The heart: an end-organ of GH action
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Abstract
Several experimental and clinical studies have indicated that the heart is an end-organ of GH action. Patients with either childhood- or adulthood-onset GH deficiency (GHD) have abnormalities of cardiac structure and function, such as reduced cardiac mass, impaired diastolic filling and reduced left ventricular response at peak exercise. These cardiovascular abnormalities can be reversed, at least partially, after GH replacement therapy. On the other hand, the chronic overproduction of GH and IGF-I in acromegaly leads to the development of a specific cardiomyopathy. Concentric cardiac hypertrophy occurs in more than two-thirds of patients at diagnosis and is commonly associated with diastolic dysfunction. In later stages, impaired systolic function ending in heart failure can occur if GH/IGF-I excess is not controlled. Additionally, acromegalic cardiomyopathy is complicated by abnormalities of cardiac rhythm and cardiac valves. Successful control of acromegaly is accompanied by a decrease of the left ventricular mass and improvement of cardiac function. These beneficial effects appear earlier in young patients with short disease duration than in elderly patients.

In conclusion, GH and IGF-I play a main role in the regulation of cardiac development and performance.

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Introduction
The growth hormone (GH) and insulin-like growth factor-I (IGF-I) axis is not only involved in the regulation of somatic growth but also in cardiac development and function (1). GH exerts its effects either directly or indirectly, by stimulating the production of IGF-I, which ultimately mediates the action of GH on peripheral tissues.

The relationship between GH/IGF-I and the heart has been demonstrated by numerous experimental studies. A detailed description of the molecular basis of the action of GH and IGF-I in the cardiovascular system lies beyond the scope of this brief review. Very briefly, GH and IGF-I receptors are expressed in cardiac myocytes (1), and IGF-I causes hypertrophy of cultured rat cardiomyocytes (2) and delays cardiomyocyte apoptosis (3). In addition, GH and IGF-I also play a direct effect on myocardial contractility, increasing the intracellular calcium content and enhancing the calcium sensitivity of myofilaments in cardiomyocytes (4, 5). The existence of a relationship between GH/IGF-I and the cardiovascular system has also been suggested by clinical studies, as reported by the increased risk for cardiovascular morbidity and mortality in both GH deficiency (GHD) and excess (6–12).

Cardiac involvement in GH deficiency
Hypopituitary patients have a reduced life expectancy, with about a twofold higher risk of death from cardiovascular disease compared with healthy controls (10–12). This is likely related to the direct and indirect effects, such as hypercoagulability, abdominal obesity, insulin resistance, impairment in lipid profile, atherosclerosis, endothelial dysfunction, reduction of pulmonary function and muscle performance, of GH and IGF-I on the cardiovascular system (13, 14).

In experimental models (15, 16), hypophysectomy induces a decrease in the size of several organs, including the heart, which is reversed by GH administration. GHD patients with childhood-onset disease were reported to have a reduction in the thickness of the left ventricular (LV) posterior wall, interventricular septum, LV internal diameter and LV mass (LVM) index, evaluated by echocardiography (17, 18). These differences were not confirmed in other studies or in GHD patients with adult-onset disease (19, 20). Using equilibrium radionuclide angiography, we first reported LV systolic dysfunction at rest and at peak physical exercise in a group of GHD patients of less than 40 years of age, without any difference between childhood- and adulthood-onset GHD (21). These results were subsequently confirmed in another cohort of adult GHD patients in whom we did not find any difference between young patients (aged <35 years) and middle-aged patients (36–60 years) (22). We have recently re-evaluated the prevalence of impaired systolic function in our cohort of adult GHD patients: 21.4% of the patients with severe GHD had impaired LV ejection fraction (LVEF) at rest compared with none.
of the patients with partial GHD, with GHD and of controls ($P < 0.0001$) (23). Impaired LVEF response at peak exercise was found in 78.6% of the patients with severe GHD, in 44.4% of the patients with partial GHD, in none of the patients without GHD and in 6.3% of the controls ($P < 0.001$) (23). The individual results for LVEF in these 100 patients and their matched controls are shown in Fig. 1. Like the young patients, the elderly patients with GHD also had cardiac impairment, despite the difficulty in diagnosing GHD during aging. We have previously demonstrated, in 11 GHD patients of more than 60 years of age, that LVEF at peak exercise was reduced as compared with age- and sex-matched controls while cardiac mass was unaffected (24). There are, however, some slight differences in the cardiac impairment in GHD patients according with the age of the patients: as already mentioned, reduced cardiac mass can be observed in young patients with childhood-onset disease while it is uncommon in adult, middle-aged or elderly patients or even in the young patients experiencing the disease in adulthood (24). Reduced heart rate with reduced systolic performance, configuring the hypokinetic syndrome, was also observed only in young GHD patients with childhood-onset disease. Whether the severity of cardiac impairment in GHD is determined by the age of onset of the disease or, more likely, by the severity of the disease is still to be determined.

**Effect of GH replacement therapy on cardiac morphology and performance in GHD patients**

Evidence that the cardiac alterations in GHD are induced by the deficiency of GH and IGF-I comes from the results of GH replacement: in fact, GH induces an increase in cardiac mass in most studies (17, 20, 25–27). In a small cohort of adult patients with childhood-onset GHD, Amato et al. (17) showed that GH replacement induces an increase in the LVM index by 26% and an increase in the LVEF at rest by 12% of pre-treatment data. These effects disappeared after 6 months of GH discontinuation (17). In another cohort of 20 young adult (<40 years) GHD patients, with either childhood-onset disease ($n = 10$) or adult-onset disease ($n = 10$), we found a significant increase in the LVM during the 12 months of GH replacement at standard doses (26). It should be noted, however, that in none of our patients was LVM increased above the threshold of cardiac hypertrophy (Fig. 2) (26). Importantly, the hypertrophic effect of GH replacement subsided during treatment and was not detectable 2 years into therapy continuation; cardiac mass was similar to pre-treatment values after 10 years of replacement (27). The effects on cardiac mass is strictly GH dependent as it was not observed in a group of 15 patients with GHD not receiving GH replacement but only in those who were treated with GH (28) (Fig. 3). Moreover, a decrease in the LVM index was recently found in GHD adolescents when GH treatment was discontinued (29). The LVM index returned to normal levels 6 months after treatment was re-instituted (29).

Besides the effects on cardiac mass, GH replacement induces improvement of cardiac performance. Improvement in both diastolic filling and systolic function was observed by radionuclide angiography after 6 months of GH replacement in small series of childhood-onset GHD adults (30, 31). An improvement in LV performance was confirmed in our young patients (26), and in childhood-onset patients the increase in LVEF at peak exercise was slightly more sustained than in adult-onset patients (Fig. 4). Strikingly, a further impairment of cardiovascular risk parameters, LV performance both at rest and at peak exercise, and exercise duration was observed in GHD patients who received complete hormone replacement (where required) except for GH (Table 1). These findings suggested that 12 months of GH deprivation could aggravate the cardiovascular risk and likely increase the risk of cardiac accidents. As further confirmation of our personal results, a very recent meta-analysis study including all the available studies on the cardiac aspects of GHD after GH replacement reported a significant positive

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**Figure 1** LV ejection fraction at rest (left panel) and its changes at peak exercise (right panel) in 100 hypopituitary patients and 80 controls matched for sex, age and BMI. Data are drawn from reference 23.

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effect on LVM, interventricular septum, LV posterior wall, LV end-diastolic diameter and stroke volume after therapy with GH in adults (32).

**Cardiac involvement in acromegaly**

Chronic GH excess in acromegaly induces a specific cardiomyopathy, characterized by concentric hypertrophy in the theoretical absence of other cardiomyopathy (33). The acromegalic cardiomyopathy develops during three main stages. The heart is involved from the very early stages of the disease as shown in patients briefly exposed to GH hypersecretion; in fact, in the early stage, generally found in young patients with short disease duration, cardiomyopathy is characterized by a hyperkinetic left ventricle with an increase in contractility and cardiac output (33). However, young patients with early-onset acromegaly have increased LVM, improved cardiac performance at rest, reduced exercise capacity and duration, with normal or mild abnormalities of diastolic ventricular filling, leading only to a decrease in cardiac performance on effort (34–36). This disorder can be asymptomatic for years before clinical and instrumental signs of cardiac involvement are noted. In a cohort of 25 patients aged less than 40 years and divided on the basis of presumed disease duration below or above 5 years, we documented an increase in heart rate at rest (84.9 ± 1.2 vs 77.8 ± 1.2 b.p.m., P < 0.001) when compared with gender- and age-matched controls (34). In addition, as expected, the patients had an increase in LVM and a decrease in LV performance that was more evident in the patients with longer disease duration (Fig. 5). There is an intermediate stage, when most adult patients are generally diagnosed, with concentric or eccentric cardiac hypertrophy, diastolic filling abnormalities at rest and impaired cardiac performance at peak physical exercise (33). It should be noted that clear-cut LV hypertrophy is present at the diagnosis of acromegaly in more than half of the cases; this prevalence increases up to 100% in patients with hypertension (37). A late stage, in elderly patients with a long history of disease, is characterized by cardiac valve disease and impaired systolic and diastolic performance with low cardiac output even at rest (33). This latter stage can also lead to diastolic congestive heart failure in particular cases (14). Although LV hypertrophy is prominent, the right ventricle can be equally involved (38); cardiac walls are thickened but generally cardiac chambers are not enlarged, because of a relative increase of the size of cardiac myocytes (39–41). At histology, the most relevant abnormalities observed in the acromegalic heart are interstitial fibrosis, increased extra-cellular collagen deposition, myofibrillar derangement, and areas of monocyte necrosis and lymphomononuclear infiltration, gradually impairing the whole organ architecture (40). This derives from an increase in apoptosis of myocytes secondary to the chronic excess of GH (42).

These structural alterations induce functional cardiac impairment in acromegaly. The most striking cardiac disorder of early acromegalic cardiomyopathy is represented by the inadequate filling capacity shown by...
the decrease in the diastolic filling wave, early to late mitral and tricuspid velocity ratio and elongation of the isovolumic relaxation time (33). Estimated disease duration and the patient’s age, together with the presence at diagnosis of cardiovascular disease, arterial hypertension and serum GH levels, are independent predictors of cardiovascular mortality and they may regulate the entity of heart derangement (33). Radio-nuclide studies have confirmed that decreased diastolic filling capacities and impairment of the ejection fraction after exercise can be recorded in 70% of patients (43). According to age stratification, in a group of non-hypertensive patients we have observed a decline in the ejection fraction response to physical exercise in 40% of patients aged below 40 years and in 95% of patients aged 41–67 years (43).

Mitral and aortic valve disease, as well as cavity dilation, may be observed in the late stage. We have found a higher prevalence of valve abnormalities in both patients with active acromegaly (86% vs 24%) and those already cured for at least 1 year (73% vs 9%) than in controls (44). Mild mitral regurgitation was found in 26% of active and 27% of cured patients, whereas mild to moderate aortic regurgitation was found in 31% of active and 18% of cured patients. The persistence of valve abnormalities in patients with cured acromegaly is likely to be correlated with the persistence of LV hypertrophy which should be

Table 1 Effect of GH replacement for 12 months or GH deprivation for 12 months on IGF-I levels, parameters of cardiovascular risk and cardiac performance in patients with GHD. Data are drawn from reference 28 and are shown as means ± S.E.M.

<table>
<thead>
<tr>
<th>GH-treated GHD patients</th>
<th>GH-untreated GHD patients</th>
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<tr>
<td><strong>Baseline</strong></td>
<td><strong>12 months</strong></td>
</tr>
<tr>
<td>IGF-I levels (µg/l)</td>
<td>79.4±6.0</td>
</tr>
<tr>
<td>Total cholesterol levels (mg/dl)</td>
<td>234.0±13.4</td>
</tr>
<tr>
<td>HDL-cholesterol levels (mg/dl)</td>
<td>45.5±3.5</td>
</tr>
<tr>
<td>Triglyceride levels (mg/dl)</td>
<td>199.7±30.6</td>
</tr>
<tr>
<td>Fibrinogen levels (mg/dl)</td>
<td>332.5±27.2</td>
</tr>
<tr>
<td><strong>At rest</strong></td>
<td><strong>Exercise</strong></td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>56.6±2.4</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>52.0±3.6</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>-9.4±3.7</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>5.6±0.4</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>62.3±6.8</td>
</tr>
</tbody>
</table>

Normal ranges: IGF-I = 110–500 µg/l in 20–30, 100–450 µg/l in 31–40, 100–300 µg/l in 41–50, 90–270 µg/l in 51–60 and 75–250 µg/l in ≥60-year-old subjects; total cholesterol 120–200 mg/dl; high density lipoprotein (HDL)-cholesterol 35–110 mg/dl; triglycerides 50–200 mg/dl; fibrinogen <400 mg/dl; normal response of the ejection fraction at peak exercise = ±5% compared with resting values.
carefully and continuously monitored because of the risk of cardiac dysfunction (44). More recently, Pereira et al. (45) have confirmed our results showing aortic valve and mitral valve regurgitation in 30% and 5% of the patients compared with 7% and none of the controls. They also reported that the high prevalence of valve disease in acromegaly was likely to be dependent on the duration of exposure to GH excess, with a 19% increase in odds per year (45).

Arrhythmias were also observed more frequently in the acromegalic patients. The frequency of supraventricular premature complexes in acromegaly is not significantly higher as compared with the normal population, while ectopic beats, paroxysmal atrial fibrillation, paroxysmal supraventricular tachycardia, sick sinus syndrome, ventricular tachycardia and bundle branch blocks are more frequently recorded than in control subjects (46–48). In addition, ventricular late potentials, which are low-amplitude, high-frequency waves in the terminal tract of QRS complexes at ECG, considered as strong predictors of arrhythmic events in patients with previous myocardial infarction, were found in 56% of patients with active acromegaly compared with 6% of patients with well-controlled acromegaly and none of the controls (47). The detection of late potentials was independent of age, gender, disease duration, body mass index and LV hypertrophy measured by echocardiography (47).

Effect of GH/IGF-I suppression on cardiac morphology and performance in acromegaly

The suppression of GH concentration below 5 mIU/l (equal to 2.5 μg/l) associated with the normalization of IGF-I values to the age-adjusted normal range reduces the cardiovascular mortality to the general population rate (6–9). Similarly, the suppression of GH/IGF-I levels improves cardiac morphology and performance in acromegalic patients (33).

Somatostatin analogues normalize serum GH and IGF-I levels in 60–70% of cases in different series (50, 51). A short treatment of 1–3 months with s.c. octreotide has been shown to reduce LV posterior wall and interventricular septum thickness (52), and a more significant effect is achieved with long-term treatments (53, 54). After 6 months of treatment, we observed a significant reduction of the LVM index, the prevalence of hypertrophy decreased from 72% to 27% of cases, diastolic filling parameters improved during the therapy, while no significant differences were observed in systolic indices (54). As further support for these data, the achievement of disease control (i.e. GH levels <2.5 μg/l in basal condition or <1 μg/l after an oral glucose test, together with normalization of plasma IGF-I levels) after treatment with octreotide for 1 year was followed by a significantly improved LV performance (55). Disease control is mandatory to improve or at least arrest the acromegalic cardiomyopathy. In fact, in a 5-year follow-up study, we demonstrated by equilibrium radionuclide angiography (56) that cardiac performance was improved only in the 13 patients achieving disease control 5 years after surgery alone or combined with octreotide, but not in the five not achieving disease control (Fig. 6).

Improvement of cardiac hypertrophy and performance has been also reported after treatment with long-lasting formulations of somatostatin analogues, such as octreotide-LAR or lanreotide (57, 58). It should be noted that the cardiac effects of somatostatin analogues or surgery appear to be related not only to the strict biochemical control of acromegaly but also to patients’ age and the duration of GH and IGF-I hypersecretion before intervention (Table 2). In a recent study including 22 patients successfully controlled for 1 year by octreotide-LAR, we observed the disappearance of LV hypertrophy in 100% of patients aged below 40 years and only in 50% of those aged above 40 years (59). In addition, LVEF at peak exercise significantly increased only in younger patients, being restored in 80% of young and in 50% of middle-aged
patients (59). Similar results were recorded when capacity and duration of exercise was analyzed. Taken together, these observations suggested that acromegalic cardiomyopathy is more likely reversed in younger patients with a short disease duration whose disease activity is successfully controlled by 12 months of treatment with octreotide-LAR. Indirectly, these results also indicated that early diagnosis and effective treatment are mandatory in acromegaly (59). Whereas cardiac valve disease is hard to reverse after disease control (44, 45), arrhythmias are improved by treatment with somatostatin analogues and ventricular premature beats were significantly decreased after 6 months of lanreotide treatment (60). Direct effects of somatostatin on the cardiac conduction system cannot be excluded (61).

Conclusions

GH and IGF-I regulate somatic growth and also several other processes, including cardiac development and the preserving of myocardial structure and function, as shown by the impairment in cardiac morphology and function in GHD and chronic excess. Furthermore, a careful evaluation of cardiac function, morphology and activity at diagnosis and during the follow-up seems, thus, to be mandatory in the management of patients with GHD and acromegaly. Normalization of GH and IGF-I levels in patients with GHD or acromegaly is therefore essential to reverse or arrest cardiovascular disease. In addition, attention has recently been focused on the potential ability of GH to increase cardiac mass directly, so as to hypothesize its use in the treatment of chronic non-endocrine heart failure (62). On the other hand, a decrease in IGF-I levels has been observed in patients with dilated cardiomyopathy (63), indicating some alterations in the GH/IGF-I axis in cardiac failure. Very recently, the association of serum IGF-I and IGF-binding protein-1 (IGFBP-1) in all causes of cardiovascular mortality, either ischemic (IHD) and non-ischemic heart disease (non-IHD), was examined in 633 men and 552 postmenopausal women not receiving estrogens (64). During the 9- to 13-year follow-up there were

Table 2

<table>
<thead>
<tr>
<th>Age &lt; 40 years</th>
<th>Age &gt; 40 years</th>
</tr>
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<tbody>
<tr>
<td>Disease duration (years)</td>
<td>6.2±1.0&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>LVMl (g/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>124.4±5.8</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>—</td>
</tr>
<tr>
<td>At rest</td>
<td>52.7±1.2</td>
</tr>
<tr>
<td>Exercise</td>
<td>53.3±2.0</td>
</tr>
<tr>
<td>Exercise-induced changes</td>
<td>1.5±2.9</td>
</tr>
<tr>
<td>Exercise duration (min)</td>
<td>7.3±0.3</td>
</tr>
<tr>
<td>Exercise capacity (watts)</td>
<td>82.5±5.3</td>
</tr>
</tbody>
</table>

<sup>a</sup><sup>P</sup> < 0.01, <sup>b</sup><sup>P</sup> < 0.05 vs middle-aged patients.
522 deaths (224 attributed to cardiovascular disease and 105 caused by IHD) (64). IGF-I and IGFBP-1 were independently and jointly related to the risk of IHD mortality. In a proportional hazards model including both IGF-I and IGFBP-1 and adjusting for cardiovascular risk factors, the relative risk of IHD mortality was 38% higher for every 40 ng/ml (1 S.D.) decrease in IGF-I and 3.1 times greater for those in the lowest quintile of IGFBP-1 (64). These recent data pointed out the relevance of low IGF-I and IGFBP-1 in the development of cardiovascular disease and death. However, at present, even if GH treatment was shown to improve hemodynamic and clinical status in some patients with dilated cardiomyopathy (65–67), the final data on LV performance and clinical status in some patients with dilated cardiomyopathy (65–67) is required to fully understand the potential application of GH in treating cardiac diseases.

References


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