0021-972X/01/$03.00/0
The Journal of Clinical Endocrinology & Metabolism

Vol. 86, No. 4
Printed in U.S.A.

Is the Acromegalic Cardiomyopathy Reversible? Effect of 5-Year Normalization of Growth Hormone and Insulin-Like Growth Factor I Levels on Cardiac Performance*

ANNAMARIA COLAO, ALBERTO CUOCOLO, PAOLO MARZULLO, EMANUELE NICOLAI, DIEGO FERONE, ANNA MARIA DELLA MORTE, ROSARIO PIVONELLO, MARCO SALVATORE, AND GAETANO LOMBARDI

Departments of Molecular and Clinical Endocrinology and Oncology (A.Co., P.M., D.F., R.P., G.L.) and Nuclear Medicine Center of the National Council of Research, Department of Biomorphological and Functional Sciences (A.Cu., E.N., A.M.D.M., M.S.), Federico II University of Naples, 80131 Naples, Italy; and Scientific Institute for Research and Care Neuromed (A.Cu., R.P.), 86077 Pozzilli, Italy

ABSTRACT

Acromegalic patients are considered to be exposed to a doubled mortality rate, mostly for cardiovascular diseases. This open prospective study was designed to evaluate whether the impairment of cardiac performance could be reversed by the long-term suppression of GH and insulin-like growth factor I (IGF-I) levels.

Eighteen patients with active acromegaly were studied before and 5 yr after surgery, followed by sc octreotide in 11 patients. Disease control (GH levels $\leq$1 μg/L after glucose load or $\leq$2.5 μg/L after fasting, respectively, together with normalized IGF-I levels for age) was achieved in seven patients after surgery and in six patients after 0.3–0.6 mg/day sc octreotide. Five patients were not controlled during the 5-yr follow-up. Cardiac performance at rest and at peak exercise was assessed by equilibrium radionuclide angiography at study entry and 5 yr after surgery alone or plus octreotide. Thirty-six sex- and age-matched healthy subjects served as controls.

At study entry, patients had a lower left ventricular ejection fraction (LVEF) at peak exercise and LVEF exercise-induced changes, exercise duration, and capacity than controls ($P < 0.001$). After 5 yr of treatment, a significant decrease of resting heart rate ($P = 0.03$) and a significant increase of LVEF at peak exercise ($P = 0.003$) was found in patients achieving disease control. LVEF response at peak exercise worsened in none of the patients with controlled disease and in three patients with uncontrolled disease (60%) ($\chi^2 = 5.5$; $P = 0.02$). Diastolic filling, exercise duration, and workload did not significantly change during the 5-yr follow-up. No difference was found between patients controlled by surgery alone or by surgery plus octreotide.

This 5-yr prospective study demonstrated that the LVEF response at peak exercise improved in all patients achieving disease control, while it was worsened in 60% of uncontrolled ones. These results strengthen the need of a stable suppression of GH and IGF-I hypersecretion to restore a normal cardiac performance in acromegaly. (*J Clin Endocrinol Metab* **86:** 1551–1557, 2001)

ACROMEGALIC PATIENTS ARE considered to be exposed to a doubled mortality rate, mostly for cardiovascular diseases (1–6). In recent years, both GH and insulin-like growth factor I (IGF-I) excess and deficiency have been found associated with several changes of cardiac structure and function (7, 8). In acromegaly, particularly, concentric cardiac hypertrophy is a frequent clinical and instrumental finding at diagnosis, even in young patients with short disease duration (9–11). As a consequence of this phenomenon, an early impairment of the left ventricular (LV) diastolic filling has been described (12–16), whereas systolic dysfunction may develop in later stages of untreated disease (7, 8). Other cardiovascular and metabolic disorders, such as arterial hypertension, coronary artery disease, ventricular arrhythmias, diabetes mellitus, and thyroid disorders are observed in some patients with acromegaly and can independently worsen the acromegalic cardiomyopathy (17, 18), which seems, however, to be a specific disease (19).

Whether the acromegalic cardiomyopathy might be reversed by achieving the biochemical control of the primary disease, is still controversial. A significant decrease of the LV mass (LVM) has been observed after long-term treatment with octreotide (20–23) or lanreotide (24, 25). The decrease of LVM was generally followed by an improvement of LV filling (20–25). Conversely, the LV systolic function, measured as LV ejection fraction (LVEF) either by echocardiography (20–25) or by radionuclide angiography (26), was unchanged after long-term treatment of acromegaly, except in a few cases of overt heart failure (27).

However, if the hypothesis that the impairment of the cardiac performance was due to chronic GH and IGF-I excess is correct, then changes of cardiac function should be related to the efficacy of treatment. Recently, we demonstrated that patients achieving disease control after 1 yr of treatment with sc octreotide had a significant improvement of LVEF, both at rest and at peak exercise, whereas those with persistently uncontrolled disease had a further impairment of cardiac performance (28). These data are insinuative that the prolonged suppression of circulating GH and IGF-I levels might normalize the cardiac perfor-

Received May 23, 2000. Revision received August 15, 2000. Rerevision received December 6, 2000. Accepted December 6, 2000.

Address correspondence and requests for reprints to: Annamaria Colao, M.D., Ph.D., Department of Molecular and Clinical Endocrinology and Oncology, Federico II University of Naples, via Sergio Pansini 5, 80131 Naples, Italy. E-mail: colao@unina.it.

* Partially supported by Grant 9906153187 from Ministero Universitá e Ricerca Scientifica e Technologica (Rome, Italy).

mance, thus helping in reversing the poor prognosis for cardiovascular disorders in acromegaly.

The aim of this open prospective study was to investigate the potential reversibility of the acromegalic cardiomyopathy during successful long-term treatment of the primary disease. To address this issue, LV diastolic and systolic functions were assessed at rest and at peak physical exercise by radionuclide angiography in patients with active acromegaly before and after 5 yr of treatment. Basal and posttreatment results were compared with those obtained in an appropriate control group. Changes of cardiac performance were correlated to the therapeutic success in terms of disease control, currently accepted as fasting or glucose-suppressed GH 2.5 μg/L per 1 μg/L or greater, respectively, and IGF-I levels were normalized for age (29, 30).

Patients and Methods

Patients

Eighteen patients with uncomplicated acromegaly constituted the patient population: nine women and nine men; age, 18–65 yr. Latent coronary artery disease was excluded using exercise myocardial perfusion tomography. The diagnosis of acromegaly was based on high serum GH levels during an 8-h time-course sampling, not suppressible below 2 μg/L after an oral glucose test (75 g), and high plasma IGF-I levels for age (9, 29). The presumed duration of acromegaly was assessed by comparison of a patient's photographs taken during a 1- to 3-decade span and by a patient's interviews to date the onset of acral enlargement; in the present series the estimated disease duration ranged from 4–30 yr. As the control group, 36 healthy volunteers sex- and age-matched with the patients (21 women and 15 men; age, 20–60 yr) were studied. All patients and controls gave their informed consent to participate in this study, approved by the ethical committee of the Medical School of the Federico II University of Naples. Five of 18 patients and 10 of the 36 controls were mild smokers (<10 cigarettes per day), and all had a sedentary lifestyle. Clinical, endocrine, and cardiac data of patients and controls are shown in Table 1.

Study protocol

At study entry, IGF-I levels were assayed twice in a single sample whereas the GH level was calculated as the mean of a 6-h blood sampling (0800–1400 h with 30-min sampling). Heart rate, blood pressure measurements, and electrocardiogram were performed in all patients. Hypertension was diagnosed in the presence of diastolic blood pressure greater than 90 mm Hg, in line with WHO criteria (31). Hormonal and clinical evaluations were carried out before treatment, monthly in the first 3 months of treatment, and quarterly during the first year of treatment, then yearly. During treatment, fasting GH level was calculated as the average value of at least three blood samples collected at 15-min intervals at 0800 h (in patients studied the first year after surgery alone) or 2 h after octreotide administration (in patients studied during octreotide treatment). However, in patients cured after surgery, the yearly evaluation of GH level was performed by calculating the mean of a 6-h blood sampling (0800–1400 h with 30-min sampling). At this time point, plasma IGF-I concentrations were assayed as single sampling. Radionuclide angiography was performed before treatment and after 1, 3, and 5 yr. In a subset of these patients, the results after the first year of follow-up have been previously reported (26, 28). The results of the 5-yr follow-up only were reported in this study.

Treatment protocol

All patients included in this study underwent surgical removal of the pituitary adenoma, producing a definitive cure in 7 of them. In the remaining 11, surgery allowed partial tumor removal. Persistent elevation of circulating GH and IGF-I levels led to start treatment with octreotide, initially administered at a dose of 0.05–0.1 mg three times daily in accordance with the individual patient's tolerability (32), then increased to achieve disease control. Six octreotide-treated patients achieved disease control, whereas no effective and continuous disease control was obtained in the remaining five patients during the follow-up, despite transient increase of octreotide dosage up to 1.5 mg/day. This

TABLE 1. Hormone levels and hemodynamic and functional parameters measured at rest and at peak exercise by equilibrium radionuclide angiography in healthy controls and patients with uncomplicated acromegaly

Parameters	Controls (n = 36)		Patients (n = 18)		*P*
	Range	Mean ± SEM	Range	Mean ± SEM	
Age (yr)	23–60	38.7 ± 1.9	18–65	40.1 ± 2.7	
Serum GH levels (μg/L)[a]	0.1–1.2	0.4 ± 0.03	8–130	43.9 ± 9	0.0001
Plasma IGF-I levels (μg/L)	130–333	230.3 ± 9.2	350–850	600.7 ± 36.4	0.0001
Heart rate (bpm)					
At rest	48–96	73.9 ± 2.0	60–105	79.4 ± 2.9	0.5
During exercise	95–191	140.7 ± 3.5	103–168	135.4 ± 4.7	0.6
Systolic blood pressure (mm Hg)					
At rest	100–135	121.4 ± 1.2	90–150	121.1 ± 3.6	1
During exercise	130–200	165.0 ± 3.1	130–210	175.0 ± 5.6	0.6
Diastolic blood pressure (mm Hg)					
At rest	60–90	79.3 ± 1.2	60–90	76.4 ± 2.4	0.5
During exercise	80–120	100.0 ± 2.2	75–140	97.2 ± 3.3	0.3
Ejection fraction (%)					
At rest	50–78	61.6 ± 1.0	46–76	58.7 ± 1.7	0.4
During exercise	56–95	72.5 ± 1.5	37–75	56.1 ± 2.4	0.001
Δ (%)	0–50.7	17.8 ± 2.2	24–11.1	−4.9 ± 2.6	0.001
PER (EDV/sec)	2.1–5.5	3.6 ± 0.1	2.4–4.5	3.6 ± 0.1	1
PFR (EDV/sec)	1.6–4.1	2.8 ± 0.1	1.2–4.9	3.1 ± 0.2	0.6
PFR (SV/sec)	2.8–6.8	4.5 ± 0.1	2.1–9.7	5.1 ± 0.4	0.7
PFR/PER	0.4–1.1	0.7 ± 0.02	0.4–1.2	0.8 ± 0.05	0.05
Exercise duration	6–12	9.4 ± 0.2	6–8	6.9 ± 0.2	0.001
Exercise potency	75–125	100.0 ± 2.8	50–125	80.0 ± 3.7	0.001

[a] GH values are the mean of a 6-h blood sampling. The normal GH value was ≤2.5 μg/L. The normal IGF-I range in 20- to 30-, 31- to 40-, 41- to 50-, and over-50-yr-old subjects was 110–502, 100–494, 100–303, and 78–258 μg/L, respectively. Normal blood pressure DBP ≤ 90 mm Hg. The normal PFR was ≥2.5 EDV/sec. The normal ejection fraction at rest was >50% and the normal response of the ejection fraction at peak exercise was >5% of resting values.

dose was no longer maintained during the follow-up because GH and IGF-I did not normalize. The maximal dose used in this study was 0.6 mg/day. All 18 patients had been treated with octreotide before surgery at doses of 0.3–0.45 mg/day for 3–6 months, as described previously (33).

Gated blood-pool cardiac scintigraphy

In vivo labeling of red blood cells was performed with 555 MBq (15 mCi) technetium-99m. Equilibrium radionuclide angiography was performed at rest and during dynamic physical exercise as previously described (15, 16, 28). A small field of view gamma camera (Starcam 300 A/M; General Electric, Milwaukee, WI) equipped with a low-energy all-purpose collimator was used. Exercise studies were performed using a bicycle ergometer with a restraining harness to minimize patient motion under the camera. Exercise loads were increased by 25 W every 2 min until angina, limiting dyspnea, or fatigue developed. Heart rate and blood pressure (by cuff sphygmomanometer) were monitored during exercise at each stage. No patient developed high-grade ventricular arrhythmia necessitating termination of exercise. Radionuclide angiography studies were performed using a standard commercial software system (General Electric). Indices of LV function were derived by computer analysis of the background corrected time-activity curve, as reported previously (15, 16, 28). Both peak ejection rate (PER) and peak filling rate (PFR) were computed in LV counts/sec, normalized for the number of counts at end-diastole and expressed as end-diastolic volume (EDV)/sec. When normalized for EDV, both PER and PFR are influenced directly by the magnitude of LVEF (34). To minimize this effect, we also analyzed the PFR using two additional normalization methods; it was expressed relative to the LV stroke volume and as the ratio between PFR and PER (35, 36). These two latter methods have the additional advantage of being background independent. LV diastolic filling was considered abnormal when the PFR was less than 2.5 EDV/sec, the LVEF was considered insufficient if less than 50% at rest and/or it increased less than 5% at peak exercise compared with resting condition (37). All of the examinations were performed by three independent observers (A.Cu., E.N., and A.M.D.M.) blind as to patient status.

Assays

Serum GH levels were measured by immunoradiometric assay (IRMA) (HGH-CTK-IRMA; Sorin, Saluggia, Italy). The sensitivity of the assay was 0.2 μg/L; 1 μg/L corresponds to 3 mU/L. The intra- and interassay coefficients of variation (CV) were 4.5% and 7.9%, respectively. Plasma IGF-I was measured by IRMA after ethanol extraction using Diagnostic Systems Laboratories kits (Webster, TX). The sensitivity of the assay was 0.8 μg/L. The intra-assay CV were 3.4, 3.0, and 1.5% for the low, medium, and high points on the standard curve, respectively. The interassay CV were 8.2, 1.5, and 3.7% for the low, medium, and high points on the standard curve, respectively.

Statistical analysis

Data are reported as mean ± SEM. Student's *t* test for paired data (to evaluate the effect of treatment in individual patients), ANOVA (to evaluate the effect of treatments in the patients groups in line with treatment efficacy and to compare patients and controls), and χ^2 test were used where appropriate. Spearman's rank correlation test was used to analyze the correlation between the patients' age and gain in the exercise-induced changes of ejection fraction. The significance was set at 5%.

Results

At study entry, acromegalic patients had a lower LVEF at peak exercise and LVEF exercise-induced changes, exercise duration, and capacity than controls (Table 1). In particular, 6 patients (33.3%) and 10 controls (27.8%) had abnormal PFR, 2 patients (11.1%) and 1 control (2.8%) had impaired LVEF at rest, whereas 14 patients (77.8%) and 5 controls (13.9%) ($\chi^2 = 18.8$; $P < 0.0001$) had abnormal LVEF response at peak exercise.

At the 5-yr follow-up, both GH (from 43.9 ± 9 to 2.6 ± 1.5 μg/L; $P < 0.0001$) and IGF-I levels (from 600.7 ± 36.4 to 316.9 ± 46.8 μg/L; $P < 0.0001$) were significantly reduced compared with baseline, but only 13 patients achieved disease control. Seven of these patients were cured by surgery alone, five within the first year and the remaining two during the second year after surgery. In the latter patients, octreotide therapy was not started because IGF-I levels were only slightly elevated during the first year after surgery, and GH levels were suppressed between 1 and 2 μg/L by glucose load. Six of the remaining 13 patients achieved disease control under increasing doses of octreotide during the first year of treatment. In 5 patients, octreotide treatment did not induce disease control during the 5-yr follow-up, but it significantly decreased GH and IGF-I levels (Table 2). Two elderly not-controlled patients showed fluctuations of GH and IGF-I levels into the normal range, indicating a partial control of the disease. No age difference was found between the groups of patients achieving or not achieving disease control, but a trend toward an older age in uncontrolled patients was found (Table 2). At the 5-yr follow-up, a significant decrease of resting heart rate (from 79.4 ± 2.9 to 72.0 ± 2.6 beats per minute (bpm); $P = 0.04$), a significant increase of LVEF at peak exercise (from 56.1 ± 2.4 to 64.1 ± 2.6%; $P = 0.004$), and a percent change after exercise (from −4.9 ± 2.6 to 6.9 ± 3.2%; $P = 0.001$) was found in the whole series. Conversely, no difference was found in blood pressure, diastolic filling, and exercise duration and capacity.

When the analysis was performed on the basis of treatment efficacy, only in patients achieving disease control were heart rate and systolic and diastolic blood pressure at rest significantly decreased and increased, respectively (Table 2). No change of heart rate and systolic and diastolic blood pressure was found at peak exercise. The LVEF at rest was unchanged both in patients with and in those without disease control (Table 2). LVEF at rest normalized in the patient with disease control, whereas it was still abnormal in the patient with poor controlled disease. LVEF at peak exercise and its exercise-induced changes were significantly increased only in the patients achieving disease control ($P = 0.003$ and $P < 0.001$, respectively; Table 2), both after surgery and after surgery plus octreotide (Fig. 1). By contrast, patients with uncontrolled disease showed a trend toward a further impairment of exercise-induced changes of LVEF (Fig. 1 and Table 2). Among the 14 patients with LVEF failure at peak exercise, 10 achieved disease control during the follow-up; LVEF significantly improved in all and normalized in 5 (Fig. 1). Two patients showing persistently high GH and IGF-I levels during the follow-up had LVEF improvement at peak exercise, whereas the remaining three patients (60%) impaired their LVEF at peak exercise (Fig. 1). The worsening of LVEF response at peak exercise was significantly associated with uncontrolled disease ($\chi^2 = 5.5$; $P = 0.02$). The LV diastolic filling, except for a decrease of PFR in controlled patients ($P = 0.03$), PER, exercise duration, and workload, did not significantly change during the 5-yr follow-up in all patients (Table 2). No difference was found in the parameters of cardiac function between patients controlled after surgery alone or after surgery plus octreotide (Fig. 2).

At the end of follow-up, patients with controlled disease

TABLE 2. Hormone levels hemodynamic and functional parameters measured at rest and at peak exercise by equilibrium radionuclide angiography in patients with acromegaly after 5 years of surgery (patient 7) or octreotide treatment (patient 11)

Parameters	Patients with controlled disease (n = 13)			Patients with uncontrolled disease (n = 5)		
	Basal	Treatment	*P*	Basal	Treatment	*P*
Age (yr)	34.7 ± 2.7			48.4 ± 8.6		
Serum GH levels (μg/L)	40.2 ± 9.6	1.5 ± 0.3	0.002	53.1 ± 22.2	5.5 ± 0.7	0.09
Plasma IGF-I levels (μg/L)	619.0 ± 44.4	373.4 ± 30.8	<0.001	553.2 ± 64.3	430.0 ± 147.3	0.4
Heart rate (bpm)						
At rest	79.4 ± 2.8	72.8 ± 3.4	0.03	79.6 ± 7.9	69.8 ± 3.0	0.4
During exercise	136.5 ± 5.7	120.5 ± 4.3	0.07	132.4 ± 8.5	131.6 ± 6.7	0.9
Systolic blood pressure (mm Hg)						
At rest	117.3 ± 3.7	129.6 ± 4.1	0.01	131.0 ± 7.8	128.0 ± 9.6	0.9
During exercise	170.0 ± 6.7	179.6 ± 6.3	0.3	188.0 ± 8.6	180.0 ± 13.8	0.6
Diastolic blood pressure (mm Hg)						
At rest	75.4 ± 2.7	82.5 ± 2.1	0.01	79.0 ± 5.1	84.0 ± 4.0	0.3
During exercise	96.9 ± 4.3	103.5 ± 4.4	0.3	98.0 ± 4.9	98.0 ± 8.0	1.0
Ejection fraction (%)						
At rest	59.5 ± 2.2	60.1 ± 2.6	0.2	56.6 ± 3.0	60.4 ± 3.6	0.2
During exercise	55.8 ± 2.9	65.9 ± 2.7	0.003	56.8 ± 4.9	59.2 ± 6.2	0.6
Δ (%)	−6.5 ± 3.4	10.8 ± 3.4	<0.001	−0.7 ± 3.8	−3.1 ± 5.8	0.6
PER (EDV/sec)	3.6 ± 0.2	3.6 ± 0.2	0.8	3.4 ± 0.3	3.4 ± 0.3	0.6
PFR (EDV/sec)	3.2 ± 0.3	2.6 ± 0.2	0.03	2.5 ± 0.6	2.8 ± 0.4	0.4
PFR (SV/sec)	5.6 ± 0.6	4.5 ± 0.4	0.06	4.3 ± 0.8	3.6 ± 0.6	0.6
PFR/PER	0.9 ± 0.06	0.7 ± 0.06	0.09	0.7 ± 0.1	0.8 ± 0.08	0.3
Exercise duration	7.1 ± 0.3	7.1 ± 0.5	1	6.4 ± 0.4	7.4 ± 0.6	0.9
Exercise potency	80.0 ± 4.8	82.7 ± 7.6	0.2	80.0 ± 5.0	80.0 ± 5.0	0.3

Patients were sub-grouped on the basis of disease control evaluated by suppression of circulating GH levels (≥2.5 or 1 μg/L fasting or after oral glucose test, respectively) and normalization of IGF-I levels for age. GH values are the mean of at least three samples. The normal GH range was ≤7.5 mU/L. The normal IGF-I range in 20- to 30-, 31- to 40-, 41- to 50-, and over-50-yr-old subjects was 110–502, 100–494, 100–303, and 78–258 μg/L, respectively. The normal blood pressure was DBP ≤90 mm Hg. The normal PFR was ≥2.5 EDV/sec. The normal ejection fraction at rest was >50% and the normal response of the ejection fraction at peak exercise was >5% of resting values.

had still a slightly but significantly lower LVEF at peak exercise than sex- and age-matched controls (65.9 ± 2.7 *vs.* 74.5 ± 1.8%; $P < 0.01$) without any difference in the exercise-induced changes of LVEF (10.8 ± 3.4 *vs.* 19.5 ± 2.8%). In addition, patients achieving disease control had significantly lower heart rate (120.5 ± 4.3 *vs.* 140.0 ± 2.9 bpm; $P < 0.001$), and higher systolic (179.6 ± 6.3 *vs.* 160.4 ± 3.9 mm Hg; $P < 0.01$), but not diastolic, blood pressure at peak exercise than controls. The parameters of LV filling were similar in controlled patients and controls (Fig. 2). Similarly, exercise duration (7.1 ± 0.5 *vs.* 9.1 ± 0.2 min, $P < 0.001$) and capacity (82.7 ± 7.6 *vs.* 100.0 ± 3.1 W, $P < 0.01$) remained significantly lower in patients than in controls.

As a whole, no correlation was found between the patients' age and the gain in LVEF at peak exercise ($r = -2.38$; $P = 0.2$).

Discussion

The most important finding of this study is that cardiac performance improved in all patients achieving disease control during the 5-yr follow-up, and was normalized in 50% of them. The LVEF response at peak exercise was further impaired in 60% of the patients showing still slightly elevated GH and IGF-I levels during the follow-up. However, after 5 yr of disease control the LVEF at peak exercise was still significantly lower in the patients than in healthy sex- and age-matched controls.

The involvement of the heart in acromegaly has been recognized for over a century (38), and it has become progressively clear that cardiac abnormalities can be considered as major determinants of morbidity and reduction of life expectancy in this chronically developing disease (1–6). To reduce the negative effects of chronic GH and IGF-I hypersecretion, hormone levels should be constantly suppressed. Recent surveys studying mortality in acromegalic patients reported a significant decrease of the standard mortality rate when a suppression of GH levels below 2.5 μg/L was achieved (3, 4). Although no extensive study has accurately ascertained any correlation between the mortality rate in acromegaly and IGF-I levels, due to the relatively recent introduction of this assay, some consensus exists that IGF-I should be lowered to the appropriate age range (6, 39, 40). Aside from the well known beneficial effects of disease control induced by surgery or pharmacotherapy on most clinical signs and symptoms (29, 41, 42), the effect of GH and IGF-I suppression on the acromegalic cardiomyopathy has been less extensively investigated. Several studies have demonstrated a significant decrease of LV hypertrophy following successful surgery or somatostatin analog treatment (20–25). LVM reduction was generally accompanied by an improvement of the LV filling (20–25), the abnormality of which is known to precede that of systolic function when the primary disease is left untreated.

Whether the successful suppression of hormone levels is followed by a consequent improvement not only of cardiac hypertrophy but also of cardiac function in acromegalic patients is still debated, because systolic function was reported to be unaffected by GH/IGF-I suppression (20–25). However, all these studies investigated cardiac function by echocardiography, which is affected by two major limitations, the intra and interobserver variability and the poor sensitivity, due to the assumptions necessary to calculate the LVEF (43). However, even using a more sensitive technique, such as the

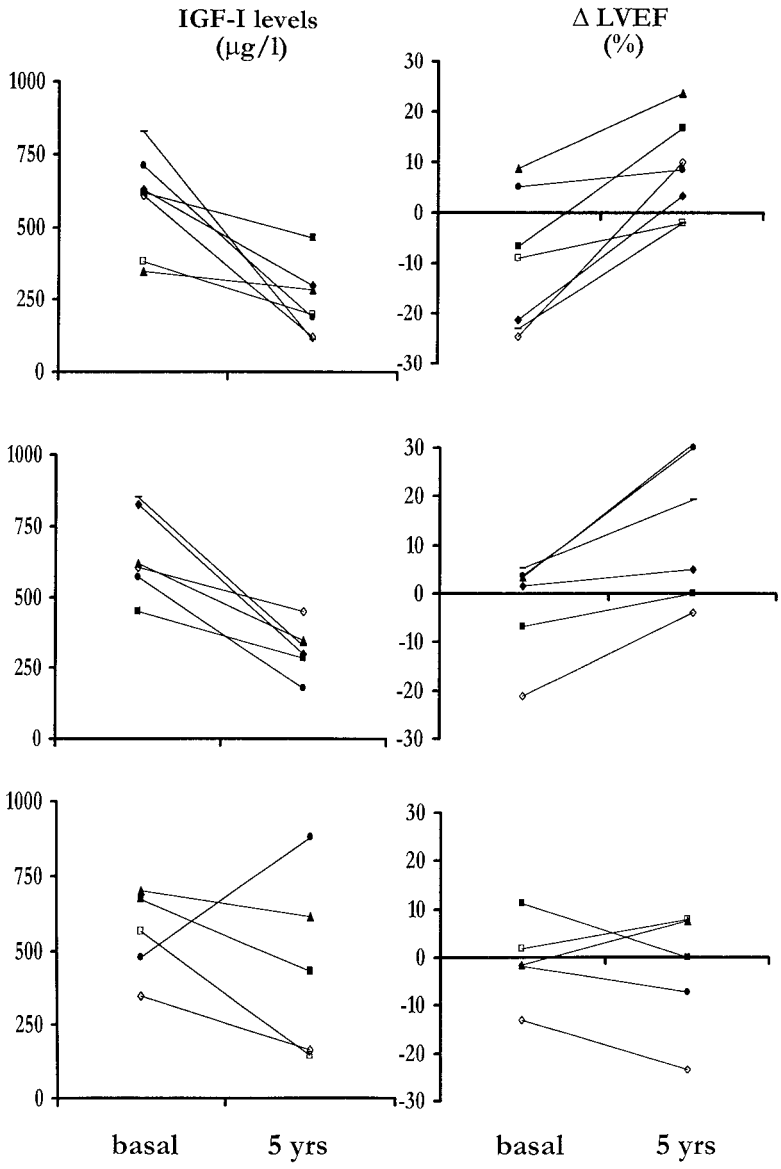

FIG. 1. Plasma IGF-I levels (*left*) and exercise-induced changes of LVEF (*right*) in patients achieving disease control after surgery (*top*) or after surgery plus octreotide (*middle*) and in those presenting elevated GH and IGF-I levels during the 5-yr follow-up (*bottom*).

equilibrium radionuclide angiography, we found no significant LVEF improvement after 12–24 months of treatment with sc octreotide (26). When the analysis of the results was performed in line with treatment effectiveness, a significant improvement of cardiac performance was observed only in patients achieving disease control (28). Interestingly, persistent disease activity led to a further impairment of LVEF response at peak exercise after 1 yr of unsuccessful octreotide treatment (28). Altogether, these data claimed the need for a strong and prolonged hormone suppression to stop the progression of the cardiomyopathy.

This long-term prospective study was designed to verify the potential reversibility of cardiac impairment characterizing acromegaly. Our results clearly demonstrated that all 13 patients achieving disease control after 5 yr of treatment either with surgery alone or combined with octreotide, reported improvement of cardiac performance, and restoration of a normal LVEF response at peak exercise was obtained in half of them. By contrast, among the five patients presenting moderately elevated GH and IGF-I levels during the follow-up, the LVEF response at peak exercise was clearly impaired in 60%. In the entire group, the parameters of diastolic filling were not significantly modified during the 5-yr follow-up and were similar to controls.

The treatment of acromegaly is also followed by some change in the hemodynamic parameters, which could affect cardiac performance *per se*. In fact, a significant reduction in heart rate at rest and at peak exercise in controlled patients and a significant increase in resting systolic blood pressure in uncontrolled patients have been previously observed after 1 yr of treatment with octreotide (28). The results of the present study confirmed that in controlled patients heart rate at rest was significantly decreased. In addition, heart rate at peak exercise was significantly reduced compared with control. Conversely, systolic and diastolic blood pressure at rest were significantly increased in controlled but not in uncontrolled patients. Whether the long-term suppression of IGF-I is followed by an increase of the vascular resistance nitric oxide mediated (44, 45), and thus

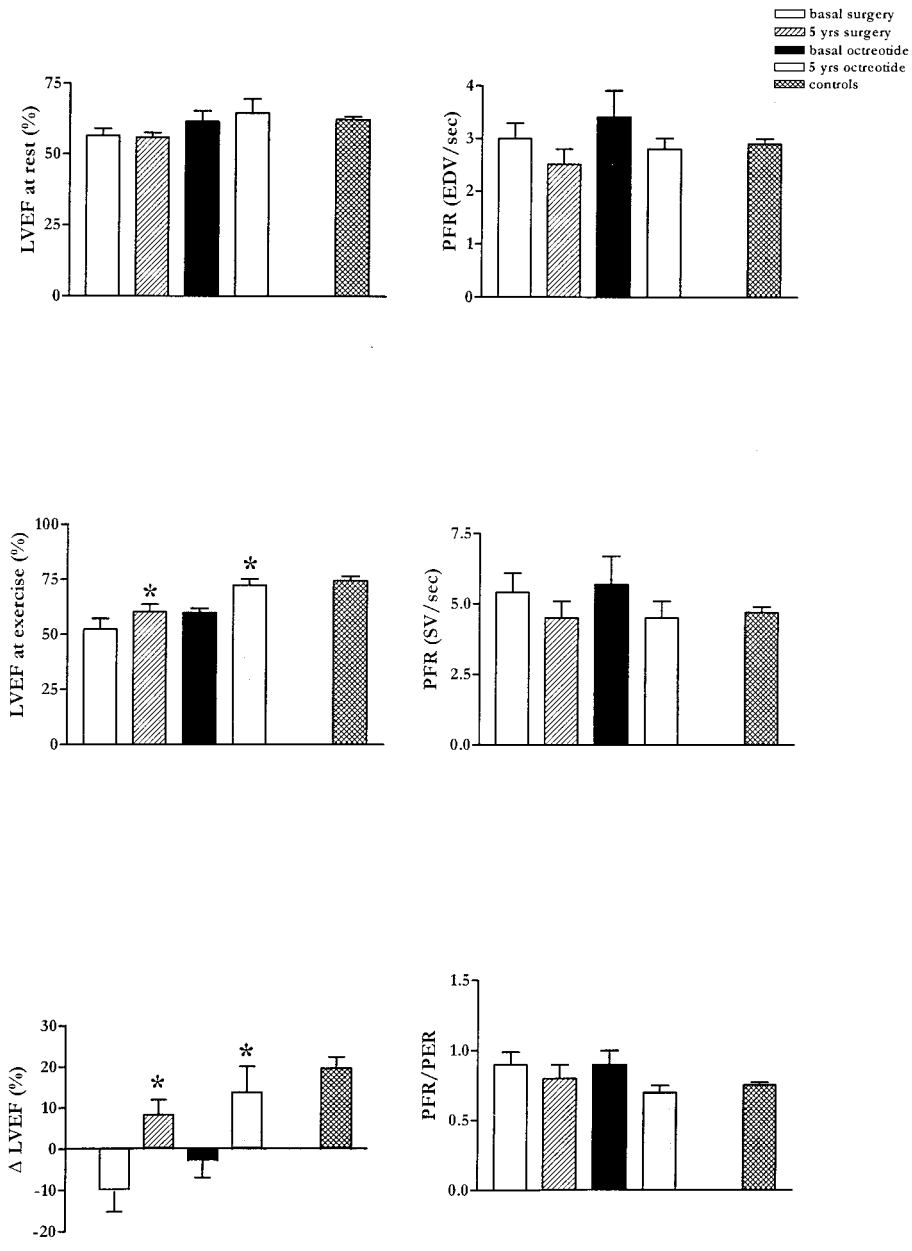

FIG. 2. LVEF at rest (*top left*) and at peak exercise (*middle left*), exercise-induced changes of LVEF (*bottom left*), PFR measured as EDV (*top right*), stroke volume (*middle right*) and as the ratio between PFR and PER (*bottom right*) in patients achieving disease control after surgery or octreotide compared with sex- and age-matched controls. *, $P < 0.01$ *vs.* baseline.

causes the increase in blood pressure in patients with disease control, cannot be ruled out. However, a similar pathogenetic mechanism has been claimed to explain the increase in blood pressure occurring in patients with GH deficiency (45). In contrast with previous data of short-term follow-ups (28), no improvement in physical performance, both exercise duration and exercise workload, was observed in this study. A direct cardiac effect of octreotide, as shown on cardiac mass in patients affected with primary hypertrophic cardiomyopathy (46, 47) or on heart rate via the conduction system (48), seems to be excluded by the evidence that the results were similar in patients controlled by surgery and in those controlled by octreotide.

In conclusion, the results of this open 5-yr prospective study indicate that the effective suppression of GH levels together with the age-adjusted normalization of plasma IGF-I levels after surgery or surgery plus pharmacotherapy with octreotide is followed by a significant improvement of cardiac performance in all patients, and by total recovery in half cases. The majority of patients still presenting with mildly elevated GH and IGF-I along the follow-up had a significant impairment of cardiac performance. These data strongly suggest that the suppression of GH and IGF-I to age-corrected normal limits is mandatory to improve or, at least arrest, the acromegalic cardiomyopathy. The increase in blood pressure after long-term GH and IGF-I control was unexpected and it cannot be ruled out whether it was a consequence of hormone suppression.

Acknowledgments

We are indebted to A. Giaccio, medical student at the Department of Molecular and Clinical Endocrinology and Oncology, Federico II University of Naples, for help in taking care of acromegalic patients.

References

1. **Nabarro JDN.** 1987 Acromegaly. Clin Endocrinol. 26:481–512.
2. **Bengtsson BA, Edén S, Ernest I, Oden A, Sjögren B.** 1988 Epidemiology and long term survival in acromegaly. Acta Med Scand. 223:327–335.
3. **Bates AS, Van't Hoff W, Jones JM, Clayton RN.** 1993 An audit of outcome of treatment in acromegaly. Q J Med. 86:293–299.
4. **Rajasoorya C, Holdaway IM, Wrightson P, Scott DJ, Ibbertson HK.** 1994 Determinants of clinical outcome and survival in acromegaly. Clin Endocrinol. 41:95–102.
5. **Wright AD, Hill DM, Lowy C, Russell Fraser T.** 1970 Mortality in acromegaly. Q J Med. 153:1–16.
6. **Orme SM, McNally RJQ, Cartwright RA, Belchetz PE.** 1998 Mortality and cancer incidence in acromegaly: a retrospective cohort study. J Clin Endocrinol Metab. 83:2730–2734.
7. **Saccà L, Cittadini A, Fazio S.** 1994 Growth hormone and the heart. Endocr Rev. 15:555–573.
8. **Lombardi G, Colao A, Marzullo P, et al.** 1997 Is growth hormone bad for your heart: cardiovascular impact of GH deficiency and excess. J Endocrinol. 155:S33–S37.
9. **Colao A, Merola B, Ferone D, Lombardi G.** 1997 Acromegaly. J Clin Endocrinol Metab. 82:2777–2781.
10. **Minniti G, Jaffrain-Rea ML, Moroni C, et al.** 1998 Echocardiographic evidence for a direct effect of GH/IGF-I hypersecretion on cardiac mass and function in young acromegalics. Clin Endocrinol. 49:101–106.
11. **Fazio S, Cittadini A, Biondi B, et al.** 2000 Cardiovascular effects of short-term growth hormone hypersecretion. J Clin Endocrinol Metab. 85:179–182.
12. **Bertoni PD, Morandi G.** 1987 Impaired left ventricular diastolic function in acromegaly: an echocardiographic study. Acta Cardiol. 42:1–10.
13. **Rodrigues EA, Caruana MP, Lahiri A, Nabarro JDN, Jacobs HS, Raftery EB.** 1989 Subclinical cardiac dysfunction in acromegaly: evidence for a specific disease of heart muscle. Br Heart J. 62:185–194.
14. **Sicolo N, Bui F, Sicolo M, et al.** 1993 Acromegalic cardiopathy: a left ventricular scintigraphic study. J Endocrinol Invest. 16:123–127.
15. **Cuocolo A, Nicolai A, Fazio S, et al.** 1995 Impaired left ventricular diastolic filling in patients with acromegaly: assessment with radionuclide angiography. J Nucl Med. 36:196–201.
16. **Colao A, Cuocolo A, Marzullo P, et al.** 1999 Impact of patient's age and disease duration on cardiac performance in acromegaly: a radionuclide angiography study. J Clin Endocrinol Metab. 84:1518–1523.
17. **Colao A, Baldelli R, Marzullo P, et al.** 2000 Systemic hypertension and impaired glucose tolerance are independently correlated to the severity of the acromegalic cardiomyopathy. J Clin Endocrinol Metab. 85:193–199.
18. **Marzullo P, Cuocolo A, Ferone D, et al.** 2000 Cardiac effect of thyrotoxicosis in acromegaly. J Clin Endocrinol Metab. 85:1426–1432.
19. **López-Velasco R, Escobar-Morreale HF, Vega B, et al.** 1997 Cardiac involvement in acromegaly: specific myocardiopathy or consequence of systemic hypertension. J Clin Endocrinol Metab. 82:1047–1053.
20. **Thuesen L, Christensen SE, Weeke J, Ørskov H, Henningsen P.** 1989 The cardiovascular effects of octreotide treatment in acromegaly: an echocardiographic study. Clin Endocrinol. 30:619–625.
21. **Merola B, Cittadini A, Colao A, et al.** 1993 Chronic treatment with the somatostatin analog octreotide improves cardiac abnormalities in acromegaly. J Clin Endocrinol Metab. 77:790–793.
22. **Tokgözoglu SL, Erbas T, Aytemir K, et al.** 1994 Effects of octreotide on left ventricular mass in acromegaly. Am J Cardiol. 74:1072–1074.
23. **Lim MJ, Barkan AL, Buda AJ.** 1992 Rapid reduction of left ventricular hypertrophy in acromegaly after suppression of growth hormone hypersecretion. Ann Intern Med. 117:719–726.
24. **Baldelli R, Ferretti E, Jaffrain-Rea ML, et al.** 1999 Cardiac effects of lanreotide, a slow release somatostatin analog, in acromegalic patients. J Clin Endocrinol Metab. 84:575–532.
25. **Hradec J, Kral J, Janota T, et al.** 1999 Regression of acromegalic left ventricular hypertrophy after lanreotide (a slow release somatostatin analog). Am J Cardiol. 83:1506–1509.
26. **Lombardi G, Colao A, Ferone D, et al.** 1996 Cardiovascular aspects in acromegaly: effects of treatment. Metabolism. 45[Suppl 1]:57–60.
27. **Chanson P, Timsit J, Masquet C, et al.** 1990 Cardiovascular effects of the somatostatin analog octreotide in acromegaly. Ann Intern Med. 113:921–925.
28. **Colao A, Cuocolo A, Marzullo P, et al.** 1999 Effects of one-year treatment with octreotide on cardiac performance in patients with acromegaly. J Clin Endocrinol Metab. 84:17–23.
29. **Colao A, Lombardi G.** 1998 Growth-hormone and prolactin excess. Lancet. 352:1455–1461.
30. **Giustina A, Barkan A, Casanueva FF, et al.** 2000 Criteria for cure of acromegaly: a consensus statement. J Clin Endocrinol Metab. 85:526–529.
31. **WHO.** 1996 Hypertension control. Report of a WHO expert committee. WHO Tech Rep Ser. 862:1–83.
32. **Colao A, Ferone D, Lastoria S, et al.** 1996 Prediction of efficacy of octreotide therapy in patients with acromegaly. J Clin Endocrinol Metab. 81:2356–2362.
33. **Colao A, Ferone D, Cappabianca P, et al.** 1997 Effect of octreotide pretreatment on surgical outcome in acromegaly. J Clin Endocrinol Metab. 82:3308–3314.
34. **Bonow RO, Bacharach SL, Green MV, et al.** 1981 Impaired left ventricular diastolic filling in patients with coronary artery disease: assessment with radionuclide angiography. Circulation. 64:315–323.
35. **Bacharach SL, Green MV, Borer JS, Hyde JE, Farkas SP, Johnston GS.** 1979 Left ventricular peak ejection rate, filling rate and ejection fraction: frame requirements at rest and exercise. J Nucl Med. 20:1889–1893.
36. **Cuocolo A, Sax FL, Brush JE, Maron BJ, Bacharach SL, Bonow RO.** 1990 Left ventricular hypertrophy and impaired diastolic filling in essential hypertension. Circulation. 81:978–986.
37. **Cuocolo A, Storto G, Izzo R, et al.** 1999 Effects of valsartan on left ventricular diastolic function in patients with mild or moderate essential hypertension: comparison with enalapril. J Hypertens. 17:1759–1766.
38. **Huchard H.** 1895 Anatomie pathologique, lesions et trouble cardiovasculaires de l'acromegalie. J Practiciens. 9:249–250.
39. **Swearingen B, Barker FG II, Katznelson L, et al.** 1998 Long-term mortality after transsphenoidal surgery and adjunctive therapy for acromegaly. J Clin Endocrinol Metab. 83:3419–3426.
40. **Freda PU, Wardlaw SL, Post KD.** 1998 Long-term endocrinological follow-up evaluation in 115 patients who underwent transsphenoidal surgery for acromegaly. J Neurosurg. 89:353–358.
41. **Melmed S, Dowling RH, Frohman LA, et al.** 1994 Consensus statement: benefits versus risks of medical therapy for acromegaly. Am J Med. 97:468–473.
42. **Lamberts SWJ, van der Lely A-J, de Herder WW, Hofland LJ.** 1996 Octreotide. N Engl J Med. 34:246–254.
43. **Feigenbaum H.** 1979 Echocardiography, ed. 2. Philadelphia: Lea and Febiger.
44. **Tsukahara H, Gordienko DV, Tonshoff B, Gelato MC, Goligorsky MS.** 1994 Direct demonstration of insulin-like growth factor I induced nitric oxide production by endothelial cells. Kidney Int. 45:598–604.
45. **Böger RH, Skamira C, Bode-Böger SM, Brabant C, Von Zur Muhlen A, Frolich JC.** 1996 Nitric oxide mediates the hemodynamic effects of recombinant growth hormone in patients with acquired growth hormone deficiency. J Clin Invest. 98:2706–2713.
46. **Gunal AI, Isik A, Celiker H, et al.** 1996 Short term reduction of left ventricular mass in primary hypertrophic cardiomyopathy by octreotide injections. Heart. 76:418–421.
47. **Demirtas E, Sag C, Kursaklioglu H, et al.** 1998 Effects of octreotide in patients with hypertrophic obstructive cardiomyopathy. Jpn Heart J. 39:173–181.
48. **Crick SJ, Sheppard MN, Ho SY, Anderson RH.** 1999 Localisation and quantitation of autonomic innervation in the porcine heart I: conduction system. J Anat. 195:341–357.