Cardiac manifestations of GH deficiency after treatment for acromegaly: a comparison to patients with biochemical remission and controls

Agatha A van der Klaauw¹, Jeroen J Bax², Gabe B Bleeker², Eduard R Holman², V Delgado², Johannes WA Smit¹, Johannes A Romijn¹ and Alberto M Pereira¹

Departments of ¹Endocrinology and Metabolic Diseases, C4-R and ²Cardiology, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, The Netherlands

(Correspondence should be addressed to A A van der Klaauw; Email: a.a.van_der_klaauw@lumc.nl)

Abstract

Objective: Both GH excess and GH deficiency (GHD) lead to specific cardiac pathology. The aim of this study was to evaluate cardiac morphology and function in patients with GHD after treatment for acromegaly.

Design: Cross-sectional study.

Patients and methods: Cardiac parameters were studied by conventional two-dimensional echocardiography and tissue Doppler imaging in 53 patients with acromegaly (16 patients with GHD, 20 patients with biochemical remission, and 17 patients with active disease). Patients with GHD were also compared with age- and gender-matched controls.

Results: Left ventricular (LV) dimensions, wall thickness, and mass did not differ between the three groups, or between the patients with GHD and healthy controls. Systolic function, assessed by LV ejection fraction, tended to be lower in patients with GHD compared with patients with biochemical remission (65.9 ± 7.3% vs 72.4 ± 8.5%, P = 0.070), but was higher when compared with active acromegaly (58.8 ± 9.3%, P = 0.047). No differences were found with healthy controls. Diastolic function, measured with early diastolic velocity (E'), was lower in patients with GHD when compared with both patients with biochemical remission (6.0 ± 2.1 cm/s vs 8.3 ± 1.5 cm/s, P = 0.005) and healthy controls (8.1 ± 1.9 cm/s, P = 0.006).

Conclusion: GHD after acromegaly results in a specific decrease in diastolic function compared with patients with biochemical remission of acromegaly and healthy controls. In addition, systolic function tends to be decreased in patients with GHD compared with patients with biochemical remission, but was higher than that in patients with active acromegaly.

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Introduction

Acromegaly is associated with increased cardiovascular morbidity and mortality (1). Active disease leads to specific cardiac pathology, which involves the myocardium, the conduction system, and the valves (1). As a consequence, clinical manifestations include biventricular concentric hypertrophy, left ventricular (LV) systolic and diastolic dysfunction, arrhythmias, and valvular regurgitation.

Treatment of GH excess can normalize mortality (2) and reverse heart failure and myocardial hypertrophy (3, 4). However, surgical treatment of GH excess followed by radiotherapy can result in GH deficiency (GHD) (5) and GHD per se is also associated with cardiomyopathy. Cardiac manifestations of GHD include a decrease in LV mass and LV ejection fraction (LVEF) (6–12), which is correlated to the severity of GHD (8). Additionally, impairment in diastolic function has also been observed in patients with GHD (13). Therefore, GHD after successful treatment of acromegaly may be another part of the spectrum of cardiac manifestations of acromegaly.

However, it is presently unknown if, and to what extent, the heart can adapt to prolonged, sequential exposure to GH excess and GHD. Therefore, the aim of this study was to make a detailed assessment of cardiac function and morphology in patients with GHD after treatment for acromegaly, and to compare these data with those obtained in patients with biochemical remission of acromegaly and patients with active acromegaly.

Patients and methods

Patients

We studied 16 patients with GHD after successful treatment of acromegaly (eight men) with a mean age of 56 ± 12 years. We compared the parameters of these patients with patients with active acromegaly and patients
with biochemical remission of acromegaly, which were previously reported in studies that assessed the prevalence of valvular regurgitation (14) and diastolic dysfunction in acromegaly (15). Since there could be residual cardiac manifestations of previous GH excess in patients with biochemical remission from acromegaly, we also compared the patients with GHD after successful treatment of acromegaly with healthy controls.

Inclusion criteria were:

i. GHD after treatment for acromegaly (n = 16): defined as a subnormal GH response to the insulin tolerance test (short-acting insulin 0.05–0.1 U/kg body weight s.c., blood samples drawn at 0, 20, 30, 45, 60, and 90 min; nadir glucose levels were all below 2.2 mmol/l). The increase in GH concentrations was considered insufficient, if peak GH response was below 3 μg/l (5, 16). Previous treatment of these patients consisted of surgery and radiotherapy (n = 15), or surgery only (n = 1). Radiotherapy was applied 17.9 years (range 4–29 years) prior to inclusion in the present study. Patients were studied just before the start of rhGH replacement.

ii. Active acromegaly (n = 17): defined as mean fasting GH concentrations (measured every 30 min for 3 h) > 2.5 μg/l and elevated age- and gender-adjusted IGF1 concentrations. These patients consisted of two groups: a) untreated acromegaly (n = 8) – no treatment to reduce GH excess had yet been instituted; b) uncontrolled acromegaly (n = 9) – elevated mean plasma GH and IGF1 concentrations despite maximal dosages of Depot octreotide acetate (30 mg i.m. every 3 weeks).

iii. Biochemical remission of acromegaly (n = 20): defined as mean fasting GH concentrations (measured for 3 h with an interval of 30 min) < 2.5 μg/l, and normal age- and gender-adjusted IGF1 concentrations. These patients consisted of two groups: a) well-controlled acromegaly (n = 14) – biochemical control of GH excess during treatment with somatostatin analogs; b) cured acromegaly (n = 6) – no GH excess after surgery only (n = 5) or primary radiotherapy (n = 1).

iv. Healthy controls (n = 16): the patients with GHD after acromegaly were compared with 16 healthy age-, body surface area-, and sex-matched controls. The controls were selected from a database with patients referred to the department of Cardiology, based on age, sex, and body surface area. Controls were excluded when referred for echocardiographic evaluation of known valvular heart disease, murmur, congestive heart failure, and cardiac transplantation. Other exclusion criteria were myocardial infarction, thyrotoxicosis, rheumatic fever, endocarditis, connective tissue disease, carcinoid syndrome, or use of anorectic drugs. We and others have previously demonstrated that recruitment of controls from a large database can also be used as representative controls (14, 17).

None of the patients had hemodynamic instability, previous myocardial infarction, thyrotoxicosis, rheumatic fever, endocarditis, or connective tissue disease. The medical ethics committee of the Leiden University Medical Center approved the study, and written informed consent was obtained from all subjects.

Echocardiography

Echocardiography was performed while the patients were in the left lateral decubitus position using a commercially available system (Vingmed Vivid-7, General Electric–Vingmed, Milwaukee, WI, USA). Standard parasternal (long and short axis) and apical views (2- and 4-, and long axis) were obtained.

M-mode images were obtained from the parasternal long-axis views for quantitative assessment of LV dimensions (interventricular septum thickness (IVST), posterior wall thickness (PWT), LV end-diastolic diameter (LVEDD), LV end-systolic diameter (LVESD), fractional shortening (FS), and LVEF) (18).

The following parameters of diastolic function were obtained: diastolic transmitral peak velocities (E and A wave) and the E/A ratio. Quantitative diastolic data were derived from tissue Doppler imaging (TDI). For TDI analysis, the digital cine-loops were analyzed using commercial software (Echopac 6.1; General Electric–Vingmed). The sample volume (4 mm²) was placed in the LV basal portion of the septum (using the four-chamber views). The following parameters (mean values calculated from three consecutive heartbeats) were derived: early diastolic velocity (’E’), late diastolic velocity (’A’), and the E’/A’ ratio.

The severity of valvular regurgitation was assessed by two independent expert readers blinded to the clinical data on a qualitative scale of trace, mild, moderate, or severe, using previously described methods (19, 20).

LV mass (LVM) was calculated by the cube formula, and using the correction formula proposed by Devereux et al. (21): 0.8 × (1.04 ((LVEDD + PWT + IVST)³ − LVEDD³)) + 0.6. LV mass index (LVMi) was corrected for body height (22). LV hypertrophy (LHV) was defined as LVMi exceeding 49.2 g/m²·7 for men and 46.7 g/m²·7 for women (22).

Assays

GH concentrations were quantitated using a sensitive time-resolved immunofluorescent assay (Wallac Oy, Turku, Finland), specific for 22 kDa GH protein. The detection limit was 0.012 μg/l. Inter-assay coefficients of variation were 8.4–1.6% in the GH range 0.1–18 μg/l (1 μg/l = 2.6 mU/l). Total serum IGF1 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
1.5 nmol/l. Age- and gender-adjusted IGF1 data were determined in the same laboratory. IGF1 was expressed as a SDS for age- and gender-related normal levels, using \( \lambda \)-\( \mu \)-\( \sigma \) smoothed reference curves based on measurements in 906 healthy individuals (23, 24).

A Hitachi 800 autoanalyzer (Roche) was used to quantify serum concentrations of glucose, total cholesterol (TC), and triglycerides (TG). High density lipoprotein (HDL) cholesterol was measured with a homogenous enzymatic assay (Hitachi 911, Roche). Low density lipoprotein (LDL) concentrations were calculated using the Friedewald formula. Unfortunately, lipid concentrations at the time of echocardiography were only available in 9 out of 17 patients with active acromegaly.

**Statistical analysis**

Statistical analysis was performed using SPSS for Windows, version 14.0 (SPSS Inc. Chicago, IL, USA). Results are expressed as the mean \( \pm \) s.e.m., unless specified otherwise. ANOVA analysis with Tukey HSD correction for multiple comparisons was used to compare patients with GHD after acromegaly with patients with biochemical remission and patients with active acromegaly. We checked all comparisons after log transformation of the variables. Results were also checked after adjustment for age by ANCOVA. Independent samples t-tests and \( \chi^2 \) tests were used to compare patients with GHD after acromegaly and healthy controls. In addition, regression analysis was performed with systolic and diastolic function as dependent variables and age, body mass index (BMI), IGF1 SDS, hypertension, and LVH as independent variables to identify predictors of cardiac function in patients with acromegaly. A \( P \) value < 0.05 was considered to represent a significant difference.

**Results**

**Clinical characteristics**

Age and gender were not different between the three patient groups (Table 1). GH concentrations and IGF1 SDS were lower in the patients with GHD after acromegaly compared with patients with active acromegaly \((P<0.001\) and \(P<0.001\), respectively). GH and IGF1 concentrations did not differ between patients with GHD after acromegaly and patients with biochemical remission \((P=0.839\) and \(P=0.195\), respectively). In patients with GHD after acromegaly, the interval between diagnosis of GHD and this study was 3.2 \( \pm \) 0.9 years. In addition, the interval between biochemical remission and the insulin tolerance test (ITT) was 12.8 \( \pm \) 7.0 years. The interval between diagnosis and remission was 4.1 \( \pm \) 5.1 years.

In patients with biochemical remission, the interval between disease remission and this study was 6.4 \( \pm \) 4.9 years, and that between diagnosis and remission 3.8 \( \pm \) 4.5 years.

In patients with active acromegaly, the estimated disease duration was 14.5 \( \pm \) 10.8 years. The number of patients with hypertension in the active disease group was \((n=7, 41\%)\), in the biochemical remission group \((n=3, 15\%)\) and GHD \((n=6, 38\%,\) overall \(P\) value 0.168). None of the patients with GHD after acromegaly compared with two patients with active acromegaly (12\%) and two with biochemical remission (10\%) suffered from diabetes mellitus (overall \(P\) value = 0.384). Two of the patients with GHD after acromegaly (13\%) compared with one with active acromegaly (5\%) and one with biochemical remission (5\%) used lipid lowering drugs (overall \(P\) value = 0.665).

ACTH deficiency was present and substituted in nine patients with GHD after acromegaly (56\%), three patients with biochemical remission (15\%), and two

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical characteristics of patients with GH deficiency after acromegaly compared with patients with biochemical remission of acromegaly and patients with active acromegaly and healthy controls.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GHD after acromegaly</td>
</tr>
<tr>
<td></td>
<td>((n=16))</td>
</tr>
<tr>
<td>Age (years)</td>
<td>56 ( \pm ) 12</td>
</tr>
<tr>
<td>Gender (male/female (%))</td>
<td>50/50</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>30.2 ( \pm ) 4.5*</td>
</tr>
<tr>
<td>GH (mU/l)</td>
<td>0.6 ( \pm ) 0.4†</td>
</tr>
<tr>
<td>IGF1 (SDS)</td>
<td>9.1 ( \pm ) 5.1</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>6.1 ( \pm ) 1.0</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>4.2 ( \pm ) 0.9</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.4 ( \pm ) 0.5</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>2.1 ( \pm ) 1.3</td>
</tr>
<tr>
<td>Surgery (%)</td>
<td>100</td>
</tr>
<tr>
<td>Radiotherapy (%)</td>
<td>94</td>
</tr>
<tr>
<td>Somatostatin analogs (%)</td>
<td>NA</td>
</tr>
<tr>
<td>No treatment yet (%)</td>
<td>NA</td>
</tr>
</tbody>
</table>

* \(P<0.05\) compared with patients with biochemical remission of acromegaly in an ANOVA with Tukey HSD post hoc comparison. † \(P<0.05\) compared with patients with active acromegaly in an ANOVA with Tukey HSD post hoc comparison. 

Healthy controls were age-, gender and BSA matched to the patients with GHD after acromegaly.
patients with active acromegaly (5%). TSH deficiency was present and substituted in five patients with GHD after acromegaly (31%), one patient with biochemical remission (5%), and one patient with active acromegaly (6%). Three male patients and two female patients with GHD after acromegaly were treated with testosterone and estrogen substitution respectively. Three male patients with biochemical remission of acromegaly and three male patients with active acromegaly were treated with testosterone substitution. None of the female patients with biochemical remission or active acromegaly needed estrogen substitution.

**GHD after acromegaly compared with biochemical remission of acromegaly**

**LV size and mass** LV size (LVEDD, LVESD), wall thickness (IVST, PWT), and mass (LVM, LVMi) did not differ between the two groups (Table 2). LVH (defined as LVMi exceeding 49.2 g/m².7 for men and 46.7 g/m².7 for women (22)) was present in 50% of patients with GHD after acromegaly compared with 30% of patients with biochemical remission of acromegaly (P=0.226). These results were confirmed after adjustment for age.

**LV systolic function** FS did not differ between the two groups. LVEF tended to be lower in patients with GHD after acromegaly compared with patients with biochemical remission (P=0.070, Fig. 1). These results were not affected after adjustment for age (P=0.030).

**LV diastolic function** No differences were noted in diastolic parameters (E and A wave velocities, E/A ratio) between the two groups. Additional data on diastolic function, as assessed by TDI, revealed that E′ was lower in patients with GHD after acromegaly compared with patients with biochemical remission (P=0.005, Fig. 2). Accordingly, E′/A′ ratio tended to be decreased (P=0.079). These results were even more marked after adjustment for age (P=0.001 and P=0.018 for the E′ and E′/A′ ratio respectively).

**Heart valves** Mitral regurgitation was absent in 81% of patients with GHD, whereas 13% had trace, and 6% mild regurgitation, compared with 70, 15, and 15% respectively of patients with biochemical remission (P=NS). Aortic regurgitation was absent in 88% of patients with GHD, whereas 13% had trace regurgitation, compared with 70 and 10% trace, and 20% mild regurgitation of patients with biochemical remission (P=NS).

**GHD after acromegaly compared with healthy controls**

**LV size and mass** LV size (LVESD, LVESD), wall thickness (IVST, PWT), and mass (LVM, LVMi) did not differ between the two groups (Table 3). LVH (defined as LVMi exceeding 49.2 g/m².7 for men and 46.7 g/m².7 for women (22)) was present in 50% of patients with GHD after acromegaly compared with 38% of the healthy controls (P=NS).

**LV systolic function** FS and LVEF did not differ between the two groups.

**LV diastolic function** E wave velocity was lower in patients with GHD after acromegaly compared with healthy controls without any differences in A wave

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**Table 2** Left ventricular dimensions, systolic function, and diastolic function in patients with GH deficiency (GHD) after acromegaly compared with patients with biochemical remission after acromegaly and patients with active acromegaly.

<table>
<thead>
<tr>
<th></th>
<th>GHD after acromegaly (n=16)</th>
<th>Biochemical remission after acromegaly (n=20)</th>
<th>P valuea</th>
<th>Active acromegaly (n=17)</th>
<th>P valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDD (mm)</td>
<td>51.6±6.1</td>
<td>53.3±6.7</td>
<td>NS</td>
<td>54.1±10.2</td>
<td>NS</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>33.5±5.0</td>
<td>34.2±6.6</td>
<td>NS</td>
<td>37.5±10.5</td>
<td>NS</td>
</tr>
<tr>
<td>IVST (mm)</td>
<td>12.3±3.5</td>
<td>10.2±2.4</td>
<td>NS</td>
<td>13.5±3.9</td>
<td>NS</td>
</tr>
<tr>
<td>PWT (mm)</td>
<td>10.3±1.8</td>
<td>9.7±1.7</td>
<td>NS</td>
<td>10.7±2.3</td>
<td>NS</td>
</tr>
<tr>
<td>FS (%)</td>
<td>36.8±5.8</td>
<td>36.9±5.8</td>
<td>NS</td>
<td>30.4±7.3</td>
<td>0.014</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>65.9±7.3</td>
<td>72.4±8.5</td>
<td>0.070</td>
<td>58.8±9.3</td>
<td>0.047</td>
</tr>
<tr>
<td>E (mm/s)</td>
<td>50.9±11.7</td>
<td>56.0±15.0</td>
<td>NS</td>
<td>56.0±16.2</td>
<td>NS</td>
</tr>
<tr>
<td>A (mm/s)</td>
<td>59.6±17.7</td>
<td>56.3±15.4</td>
<td>NS</td>
<td>63.6±16.0</td>
<td>NS</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>0.9±0.2</td>
<td>1.0±0.5</td>
<td>NS</td>
<td>0.92±0.38</td>
<td>NS</td>
</tr>
<tr>
<td>E'/A' ratio</td>
<td>6.0±2.1</td>
<td>6.3±1.5</td>
<td>0.005</td>
<td>6.0±2.4</td>
<td>NS</td>
</tr>
<tr>
<td>LVM (g)</td>
<td>235.2±68.4</td>
<td>211.8±84.5</td>
<td>NS</td>
<td>289.8±158.3</td>
<td>NS</td>
</tr>
<tr>
<td>LVMi (g/m².7)</td>
<td>50.9±15.3</td>
<td>45.8±18.1</td>
<td>NS</td>
<td>65.8±38.4</td>
<td>NS</td>
</tr>
<tr>
<td>LVH (%)</td>
<td>50%</td>
<td>30%</td>
<td>NSb</td>
<td>71</td>
<td>NSb</td>
</tr>
</tbody>
</table>

LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; FS, fractional shortening; LVEF, left ventricular ejection fraction; E, E wave (early filling phase); A, A wave (atrial contraction); E′, tissue Doppler E wave; A′, tissue Doppler A wave; IVST, interventricular septum thickness; PWT, posterior wall thickness; LVMi, left ventricular mass index; LVH, left ventricular hypertrophy.

aANOVA analysis with Tukey HSD correction for multiple comparisons was used to compare patients with GHD after acromegaly with patients with biochemical remission and patients with active acromegaly.

bχ² test.
velocity and E/A ratio. Additional data on diastolic function, as assessed by TDI, revealed that E' was also lower in patients with GHD after acromegaly compared with healthy controls \((P = 0.006, \text{Fig. 2})\). Accordingly, \(E'/A'\) ratio tended to be decreased \((P = 0.079)\).

**Heart valves** Mitral regurgitation was absent in 81% of patients with GHD, whereas 13% had trace, and 6% mild regurgitation, compared with 73, 25, and 6% respectively in healthy controls \((P = \text{NS})\). Aortic regurgitation was absent in 88% of patients with GHD, whereas 13% had trace regurgitation, compared with 94% no and 13% trace regurgitation of healthy controls \((P = \text{NS})\).

**GHD after acromegaly compared with active acromegaly**

**LV size and mass** LVESD and LVEDD did not differ between the two groups (Table 2, Fig. 1). Remarkably, IVST, PWT, and LVM were not different in patients with GHD after acromegaly compared with patients with active acromegaly. LVH (defined as LVMi exceeding 49.2 g/m\(^2.7\) for men and 46.7 g/m\(^2.7\) for women (22)) was present in 50% of patients with GHD after acromegaly compared with 71% of patients with active acromegaly \((P = \text{NS})\). These results were confirmed after adjustment for age.

**LV systolic function** FS and LVEF were significantly higher in patients with GHD after acromegaly compared with patients with active acromegaly \((P = 0.014 \text{ and } P = 0.047)\). These results were confirmed after adjustment for age \((P = 0.005 \text{ and } P = 0.021 \text{ for FS and LVEF respectively})\).

**LV diastolic function** No differences were observed in diastolic parameters (E and A wave velocities, E/A ratio).

### Table 3 Left ventricular dimensions, systolic function, and diastolic function in patients with GH deficiency (GHD) after acromegaly compared with healthy controls.

<table>
<thead>
<tr>
<th></th>
<th>GHD after acromegaly ((n = 16))</th>
<th>Healthy controls ((n = 16))</th>
<th>(P) value(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDD (mm)</td>
<td>51.6 ± 6.1</td>
<td>50.0 ± 6.3</td>
<td>NS</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>33.5 ± 5.0</td>
<td>30.6 ± 4.4</td>
<td>NS</td>
</tr>
<tr>
<td>IVST (mm)</td>
<td>12.3 ± 3.5</td>
<td>10.8 ± 1.9</td>
<td>NS</td>
</tr>
<tr>
<td>PWT (mm)</td>
<td>10.3 ± 1.8</td>
<td>10.6 ± 1.5</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>65.9 ± 7.3</td>
<td>68.8 ± 5.5</td>
<td>NS</td>
</tr>
<tr>
<td>FS (%)</td>
<td>36.8 ± 5.7</td>
<td>38.8 ± 4.4</td>
<td>NS</td>
</tr>
<tr>
<td>E (mm/s)</td>
<td>50.9 ± 11.7</td>
<td>62.5 ± 17.4</td>
<td>0.035</td>
</tr>
<tr>
<td>A (mm/s)</td>
<td>59.6 ± 17.7</td>
<td>68.2 ± 17.9</td>
<td>NS</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>0.90 ± 0.24</td>
<td>0.99 ± 0.55</td>
<td>NS</td>
</tr>
<tr>
<td>E'/A' (mm/s)</td>
<td>6.0 ± 2.1</td>
<td>8.1 ± 1.9</td>
<td>0.006</td>
</tr>
<tr>
<td>A'/A' ratio</td>
<td>7.4 ± 1.8</td>
<td>7.8 ± 2.4</td>
<td>NS</td>
</tr>
<tr>
<td>E'/A' ratio</td>
<td>0.85 ± 0.36</td>
<td>1.27 ± 0.85</td>
<td>0.084</td>
</tr>
<tr>
<td>LVM (g)</td>
<td>235.2 ± 68.4</td>
<td>207.9 ± 55.4</td>
<td>NS</td>
</tr>
<tr>
<td>LVMi (g/m(^2.7))</td>
<td>50.9 ± 15.3</td>
<td>44.3 ± 9.8</td>
<td>NS</td>
</tr>
<tr>
<td>LVH, n (%)</td>
<td>8 (50)</td>
<td>6 (38)</td>
<td>(\text{NS})(^b)</td>
</tr>
</tbody>
</table>

LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; FS, fractional shortening; LVEF, left ventricular ejection fraction; E, E wave (early filling phase); A, A wave (atrial contraction); E', tissue Doppler E wave; A', tissue Doppler A wave; IVST, interventricular septum thickness; PWT, posterior wall thickness; LVMi, left ventricular mass index; LVH, left ventricular hypertrophy. 

\(^a\)Independent samples t-test. 

\(^b\)\(\chi^2\) test.
between the two groups. Diastolic function, assessed by TDI, did not reveal differences between the two groups. These results were confirmed after adjustment for age.

**Heart valves** The prevalence of mitral regurgitation was not different between the two groups (GHD: 81% absent, 13% trace, and 6% mild versus active acromegaly: 60% absent, 24% trace, 6% mild, and 12% severe (two patients), P=NS). The prevalence of aortic regurgitation was also not different between the groups (GHD: 88% absent, 13% trace versus 71% absent, 6% trace, 18% mild, 6% severe, in active acromegaly, P=NS).

**Multiple linear regression analysis**

Regression analysis was performed with systolic and diastolic function as dependent variables and age, BMI, IGF1 SDS, hypertension, and LVH as independent variables. All patients with acromegaly were included as one group in this analysis. Age was found to influence diastolic function as measured with conventional echocardiography (β=0.386, P=0.021 for A and β=−0.010, P=0.007 for E/A ratio). LVH and IGF1 SDS influenced diastolic function as measured with TDI (β=−1.9, P=0.010 for LVH on E′ and β=0.135, P=0.032 for IGF1 SDS on A′). We did not find any predictors for systolic function.

**Discussion**

In this study, we characterized cardiac function and morphology in patients with GHD after treatment for acromegaly. Because both acromegaly per se and GHD per se lead to specific structural and functional cardiac alterations, we wanted to assess to which extend GHD after previous exposure to GH excess influences cardiac parameters. This study indicates that GHD after acromegaly results in specific cardiac changes in diastolic function and that normal cardiac function is dependent on normal GH and IGF1 regulation.

To our knowledge, data on the cardiac manifestations of GHD after treatment for acromegaly have not been reported previously. In active acromegaly, a specific cardiomyopathy develops characterized by concentric LVH, and LV systolic and diastolic dysfunction. Adequate treatment with stringent control of GH and IGF1 levels ameliorates signs and symptoms of acromegalic cardiomyopathy. Successful transsphenoidal surgery tends to reverse LVH and to improve diastolic function (25). A recent meta-analysis, which evaluated the impact of this treatment on the heart in acromegaly, demonstrated that somatostatin analog treatment (with a duration ranging from a few days to 18 months) consistently improved markers of LVH (LVM index, IVST, and LV PWT) and diastolic function (26). The findings in our patients with active acromegaly compared with those with biochemical remission are in line with the data from these intervention studies.

Treatment of acromegaly, however, can result in GHD in some patients, especially after previous radiotherapy (5). Several parameters of cardiac morphology and function were altered in our patients with GHD after acromegaly.

First, systolic function at rest tended to be decreased compared with patients with biochemical remission. However, when compared with healthy controls systolic function was not affected in GHD after acromegaly. Therefore, we should be careful in interpreting this trend, since previous acromegaly might have influenced systolic function in patients with biochemical remission. Systolic function was found to be decreased in patients with adult-onset GHD not previously exposed to GH excess. This was found to be correlated with both age and the severity of GHD (7,8). In addition, we noted that systolic function was lower in patients with active acromegaly than in those with GHD after acromegaly. Hypertension and LVH are major determinants of systolic function. About 41% of patients with active acromegaly suffered from hypertension and 71% had LVH compared with 38 and 50% in patients with GHD respectively. Apparently, most probably among many others, these factors result in cardiac systolic function being more affected in states of GH excess than in GHD.

Secondly, TDI revealed a decrease in parameters reflecting diastolic function in patients with GHD after acromegaly compared with those with biochemical remission and healthy controls. To our knowledge, only one study assessed diastolic function in adults with GHD with TDI (13). In that study, E′ was decreased compared with controls (13), in line with the observed decrease in E′ in our patients. In active acromegaly, however, diastolic function was also affected (15). Indeed, there was no difference in diastolic function in patients with GHD after acromegaly compared with patients with active acromegaly.

Indices of LVM, wall thickness, and LV diameters were unaltered in patients with GHD after acromegaly compared with patients with biochemical remission of acromegaly and healthy controls. Indeed, in patients with adult-onset GHD due to other diseases, IVST does not differ from healthy controls (7). However, in adults with childhood-onset GHD, it was found to be decreased (9,10). LVM was unaffected in our patients with GHD after acromegaly compared with patients with biochemical remission of acromegaly and compared with patients with active acromegaly. Several studies in patients with childhood-onset GHD revealed a decreased LVM (6,9,10), whereas it was unaffected in patients with adult-onset GHD, as was the case in our patients (7).

The effects of rhGH on the myocardium in adults with GHD without previous exposure to acromegaly have been reported in a meta-analysis (27). The rhGH replacement with a maximum duration of 18 months...
increased LVM and IVST, whereas diastolic function was not affected (27). Additionally, a trend in improvement in ES was observed (27). It is unknown, however, whether these beneficial changes can also occur in patients with GHD induced by previous treatment for active acromegaly.

In conclusion, GHD after acromegaly results in specific cardiac alterations in diastolic function. In addition, systolic function tended to be decreased in patients with GHD after acromegaly compared with patients with biochemical remission but not when compared with healthy controls, but was higher than in patients with active acromegaly. This study shows that normal cardiac function is dependent on normal GH and IGF1 regulation. It remains to be determined whether these specific cardiac changes after previous prolonged exposure to GH excess followed by GHD affect the response to rhGH replacement.

Declaration of interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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