CLINICAL STUDY

Persistent diastolic dysfunction despite successful long-term octreotide treatment in acromegaly

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Abstract

Introduction: This study was designed to evaluate potential reversibility of left-ventricular (LV) dysfunction in patients with acromegaly following long-term control of disease. It is unknown whether the cardiac changes induced by acromegaly can be reversed completely by long-term strict control of growth hormone excess by octreotide.

Patients and methods: We compared LV systolic and diastolic function in inactive patients with acromegaly ($n = 22$), who were divided into patients with long-term control by octreotide ($n = 14$) and patients with long-term cure by surgery/radiotherapy ($n = 8$). We also assessed these parameters in patients with active acromegaly ($n = 17$).

Results: In patients with active acromegaly, systolic function at rest was decreased by 18% ($P < 0.01$), LV mass index increased by 40% ($P < 0.04$) and isovolumetric relaxation time increased by 19% ($P < 0.01$), compared with patients with inactive acromegaly. These parameters were not different between well-controlled and cured patients. Using tissue Doppler imaging, the ratio between early and late diastolic velocity (E'/A' ratio) was decreased in active, compared with inactive acromegaly (0.75 ± 0.07 versus 1.24 ± 0.15 ; $P < 0.01$). This E'/A' ratio was considerably higher in cured, compared with octreotide-treated, patients (1.75 ± 0.41 versus 1.05 ± 0.1 ; $P < 0.01$).

Conclusion: Diastolic function is persistently and significantly more impaired in acromegalic patients with long-term control by octreotide than in surgically cured patients, which points to biological effects of subtle abnormalities in growth hormone secretion. Criteria for strict biochemical control of acromegaly should thus be reconsidered.

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Introduction

Prolonged growth hormone (GH) excess can induce myocardial changes (1–4). These changes include left-ventricular (LV) hypertrophy, diastolic dysfunction, systolic dysfunction during exercise, arrhythmias and heart failure (5). Recently, regurgitant valve disease has also been documented in acromegalic patients (6, 7). The incidence and severity of these cardiac changes are related to disease activity and disease duration. LV hypertrophy appears to be an early consequence of GH excess (8–11), whereas arrhythmias and valvular disease are associated with long-standing disease (6, 12).

Adequate treatment of GH excess can arrest, and even reverse, several of these cardiac changes. A total of 19 studies evaluated the effect of long-term suppression – that is, 6 months or more – of GH excess on cardiac function, summarized in Table 1. From these studies it is evident that LV mass decreases in association with improved systolic and diastolic function in patients, in

whom GH excess is well-controlled. Nonetheless, it is not entirely clear to which extent long-term successful biochemical control of GH excess can reverse cardiac function. For instance, although octreotide treatment improved LV ejection fraction (LVEF), measured after 1 year of treatment, LVEF did not normalize completely (8). Only one study compared cardiac function 5 years after normalization of GH/insulin-like growth factor I (IGF-I) excess and compared patients with controlled disease and patients with cured disease. There were no differences in cardiac function, assessed by radionuclide ventriculography, between patients who were well controlled by octreotide and those cured by surgery (13). However, all non-invasive techniques have major pitfalls in so far as they cannot measure LV pressures directly.

Recent data raise questions about whether the currently accepted definition of biochemical control of GH excess – that is, GH levels $< 2.5 \mu\text{g/l}$ and normal age- and sex-related IGF-I levels – can be equated with normalization of all aspects of GH secretion in all

Table 1 The effect of long-term suppression of GH excess (6 months or more) on cardiac function in acromegaly.

Study	No. of patients	Definition of cure/well-controlled disease	No. of patients achieving treatment goals (%)	Method of assessment	Duration of treatment	Effect on cardiac performance
26	9	Decrease of GH by 62%	Not defined	2D echo	1 year	Systolic function at rest: ↑ LV mass ↓ (but still above ref values) Diastolic function: not assessed
35	3	Mean GH 5.2 µg/l Normal IGF-I	Not defined	Right heart cath	2–3 years	Cardiac index: normalization ↓ Filling pressures
29	5	24 GH profiles: < 5 µg/l IGF-I not measured	4 (80%)	2D echo/Doppler	6 months	Systolic function at rest: no change LV mass ↓ ↑ Early diastolic transmitral flow velocity
25	11	Mean GH 4.6 µg/l Mean IGF-I 235 µg/l	11 (100%)	2D echo/Doppler	6 months	Systolic function at rest: no change LV mass ↓ ↑ Diastolic filling indices
18	22	Mean GH < 5 µg/l OGTT nadir < 1 µg/l IGF-I < 450 µg/l	11 (50%)	2D echo/Doppler	10 years	Systolic function at rest: ↑ LV mass ↓ Diastolic function: not assessed
27	6	Mean GH 4 µg/l IGF-I not measured	None	2D echo/max treadmill test	6 months	Systolic function at rest: no change LV mass ↓ Diastolic function: not assessed
24	30	Mean GH < 2.5 1 µg/l Nadir GH < 1 µg/l Normal IGF-I	13 (43%)	Gated blood-pool scintigraphy	1 year	Inactive: ↑ LVEF, but no normalization; no changes in diastolic filling Persistent active: ↓ cardiac performance
23	13	Not defined (mean GH and IGF-I not normalized)	Not available	2D echo/Doppler	18 months	Systolic function at rest: no change LV mass ↓ Diastolic function: ↑
36	13	GH < 2.5 µg/l and/or normal IGF-I	8 (62%)	2D echo/Doppler	1 year	Systolic function at rest: no change LV mass ↓ ↓ IRT and A
21	15	GH < 3.5 µg/l/nadir < 1.5 µg/l Normal IGF-I	9 (60%)	2D echo/Doppler/gated blood-pool scintigraphy	6 months	Systolic function: LVEF rest/exercise ↑ LV mass ↓ Diastolic function ↑
13	18	Fasting GH < 2.5 µg/l, or < 1 µg/l after OGTT and normal IGF-I	13 (72%) (7 cured, 6 well-controlled)	gated blood-pool scintigraphy	5 years	Controlled: LVEF during exercise ↑ Diastolic function: no change
37	30	OGTT GH nadir < 0.75 µg/l Normal IGF-I	15 (50%)	2D echo and Doppler	6 months	Systolic function at rest: no change LV mass ↓ Diastolic function ↑
38	32	OGGT GH nadir < 1 µg/l and normal IGF-I; Well-controlled: normal IGF-I	19 (59%)	2D echo/Doppler and TDI	Not documented	Systolic function at rest: ↑ Diastolic function: no difference between cured/well-controlled and controls
39	15	Basal GH < 5 µg/l OGTT GH nadir < 2 µg/l normal IGF-I	15 (100% preselected)	2D echo and Doppler	2.7 years	LV mass ↓ Diastolic function ↑
9	25	Fasting GH < 2.5 µg/l normal IGF-I	13 (53%)	2D echo/Doppler and gated blood-pool scintigraphy	6 months	Systolic function: ↑ (normalization of LVEF peak exercise) LV mass ↓
40	19	Fasting GH < 2.5 µg/l normal IGF-I	11 (58%)	2D echo and Doppler	6 onths	Systolic function at rest: unchanged LV mass ↓ Diastolic function: ↑
22	8	Fasting GH < 2.5 µg/l normal IGF-I	1 (13%)	2D echo	6 months	Systolic function: ↑ LV mass ↓ Diastolic function: not assessed
41	22	Mean GH < 2.5 µg/l normal IGF-I	22 (100% preselected)	2D echo/Doppler and gated blood-pool scintigraphy	1 year	Systolic function: ↑ (LVEF at peak exercise normalized in 80% young/50% middle age patients) LV mass ↓ Diastolic function: no change
42	16	Mean GH < 2.5 µg/l normal IGF-I	6 (38%)	2D echo/Doppler and ultrasonic tissue characterization	6–9 months	Systolic/diastolic function: no change LV mass ↓ Normalization of heart collagen content
Present series	39	Mean GH < 2.5 µg/l, or OGTT GH nadir < 0.5 µg/l normal IGF-I	22 (56%)	2D echo/Doppler and TDI	Median 6 years (range 1–14)	LV mass ↓ Systolic function at rest: ↑ Diastolic function: conventional Doppler: ↑ TDI: ↑, but persistently impaired in well-controlled Disease

2D echo, two-dimensional echocardiography; IRT, isovolumetric relaxation time; A, late transmural peak velocity; OGTT, oral glucose tolerance test.

circumstances. First, we showed (14), that long-term treatment of patients with active acromegaly with somatostatin analogues does not normalize 24-h GH secretion, even though all these patients fulfilled the above-mentioned criteria for strict biochemical control. In contrast, 24-h GH secretion in acromegalic patients cured by transsphenoidal surgery was not different from the values in matched controls. Second, discordant results between IGF-I and GH concentrations have been reported in a significant proportion of newly diagnosed acromegalic patients (15, 16). Because somatostatin analogues do not completely normalize GH secretion, it is possible that treatment with these analogues aiming at strict biochemical control of GH excess may not normalize cardiac abnormalities to the extent of the effects of curation by transsphenoidal surgery.

Therefore, we investigated whether there were differences in cardiac parameters between patients with long-term 'control' of GH excess by treatment with octreotide and patients cured by surgery, using a group of patients with active acromegaly as a reference group. We used echocardiography including tissue Doppler imaging (TDI), which allows for a detailed and quantitative assessment of cardiac parameters including diastolic and systolic function (17).

Materials and methods

Patients

We studied 39 consecutive patients with acromegaly (19 men) referred from the outpatient clinic of the Leiden University Medical Center, Leiden, The Netherlands (Table 2). The mean age of the patients was 56 years (range 20–83 years). The diagnosis of

acromegaly was based on the characteristic clinical features and confirmed by insufficient suppression of GH during a glucose tolerance test (GH nadir below 0.5 µg/l), and the presence of a pituitary adenoma on radiological imaging.

We classified patients according to the presence or absence of GH excess as having active or inactive acromegaly, respectively. The patients with inactive acromegaly consisted of two groups: (1) well-controlled patients ($n = 14$): mean fasting GH concentration (measured for 3 h with an interval of 30 min) of < 2.5 µg/l, and normal age- and gender-adjusted IGF-I concentrations during treatment with depot octreotide acetate; (2) patients cured after surgery ($n = 8$): no treatment with depot octreotide acetate, GH nadir after oral glucose loading (75 g) of < 0.5 µg/l, and normal age- and gender-adjusted IGF-I concentrations. Pre-therapy disease severity was not different between the two groups. The patients with active acromegaly consisted of two other groups: (3) untreated patients ($n = 8$): no treatment to reduce GH excess had yet been instituted; (4) uncontrolled patients ($n = 9$): mean fasting GH concentrations (measured every 30 min for 3 h) of > 2.5 µg/l, and/or elevated age- and sex-adjusted IGF-I concentrations despite treatment with maximal dosages of depot octreotide acetate (30 mg i.m. every 3 weeks). Cardiac parameters (see below) were analysed in groups of cured and controlled acromegaly, using untreated and uncontrolled patients as reference/control groups. None of the patients had haemodynamic instability, previous myocardial infarction, thyrotoxicosis, rheumatic fever, endocarditis, anorexigen use or connective-tissue disease. If hypertension was present (blood pressure $> 140/95$ mmHg), medication was prescribed to reduce blood pressure to values of

Table 2 Baseline characteristics.

	Active acromegaly		Inactive acromegaly	
	Untreated	Uncontrolled	Well-controlled	Cured
No. of patients	8	9	14	8
Age (years)	54.4±4.6	54.1±6.3	56.1±3.2	60.4±6.2
Gender (females/males)	6/2	2/7	6/8	6/2
Estimated disease duration (years)	9.9±1.51	18.6±4.4*	12.4±1.3	8.8±2.3†
Controlled GH/normal IGF-I levels (mean + range; years)	—	—	5.8 (1–14)	7.9 (2–16)
GH (µg/l)	9.7±3.6	9.8±2.8	1.2±0.2‡§	0.9±0.4†¶
IGF-I (SDS)	+7.63±1.96	+5.56±0.58	+1.22±0.27‡§	+1.07±0.42†¶
Transsphenoidal surgery (no.)	—	5	10	8
Radiotherapy (no.)	—	2	2	2
Body mass index (kg/m ²)	29.8±1.5	27.6±1.1	27.1±1.3	26.2±0.9
Body surface area (m ²)	1.96±0.04	2.08±0.6	2.04±0.07	1.95±0.06
Treated hypertension (no.)	5	2	0	3
Diabetes mellitus/impaired fasting glucose (no.)	2/2	2/1	2/1	1/1
Duration of octreotide treatment (mean + range; years)	—	3.5 (1–8.5)	5.8 (1–14)	—

* $P < 0.05$ untreated versus uncontrolled.

† $P < 0.05$ uncontrolled versus cured.

‡ $P < 0.05$ untreated versus well-controlled.

§ $P < 0.05$ uncontrolled versus well-controlled.

¶ $P < 0.05$ untreated versus cured.

<140/90 mmHg. All subjects had a normal blood pressure for at least 1 year prior to the study. Glucose tolerance was assessed according to the 1997 American Diabetes Association (ADA) criteria: (i) normal was defined as fasting plasma glucose below 6.1 mM; (ii) impaired fasting glucose was defined as between 6.1 and 7.0 mM; (iii) diabetes mellitus, defined as fasting plasma glucose of ≥ 7.0 mM. None of the female patients were pregnant during the 9 months following echocardiography. The duration of disease was defined by the onset of clinical symptoms related to GH excess (carpal tunnel syndrome, sleep apnoea and arthralgias), and by careful comparison of old photographs. The end of disease duration was defined as the time of successful treatment (that is, cured or well-controlled disease). The duration of well-controlled disease or cure was defined as the time of successful medical treatment and/or transsphenoidal surgery with or without adjuvant radiotherapy, until the time of echocardiography.

The local institutional ethics committee approved the study, and written informed consent was obtained from all subjects.

Echocardiography, data acquisition

Echocardiography was performed with the patients in the left lateral decubitus position using a commercially available system (Vingmed system FiVe/Vivid-7; General Electric – Vingmed, Milwaukee, WI, USA). Standard parasternal (long and short axis) and apical views (two-, four- and five-chamber) were obtained. Standard continuous-wave and pulsed-wave Doppler examinations were performed. M-mode images were obtained from the parasternal long-axis views for quantitative assessment of LV dimensions, fractional shortening (FS) and LVEF (10, 18). LV mass was calculated by the cube formula, and using the correction formula proposed by Devereux *et al.* (19; see also 20):

$$\text{LV mass} = 0.8 \times \{1.04(\text{LVEDD diameter} + \text{PWD} + \text{IVSD})^3 + \text{LVEDD}^3\} + 0.6$$

LVEDD, PWD and IVSD are defined in Table 3 (below). LV mass index (LVMI) was corrected for body surface area. LV hypertrophy was defined as a LVMI value above 135 g/m² for men and 110 g/m² for women. Systolic function was evaluated by measurements of FS and LVEF. The following parameters of diastolic function were measured: diastolic transmitral peak velocities (E and A wave), the E/A ratio, the isovolumetric relaxation time (IVRT) and the E-deceleration time. Quantitative diastolic data were derived from TDI analysis. For TDI analysis, the digital cine-loops were analysed using commercial software (Echopac 6.1; General Electric – Vingmed). The sample volume (4 mm³) was placed in the LV basal portion of the septum (using the four-chamber images). The following parameters (mean values calculated from three consecutive beats) were derived: early diastolic velocity (E'), late diastolic velocity (A') and the E'/A' ratio. All echocardiographic examinations and analyses were performed by a single observer, blinded for treatment modalities.

Hormone assays

GH concentrations were quantitated in duplicate using a sensitive time-resolved immunofluorescence assay (Wallac, Turku, Finland), specific for 22 kDa GH protein, and calibrated against WHO IRP 80/505. The detection limit was 0.012 µg/l. Intra-assay coefficients of variation were 1.6–8.4% in the GH range 0.012–18 µg/l. The total serum IGF-I concentration was determined by RIA after extraction and purification on ODS-silica columns (Incstar Corp., Stillwater, MN, USA). The intra- and inter-assay coefficients of variation were less than 11%. The detection limit was

Table 3 LV dimensions and systolic function at rest.

	Active acromegaly		Inactive acromegaly	
	Untreated	Uncontrolled	Well-controlled	Cured
LVEDD (mm)	49.8±2.5	57.9±3.8	53.6±1.7	50.4±3.5
LVESD (mm)	34.4±2.7	40.2±4.1	34.1±1.9	32.6±2.7
IVSD (mm)	13.1±1.6	13.8±1.1	9.6±0.5*†	10.6±1.3
PWD (mm)	11.0±0.9	10.3±0.8	9.7±0.5	9.4±0.5
LVM (g)	250±48	314±57	201±20†	199±43
LVMI (g/m ²)	126.0±22.5	153±27.7	99.6±9.5†	100.3±19.5
FS (%)	30.9±2.5	29.9±2.6	36.8±1.7†	37.4±1.4‡
LVEF (%)	57.8±3.8	59.7±2.81	72.4±2.6*†	73±1.8‡§

LVEDD, LV end-diastolic diameter; LVESD, LV end-systolic diameter; IVSD, inter-ventricular septum diameter; PWD, posterior wall diameter; LVM, LV mass; LVMI, LVM/body surface area.

* $P < 0.05$ untreated versus well-controlled.

† $P < 0.05$ uncontrolled versus well-controlled.

‡ $P < 0.05$ uncontrolled versus cured.

§ $P < 0.05$ untreated versus cured.

1.5 nM. Age-related normal data were determined in the same laboratory. IGF-I was also expressed as a SDS from age-related normal levels.

Statistical analysis

Univariate analysis of variance was performed to compare groups, and the Bonferroni multiple comparison as a *post hoc* test. Linear-by-linear association was performed to investigate a trend for having untreated, uncontrolled, well-controlled or cured disease with an E'/A' ratio of <1. Data are expressed as means $\pm$ S.E.M. SPSS software version 11.0 (SPSS, Chicago, IL, USA) was used. Differences were considered statistically significant at the $P < 0.05$ level.

Results

Clinical characteristics

The clinical characteristics are provided in Table 2. GH and IGF-I concentrations were much higher in patients with active acromegaly, compared with the values obtained in patients with inactive acromegaly, reflecting the different inclusion criteria for the different groups. However, there were no differences in GH/IGF-I levels between untreated and uncontrolled patients, nor between well-controlled and cured patients. The duration of controlled GH/IGF-I levels was not different between well-controlled patients and cured patients (mean 5.8 years, range 1–14 years, versus mean 7.9 years, range 2–16 years, respectively; not significant).

LV dimensions and systolic function at rest

LV dimensions were not different between patients with active and inactive acromegaly (Table 3). However, LVMI was above the normal range and 40% higher in patients with active acromegaly, compared with patients with inactive acromegaly (140 ± 17.9 versus 99.8 ± 8.8 g/m², respectively; $P < 0.04$). LVMI was within the normal range and not different between well-controlled and cured patients.

Systolic function at rest, reflected by FS and LVEF, was decreased by 18–19% in patients with active acromegaly, compared with patients with inactive acromegaly. FS was 30.3 ± 1.8 versus $37.0 \pm 1.2\%$, respectively ($P < 0.01$) and LVEF was 58.8 ± 2.3 versus $72.6 \pm 1.8\%$, respectively ($P < 0.01$). However, FS and LVEF were not different between well-controlled and cured patients.

Diastolic function

There were no statistically significant differences in diastolic transmural peak velocities (E and A waves) between patients with active and inactive acromegaly. The IVRT was increased by 19% in patients with active acromegaly compared with patients with inactive acromegaly (109.7 ± 4.0 versus 88.7 ± 2.5 ms; $P < 0.01$). However, there were no significant differences between untreated and uncontrolled patients, nor between well-controlled and cured patients.

Diastolic function, assessed by TDI (Fig. 1), showed that the early diastolic velocity (E') was significantly

Figure 1 Diastolic function in patients with acromegaly as assessed by TDI.

higher in cured patients as compared with the other patient groups (Table 4 and Fig. 1). A significant difference in E' was also noted between uncontrolled and well-controlled patients: E' was higher in well-controlled patients ($P < 0.01$), but was still significantly lower than in those who were cured of disease ($P < 0.04$). The E'/A' ratio was considerably decreased in patients with active acromegaly compared with patients with inactive acromegaly (0.75 ± 0.07 versus 1.24 ± 0.15 ; $P < 0.01$). In cured patients, the E'/A' ratio was significantly higher when compared with well-controlled patients (1.75 ± 0.41 versus 1.05 ± 0.1 , respectively; $P < 0.01$). Remarkably, the E'/A' ratio was < 1 in all untreated patients and in 75% of uncontrolled patients. The E'/A' ratio was < 1 in 50% of the well-controlled patients compared with only 12% of the cured patients ($P = 0.003$).

Discussion

The present study demonstrates that surgically cured acromegalic patients had significantly improved cardiac function compared with those in long-term remission by octreotide treatment. During long-term follow up, diastolic function was significantly more impaired in the patients on medication despite optimal treatment with somatostatin analogues, according to strict criteria of GH/IGF-I concentrations.

The question arises as to whether other factors may have affected our observations, other than these related to the disease activity of acromegaly. First, the duration of GH excess is a determinant of cardiac abnormalities (6, 8). The group characterized as having active disease had a longer duration of disease than the cured patients, which will have affected cardiac function. However, there were no significant differences in disease duration between well-controlled and cured patients. Second, the degree of GH excess is a determinant of cardiac abnormalities. However, there were no differences in

GH levels obtained over several hours or IGF-I levels between well-controlled and cured patients. Third, there were no differences in duration of strict control between both groups. Fourth, there were no differences in body mass index or age, which may have affected our conclusions. Fifth, treated hypertension, which may have induced diastolic dysfunction, was present in 38% (3/8) of the cured patients but in none of the well-controlled group. Moreover, all patients with treated hypertension had a blood pressure of $< 140/90$ mmHg during the year prior to the study. Finally, the prevalence of diabetes mellitus and impaired glucose tolerance was not different between cured and well-controlled patients (25 versus 21%, respectively). Therefore, our observations are not affected by differences in blood pressure or carbohydrate metabolism. Based on these arguments, we feel that it is unlikely that our interpretation of the data is confounded by parameters other than those related to disease activity of acromegaly. However, we cannot exclude the possibility that the persistent cardiac impairment could be due to still-unknown factors other than GH hypersecretion, like asymptomatic ischaemia.

Treatment of GH excess favourably affects cardiac function and mass. To our knowledge, a total of 19 studies involving 312 acromegalic patients have been published, which have assessed the effect of treatment on cardiac function (Table 1). Treatment of GH excess decreased LV mass and improved diastolic function invariably, whereas systolic function at rest remained unchanged in most of the studies. Our data are in accordance with these conclusions from the other studies. Of the 312 patients, 53% (166 patients) achieved treatment goals, defined by normalization of IGF-I and fasting GH levels below $2.5 \mu\text{g/l}$ or glucose-suppressed GH levels below $1 \mu\text{g/l}$. The majority of these patients, 120/166 (72%), were well-controlled by somatostatin analogue treatment. In these 120 patients, LV mass normalized and cardiac function improved. This was reflected mainly by an increase in LVEF during exercise (21–29), a feature that has already

Table 4 Diastolic function as assessed by echocardiography and TDI.

	Active acromegaly		Inactive acromegaly	
	Untreated	Uncontrolled	Well-controlled	Cured
E (mm/s)	55.5 ± 3.9	56.4 ± 6.8	52.7 ± 3.3	65 ± 5.8
A (mm/s)	59.4 ± 4.9	67.4 ± 5.8	55.7 ± 4.7	55.8 ± 3.7
E/A ratio	1.0 ± 0.2	0.83 ± 0.5	1.01 ± 0.1	1.18 ± 0.1
Edec (ms)	171 ± 10.2	180.3 ± 19.4	180.1 ± 17.2	163.8 ± 12
IVRT (ms)	109.9 ± 3.0	109.6 ± 7.3	$90.6 \pm 3.0^{\dagger}$	$84.2 \pm 4.1^{\dagger}\S$
E' (cm/s)	6.83 ± 0.99	5.23 ± 0.76	$7.89 \pm 0.34^{\dagger}$	$10.06 \pm 0.84^{\dagger}\S\parallel$
A' (cm/s)	9.38 ± 1.21	$6.71 \pm 0.36^{**}$	8.00 ± 0.52	$6.6 \pm 0.93^{\dagger}$
E'/A' ratio	0.72 ± 0.07	0.79 ± 0.19	1.05 ± 0.09	$1.75 \pm 0.41^{\dagger}\S\parallel$

E, early transmitral peak velocity; A, late transmitral peak velocity; Edec, E-deceleration time; E' , early diastolic velocity; A' , late diastolic velocity.

* $P < 0.05$ untreated versus well-controlled.

† $P < 0.05$ uncontrolled versus well-controlled.

§ $P < 0.05$ untreated versus cured.

$^{\parallel}$ $P < 0.05$ uncontrolled versus cured.

$^{\dagger}\S$ $P < 0.05$ well-controlled versus cured.

** $P < 0.05$ untreated versus uncontrolled.

been observed within a few months of treatment with somatostatin analogues. Prolonged suppression of basal or glucose-suppressed GH levels to values below 2.5 or 1 µg/l, respectively, in combination with normalization of plasma IGF-I levels for at least 1 year, resulted in significant improvement, but not complete normalization, of LVEF either at rest or at peak exercise without significant changes in diastolic filling (24). These data suggest that prolonged suppression of circulating GH and IGF-I levels normalizes systolic cardiac performance. 46 of the 166 patients (27%) with inactive acromegaly were biochemically cured by surgery and/or radiotherapy and were not treated with somatostatin analogues. Hradec *et al.* (18) demonstrated a clear beneficial effect of long-term cure on LVMI, but diastolic function was not assessed in that particular study. This beneficial effect of cure of GH excess on LVMI was confirmed in other studies, with a concomitant improvement, but not normalization, in diastolic function (28, 29). The biochemical criteria used in the studies on cardiac function in acromegaly are based on other studies, which have shown that these criteria are associated with a reversal of the increased risk for malignancies and mortality, associated with GH excess (18, 30, 31). However, it is unknown whether biochemical control of GH/IGF-I excess, according to these criteria, is also sufficient to normalize other GH-related morbidity, like acromegalic cardiomyopathy.

The findings in the current study, in patients with long-term control of GH excess (median of 6 years), demonstrated that two independent parameters of diastolic function, the E'/A' ratio and the IVRT, improved significantly, indicating ameliorated relaxation and decreased stiffness of the heart muscle (see also 32). However, a significantly higher E'/A' ratio was found in patients cured by surgery when compared with those well-controlled with long-term octreotide. Furthermore, Siculo *et al.* (33) showed that in the presence of diastolic impairment the incomplete recovery of an adequate preload can affect systolic parameters during physical effort. Since systolic function was only measured at rest, it is possible that systolic function could still be impaired on effort and hence there might be a difference between those cured and those in remission. Therefore, these data suggest that acromegalic patients, well controlled according to stringent criteria, still reveal biological effects of slight GH overproduction. In accordance, there are indications that treatment of active acromegaly with somatostatin analogues resulting in normal IGF-I and GH levels does not completely normalize GH secretion. Recently, we investigated 24-h GH profiles in uncontrolled and well-controlled acromegaly patients, treated with long-acting somatostatin analogues (34). We applied the same strict biochemical criteria for well-controlled disease (normal IGF-I levels and a GH profile during 24-h GH sampling of <2.5 µg/l) in both groups. However, GH was actually sporadically below 0.5 µg/l, although chronic treatment with somatostatin analogues repressed amplitude-dependent measures of

excessive GH secretion in acromegaly. Moreover, tumoral endocrine autonomy was inferred by continued elevations of event frequency, overall pattern disruption (irregularity), and nonsuppressible basal GH secretion. We postulate that these subtle abnormalities in GH secretion relate to the persistently impaired diastolic function despite clinically normal GH and IGF-I levels.

In conclusion, long-term control of GH/IGF-I excess is associated with normal LV mass and LV dimensions. Nonetheless, diastolic function is more impaired in well-controlled patients than in surgically cured patients, which proves that the current criteria for strict biochemical control of acromegaly may still be associated with subtle effects of excessive GH secretion. Although the clinical relevance of this observation remains to be determined, these patients might benefit from more aggressive control of GH production than obtained by applying the current 'strict' criteria of biochemical control of GH excess.

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