Chapter 3

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 completely reversed by long-term strict control of growth hormone (GH) excess by octreotide.

Patients and Methods: We compared LV systolic and diastolic function in inactive patients with acromegaly (n=22) between 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 (LVMI) increased by 40 % (p<0.04) and isovolumetric relaxation time (IVRT) increased by 19 % (p<0.01), compared to 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 to inactive acromegaly (0.75 ± 0.07 vs. 1.24 ± 0.15, p < 0.01). This E’/A’ ratio was considerably higher in cured, compared to octreotide treated patients (1.75 ± 0.41 vs. 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 GH secretion. Criteria for strict biochemical control of acromegaly, should thus be reconsidered.
Introduction

Prolonged Growth Hormone (GH) excess can induce myocardial changes (1-4). These changes include left ventricular 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. Left ventricular hypertrophy (LVH) appears to be an early consequence of GH excess (8-11), whereas arrhythmias and valvular disease are associated with longstanding 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, i.e. 6 months or more, of GH excess on cardiac function, summarized in Table 1. From these studies, it is evident, that LV mass decreases, associated 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 one year of treatment, LVEF did not normalize completely (8). Only one study compared cardiac function 5 years after normalization of GH/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 wellcontrolled by octreotide and those cured by surgery (13). However, all non-invasive techniques have major pitfalls insofar as they cannot measure directly LV pressures.

Recent data question, whether the currently accepted definition of biochemical control of GH excess, i.e. GH levels < 2.5mg/L and normal age- and sex-related IGF-1 levels, can be equated with normalization of all aspects of GH secretion in all circumstances. First, we showed (15), that long-term treatment of patients with active acromegaly with somatostatin analogues does not normalize 24-hour GH secretion, even though all these patients fulfilled the abovementioned
criteria for strict biochemical control. In contrast, 24-hour GH secretion in acromegalic patients cured by transsphenoidal surgery was not different from the values in matched controls. Second, discordant results between IGF-1 and GH concentrations have been reported in a significant proportion of newly diagnosed acromegalic patients (16,17). 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 (14).
Materials and methods

Patients

We studied 39 consecutive patients with acromegaly (19 men) referred from the outpatient clinic (Table 2). The mean age of the patients was 56 years (range 20-83 yrs). 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, resp. The patients with inactive acromegaly consisted of two groups: 1) well-controlled patients (n=14): mean fasting GH concentration (measured for 3 hours with an interval of 30 minutes) < 2.5mg/L, and normal age- and gender-adjusted IGF-1 concentrations during treatment with depot octreotide acetate, and 2) patients cured after surgery (n=8): no treatment with depot octreotide acetate, GH nadir after a 75 gram oral glucose loading < 0.5mg/L, and normal age- and gender-adjusted IGF-1 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 was yet instituted, and 4) uncontrolled patients (n=9): mean fasting GH concentrations (measured every 30 min for 3 hours) > 2.5mg/L, and/or elevated age- and sex adjusted IGF-1 concentrations despite treatment with maximal dosages of depot octreotide acetate (30 mg i.m. every 3 weeks). Cardiac parameters (see below) were analyzed in groups of cured and controlled acromegaly, using untreated and uncontrolled patients as a reference/control groups. None of the patients had hemodynamic 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 < 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 ADA criteria: normal: fasting plasma glucose below 6.1 mmol/L,
impaired fasting glucose (IFG): between 6.1-7.0 mmol/L, and diabetes mellitus: fasting plasma glucose equal to or greater than 7.0 mmol/L. None of the female patients was pregnant during 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 (= cure or well-controlled) treatment. The duration of well-controlled disease or cure was defined as the time of successful medical treatment and/or transsphenoidal surgery with/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 (2-, 4-, and 5-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 left ventricular (LV) dimensions, fractional shortening (FS) and left ventricular ejection fraction (LVEF) (10;29). LV mass was calculated by the cube formula, and using the correction formula proposed by Devereux, et al.(18;19): 

\[
0.8 \times \{1.04 \times (LVEDD + IVSD + PWD)^3 + LVEDD^3\} + 0.6.
\]

LVMI was corrected for body surface area (BSA). LV hypertrophy was defined as a LVMI 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 tissue Doppler imaging (TDI) analysis. For TDI analysis, the digital cineloops were analyzed using commercial
software (Echopac 6.1, General Electric – Vingmed, Milwaukee, WI, USA). The sample volume (4 mm$^3$) was placed in the LV basal portion of the septum (using the 4-chamber images). The following parameters (mean values calculated from 3 consecutive beats) were derived: early diastolic velocity ($E'$) and 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 immunofluorescent assay (Wallac, Turku, Finland), specific for 22 kDa GH protein, and calibrated against WHO IRP 80/505. The detection limit was 0.012 ìg/L. Intra-assay coefficients of variation were 1.6-8.4% in the GH-range 0.012-18 ìg/L. The total serum IGF-1 concentration was determined by radioimmunoassay (RIA) after extraction and purification on ODS-silica columns (Incstar corp., Stillwater, MN, USA). The intra- and inter-assay coefficient of variation was less than 11%. The detection limit was 1.5 nmol/l). Age related normal data were determined in the same laboratory. IGF-1 was also expressed as a standard deviation score form 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 $E'/A'$ ratio <1. Data are expressed as mean ± SEM. SPSS software version 11.0 (Inc, Chicago, USA) was used. Differences were considered statistically significant at the P<0.05 level.
Table 1. The effect of long-term suppression of GH excess (6 months or more) on cardiac function in acromegaly

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (n)</th>
<th>Definition of care / well controlled disease</th>
<th>No of patients achieving treatment goals (%)</th>
<th>Method of assessment</th>
<th>Duration of treatment</th>
<th>Effect on cardiac function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thaerum L, et al</td>
<td>9</td>
<td>decrease of GH by 62%</td>
<td>not defined</td>
<td>2D echo</td>
<td>1 yr</td>
<td>systolic function</td>
</tr>
<tr>
<td>Channon B, et al</td>
<td>3</td>
<td>mean GH 3.5 μg/L, normal IGF-1</td>
<td>not defined</td>
<td>right heart cath</td>
<td>2-3 yrs</td>
<td>diastolic function (but)</td>
</tr>
<tr>
<td>Persiani J, et al</td>
<td>5</td>
<td>3 MGH profiles: &lt;5 μg/L IGF-1 not measured</td>
<td>4 (80%)</td>
<td>2D echo Doppler</td>
<td>6 months</td>
<td>systolic function</td>
</tr>
<tr>
<td>Aberola B, et al</td>
<td>11</td>
<td>mean GH 4.4 μg/L, mean IGF-1 235 μg/L</td>
<td>11 (100%)</td>
<td>2D echo Doppler</td>
<td>6 months</td>
<td>LV mass</td>
</tr>
<tr>
<td>Hindemor, et al</td>
<td>22*</td>
<td>mean GH &lt; 3 μg/L, OGTT nadir 4 μg/L and IGF-1 &lt; 450 μg/L</td>
<td>11 (50%)</td>
<td>2D echo Doppler</td>
<td>10 yrs</td>
<td>systolic function</td>
</tr>
<tr>
<td>Tokgozolu, et al</td>
<td>6</td>
<td>mean GH 4 μg/L, IGF-1 not measured</td>
<td>none</td>
<td>2D echo / max treadmil</td>
<td>6 months</td>
<td>diastolic function</td>
</tr>
<tr>
<td>Collao A, et al</td>
<td>30</td>
<td>mean GH &lt; 2.5 μg/L, nadir GH &lt; 1 μg/L and normal IGF-1</td>
<td>13 (43%)</td>
<td>gated blood pool</td>
<td>1 yr</td>
<td>inactive: LV function</td>
</tr>
<tr>
<td>Hindemor, et al</td>
<td>13</td>
<td>not defined (mean GH and IGF-1 not available)</td>
<td>not available</td>
<td>2D echo Doppler</td>
<td>18 months</td>
<td>diastolic function (a)</td>
</tr>
<tr>
<td>Balin B, et al</td>
<td>13</td>
<td>GH &lt; 2.5 μg/L and/or normal IGF-1</td>
<td>8 (62%)</td>
<td>2D echo Doppler</td>
<td>1 yr</td>
<td>systolic function</td>
</tr>
<tr>
<td>Collao A, et al</td>
<td>15</td>
<td>GH &lt; 3.5 μg/L / nadir &lt; 1.5 μg/L and normal IGF-1</td>
<td>9 (60%)</td>
<td>2D echo Doppler / gated blood pool scintigraphy</td>
<td>6 months</td>
<td>diastolic function (a)</td>
</tr>
<tr>
<td>Study</td>
<td>Patients (n =)</td>
<td>Definition of cure / well-controlled disease</td>
<td>No of patients achieving treatment goals (%)</td>
<td>Method of assessment</td>
<td>Duration of treatment</td>
<td>Effect</td>
</tr>
<tr>
<td>-------</td>
<td>---------------</td>
<td>--------------------------------------------</td>
<td>--------------------------------------------</td>
<td>---------------------</td>
<td>----------------------</td>
<td>--------</td>
</tr>
<tr>
<td>Coho A, et al (2001) (ref 13)</td>
<td>18</td>
<td>fasting GH ≤2.5 μg/L, or &lt;1 μg/L after OGGT and normal IGF-I</td>
<td>13 (72%) (7 cured, 6 well-controlled)</td>
<td>Blood pool scintigraphy</td>
<td>5 yrs</td>
<td>Persistent diastolic dysfunction</td>
</tr>
<tr>
<td>Munshi G, et al (2001) (ref 37)</td>
<td>30</td>
<td>OGGT GH nadir ≤0.75 μg/L, normal IGF-I</td>
<td>15 (50%)</td>
<td>2D echo and Doppler</td>
<td>6 months</td>
<td>↓ LV mass, ↓ diastolic dysfunction</td>
</tr>
<tr>
<td>Herrmann H, et al (2002) (ref 38)</td>
<td>32</td>
<td>OGGT GH nadir &lt;1 μg/L, and normal IGF-I; WC: normal IGF-I</td>
<td>19 (59%)</td>
<td>2D echo/Doppler + Tissue Doppler Imaging</td>
<td>not documented</td>
<td>Persistent diastolic dysfunction cured with Laron IGF-I</td>
</tr>
<tr>
<td>Vianna C, et al (2002) (ref 39)</td>
<td>13 (study OK = RT)</td>
<td>fasting GH&lt;5 μg/L, OGGT GH nadir &lt;2 μg/L, normal IGF-I</td>
<td>15 (100%) (preselected)</td>
<td>2D echo and Doppler</td>
<td>2.7 yr</td>
<td>↓ LV mass, ↓ diastolic dysfunction</td>
</tr>
<tr>
<td>Coho A, et al (2002) (ref 59)</td>
<td>25</td>
<td>fasting GH ≤2.5 μg/L, normal IGF-I</td>
<td>13 (53%)</td>
<td>2D echo/Doppler + gated blood pool scintigraphy</td>
<td>6 months</td>
<td>↑ diastolic function, ↑ LVEF peak ex, ↑ LV mass</td>
</tr>
<tr>
<td>Lombardi G, et al (2002) (ref 40)</td>
<td>19</td>
<td>fasting GH ≤2.5 μg/L, normal IGF-I</td>
<td>11 (58%)</td>
<td>2D echo and Doppler</td>
<td>6 months</td>
<td>↓ diastolic function, ↓ LV mass</td>
</tr>
<tr>
<td>Gilbert J, et al (2003) (ref 20)</td>
<td>8</td>
<td>fasting GH ≤2.5 μg/L, normal IGF-I</td>
<td>1 (13%)</td>
<td>2D echo</td>
<td>6 months</td>
<td>↓ diastolic function, ↓ LV mass</td>
</tr>
<tr>
<td>Coho A, et al (2003) (ref 41)</td>
<td>22</td>
<td>mean GH&lt;2 μg/L, normal IGF-I</td>
<td>22 (100%) preselected</td>
<td>2D echo/Doppler + gated blood pool scintigraphy</td>
<td>1 yr</td>
<td>↑ diastolic function normalized in 8 yrs, ↓ LV mass, ↓ diastolic function</td>
</tr>
<tr>
<td>Cilia M, et al (2006) (ref 42)</td>
<td>16</td>
<td>mean GH&lt;2 μg/L, normal IGF-I</td>
<td>6 (38%)</td>
<td>2D echo/Doppler + Ultrasound Tissue Characterization</td>
<td>6.0 yrs</td>
<td>Persistent diastolic dysfunction, ↓ LV mass, normalization of diastolic dysfunction</td>
</tr>
<tr>
<td>Present series</td>
<td>39</td>
<td>mean GH&lt;2 μg/L, or OGGT GH nadir &lt;0.5 μg/L, normal IGF-I</td>
<td>22 (56%)</td>
<td>2D echo/Doppler + Tissue Doppler Imaging</td>
<td>median 6 yrs (range 1-14)</td>
<td>Persistent diastolic dysfunction, ↓ LV mass, ↓ diastolic function, TTR ~7, but persistently controlled disease</td>
</tr>
</tbody>
</table>
Results

Clinical Characteristics

The clinical characteristics are provided in Table 2. GH and IGF-1 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-1 levels between untreated and uncontrolled patients nor between well-controlled and cured patients. The duration of controlled GH/IGF-1 levels was not different between well-controlled patients and cured patients (mean 5.8 years, range 1-14 years, vs. mean 7.9 years, range 2-16 years, resp., P=NS).

Table 2. Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Untreated</th>
<th>Untreated</th>
<th>Well-controlled</th>
<th>Cured</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>8</td>
<td>9</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>Age (y)</td>
<td>54±9.6</td>
<td>54±9.3</td>
<td>56±1±3.2</td>
<td>60±4±6.2</td>
</tr>
<tr>
<td>Gender (%)</td>
<td>62</td>
<td>27</td>
<td>68</td>
<td>62</td>
</tr>
<tr>
<td>Estimated average duration (m)</td>
<td>9.9±3.1</td>
<td>18.6±4.8</td>
<td>12.4±1.3</td>
<td>18±2.3</td>
</tr>
<tr>
<td>Control GH/normal IGF-1 levels (mean ± (IQR) (y))</td>
<td>*</td>
<td>*</td>
<td>5.8</td>
<td>7.9</td>
</tr>
<tr>
<td>GH (µg/L)</td>
<td>9.7±6.3</td>
<td>9.8±2.8</td>
<td>1.2±0.2</td>
<td>7.9</td>
</tr>
<tr>
<td>IGF-1 (µg/dL)</td>
<td>*7.2±3.96</td>
<td>5.5±4.05</td>
<td>1.2±0.2</td>
<td>7.9</td>
</tr>
<tr>
<td>Transplantation Society (%)</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Radiation (%)</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29±6±1.5</td>
<td>27±6±1.1</td>
<td>27±4±1.3</td>
<td>36±2±0.9</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.5±0±0.84</td>
<td>1.6±0±0.6</td>
<td>1.6±0±0.7</td>
<td>1.5±0±0.6</td>
</tr>
<tr>
<td>Transplant history (%)</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Diabetes mellitus / Type II diabetes (N)</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Duration of renal failure (mean ± (IQR) (y))</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
</tr>
</tbody>
</table>

1 [%] Overall controlled
2 [%] Well controlled
3 [%] Poorly controlled
4 [%] Not controlled
5 [%] Diabetic nephropathy
6 [%] Type II diabetes

LV Dimensions and Systolic Function at Rest (Table 3)

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

Systolic function at rest, reflected in 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 vs. 37.0 ± 1.2 %, resp (P<0.01) and LVEF was 58.8 ± 2.3 vs. 72.6 ± 1.8 %, resp. (P<0.01). However, FS and LVEF were not different between well-controlled and cured patients.

Table 3. LV dimensions and systolic function at rest

<table>
<thead>
<tr>
<th></th>
<th>active acromegaly</th>
<th>inactive acromegaly</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Untreated</td>
<td>Uncontrolled</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>49.8±2.5</td>
<td>57.9±3.8</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>34.4±2.7</td>
<td>40.2±1.1</td>
</tr>
<tr>
<td>IVSD (mm)</td>
<td>13.1±1.6</td>
<td>13.8±1.1</td>
</tr>
<tr>
<td>PWD (mm)</td>
<td>11.0±0.9</td>
<td>10.3±0.8</td>
</tr>
<tr>
<td>LVM (g)</td>
<td>250±48</td>
<td>314±57</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>126.0±22.5</td>
<td>153±27.7</td>
</tr>
<tr>
<td>FS (%)</td>
<td>30.9±2.5</td>
<td>29.9±2.6</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>57.8±3.8</td>
<td>59.7±2.81</td>
</tr>
</tbody>
</table>

1 P<0.05 untreated vs uncontrolled
2 P<0.05 untreated vs well-controlled, and 3 uncontrolled vs well-controlled
4 P<0.05 untreated vs cured, and 5 uncontrolled vs cured

LVEDD= Left Ventricular End-Diastolic Diameter, LVESD= Left Ventricular End-Systolic Diameter, IVSD= Interventricular Septum Diameter, PWD= Posterior Wall Diameter, LVM= Left Ventricular Mass, LVMI= LVM/BSA, FS= Fractional Shortening, LVEF= Left Ventricular Ejection Fraction
Diastolic Function (Table 4 and Figure 1)

There were no statistically significant differences in diastolic transmural peak velocities (E and A waves) between patients with active and with inactive acromegaly. The isovolumetric relaxation time (IVRT) was increased by 19% in patients with active acromegaly compared with patients with inactive acromegaly (109.7 ± 4.0 vs. 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 (Figure 1), showed that the early diastolic velocity (E') was significantly higher in cured patients as compared to the other patient groups (Table 4 and Figure 1). A significant

| Table 4. Diastolic function as assessed by echocardiography and tissue Doppler imaging. |
|---------------------------------------------|---------------------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                             | 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±3.0        | 84.2±4.1°       |
| E' (cm/s)                                   | 6.83±0.99                                  | 5.23±0.76       | 7.89±0.34       | 10.06±0.84°     |
| A' (cm/s)                                   | 9.38±1.21                                  | 6.71±0.36       | 8.00±0.52       | 6.6±0.93°       |
| E'/A'                                       | 0.72±0.07                                  | 0.79±0.19       | 1.05±0.09       | 1.75±0.41°      |

1 P<0.05 untreated vs uncontrolled
2 P<0.05 untreated vs well-controlled, and 3 uncontrolled vs well-controlled
4 P<0.05 untreated vs cured, and 5 uncontrolled vs cured
6 P<0.05 well-controlled vs cured

E= early transmural peak velocity, A= late transmural peak velocity, IVRT= isovolumetric relaxation time, Edec= E-deceleration time, E'= early diastolic velocity, A'= late diastolic velocity.
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 vs 1.24 ± 0.15, P<0.01). In cured patients, the E’/A’ ratio was significantly higher when compared to well-controlled patients (1.75±0.41 vs 1.05±0.1, resp, 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 versus in 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 to 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-1 concentrations.

The question arises whether other factors may have affected our observations, other than those related to 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 during several hours or IGF-1 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 BMI 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 <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 vs 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 other parameters 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 ischemia.

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 decreases LV mass and improves diastolic function invariably, whereas systolic function at rest remained unchanged in most of the studies. Our data are in accordance with these conclusions of the other publications. Of the 312 patients, 53% (166 patients) achieved treatment goals, defined by normalization of IGF-1 and fasting GH levels below 2.5 ìg/L or glucose-suppressed GH levels below 1 ìg/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 mainly reflected by an increase in LVEF during exercise (20-28), a feature which is already 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 ìg/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 (23). These data suggest that prolonged suppression of circulating GH and IGF-I levels normalizes systolic cardiac performance. Forty-six 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. demonstrated a clear beneficial effect of long-term cure on LVMI, but diastolic function was not assessed in that particular study (29). 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 (27,28). 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 (29,30). However, it is unknown whether biochemical control of GH/IGF-1 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 (median of 6 years) control of GH excess, 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 (32). However, a significantly higher E'/A' ratio was found in patients cured by surgery when compared

Figure 1
Diastolic function in patients with acromegaly as assessed by Tissue Doppler imaging
to those well-controlled with long-term octreotide. Furthermore, Sicolo, *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-1 and GH levels does not completely normalize GH secretion. Recently, we investigated 24-hour GH profiles in uncontrolled and well-controlled acromegaly patients, treated with long acting somatostatin analogs (34). We applied the same strict biochemical criteria for well-controlled disease (normal IGF-I levels and a GH profile during 24-hour GH sampling < 2.5 mg/L) in both groups. However, GH actually was sporadically below 0.5 mg/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-1 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.
Persistent diastolic dysfunction in well-controlled acromegaly

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Chapter 3

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