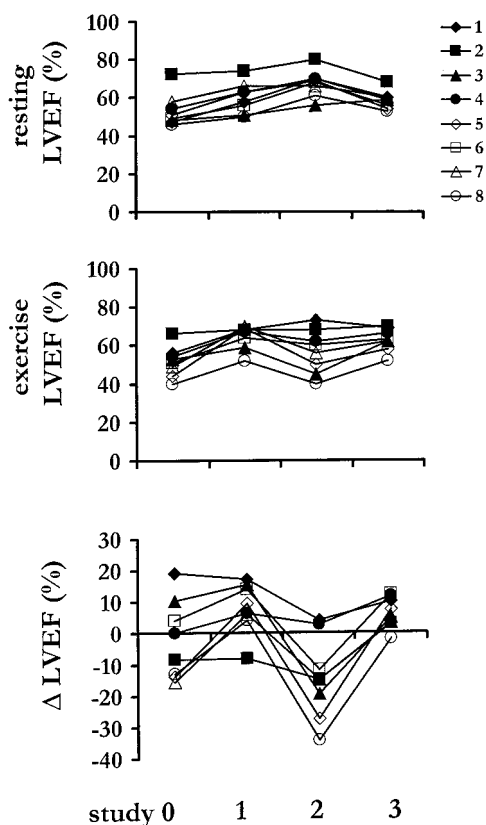
FIG. 4. Individual data of LVEF in the resting condition (*top*), at peak exercise (*middle*), and as exercise-induced change (Δ LVEF; *bottom*) in acromegalic patients during the different follow-up evaluations (longitudinal study). Patients are numbered as described in the text.

presenting hyperthyroidism after having received a diagnosis of acromegaly and 1 other patient coming to our attention with both diseases concomitantly accounted for a prevalence of 10.7%. Of these 10 patients, 8 were included in the present study and were receiving treatment for acromegaly at the onset of hyperthyroidism. In particular, 1 patient had been cured by surgery and radiotherapy, whereas the remaining 7 were subjected to chronic octreotide therapy. Whether octreotide treatment could have triggered thyroid hyperfunction is difficult to estimate. Neither previous report supports this evidence (26–29). Instead, it has been proposed that chronic GH and IGF-I excess could stimulate the thyroid to develop morphological and functional changes, in a fashion that would be TSH independent (26–29). Therefore, in our series of hyperthyroid acromegalic patients, hyperthyroidism seems to have occurred as a complication in the natural course of acromegaly itself. Among our patients, biochemical and clinical features suggestive of Graves' disease were present in 4 subjects, 2 of whom showed ultrasonographic and scintigraphic features of toxic multinodular goiter, at variance with the classical presentation of Graves' disease (34). All of the remaining hyperthyroid patients had toxic multinodular goiter.

The majority of our patients exhibited signs and symptoms of cardiovascular involvement. In acromegaly, heart disorders are prominent factors in rising morbidity and mortality (7–10). Nevertheless, patients may be clinically asymptom-

atic for long, that is because cardiac impairment develops stepwise (5). Initially, cardiac performance is increased and predisposes to concentric myocardial hypertrophy. This, in turn, weakens diastolic filling and impairs systolic performance (5, 11–16), although other complications, such as arterial hypertension, arrhythmias, and coronary artery disease, may be synergistically harmful (5, 15). It is conceivable that unless a prompt suppression of GH and IGF-I excess is achieved (35–37), cardiac performance may progressively worsen, and in more advanced stage of disease, ventricular dilatation and congestive heart failure may occur (5, 12–15).

There is general agreement, on the other hand, that cardiac arrhythmias and hyperdynamic circulatory state are integral parts of the hyperthyroid syndrome (19). It has been demonstrated that both thyroid hormone administration and hyperthyroidism can be accompanied by reduced vascular resistance and increased cardiac output (6, 17–21, 25). The overall effect of these changes is to alter the loading condition in the heart and to realize, in a sequence sharing some homology with that observed in the early stages of acromegaly (6, 20, 22), a hyperkinetic syndrome. Although in a very recent study the treatment with T_3 was shown useful after surgery in chilidren with congenital heart disease (40), the hemodynamic change can contribute to cardiac hypertrophy (6, 25). It has been shown that not only is the contractile reserve reduced and the ejection fraction inadequate to effort (18–20), but heart failure may also develop (19, 24, 37, 38, 39). As aging and/or preexisting cardiac disorders have been claimed to increase the risk of congestive heart failure during hyperthyroidism (17, 19), it could be speculated that the concomitant presence of acromegalic cardiomyopathy might have accelerated cardiac impairment.

In our series of acromegalic patients, the increase in LVMi, the enhancement of cardiac performance at rest, and the presence of an overt failure at peak exercise were clearly observed. Four patients, showing unsuppressed GH values when hyperthyroidism was diagnosed, showed a significant increase in LVMi and a significant reduction of LVEF at peak exercise compared with patients showing controlled disease. A positive correlation was found between GH levels and cardiac mass, whereas they inversely correlated to the LVEF at peak exercise. These findings are emblematic of a reduction of the functional cardiac reserve when hyperthyroidism develops in the setting of acromegaly. As the worsening of cardiac morphology and function is particularly evident in patients with unsuppressed GH and IGF-I, this is indicative of persisting cardiovascular impairment unless hormone suppression is achieved. To this extent, effective and prolonged GH and IGF-I suppression undoubtedly represents a restraining factor for the patient's well-being. The observations presented in this report are therefore in agreement both with data showing incomplete reversal of cardiac abnormalities after recovery of acromegaly (5, 12, 13, 36) and with other reports indicating a correlation between GH suppression and cardiovascular performance (35) or mortality (7–10).

Although the results of this study could be biased by the limited number of patients, any randomized or prospective investigation seems inapplicable due to the scant prevalence of hyperthyroidism in acromegaly. Rather, these findings eventually support the concept that cardiovascular instabil-

ity in acromegaly, which is aggravated by the presence of hypertension and glucose tolerance abnormalities (41), may benefit by prompt recognition of concomitant endocrine disorders and a combined curative approach. Although current therapeutic solutions for acromegaly can lead to clinical and cardiovascular improvement in many cases, incomplete hormonal suppression seems to limit further progression. Thus, a constant surveillance of other endocrine circuits as well as of the cardiovascular system remains a crucial step in the follow-up of acromegalic patients.

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