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Growth hormone and the heart

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Summary

Impaired cardiovascular function has recently been demonstrated to potentially reduce life expectancy both in GH deficiency and excess. Experimental and clinical studies have supported the evidence that GH and IGF-I are implicated in cardiac development. In most patients with acromegaly a specific cardiomyopathy, characterized by myocardial hypertrophy with interstitial fibrosis, lympho-mononuclear infiltration and areas of monocyte necrosis, results in biventricular concentric hypertrophy. In contrast, patients with childhood or adulthood-onset GH deficiency (GHD) may suffer both from structural cardiac abnormalities, such as narrowing of cardiac walls, and functional impairment, that combine to reduce diastolic filling and impair left ventricular response to peak exercise. In addition, GHD patients may have an increase in vascular intima-media thickness and a higher occurrence of atheromatous plaques, that can further aggravate the haemodynamic conditions and contribute to increased cardiovascular and cerebrovascular risk. However, several lines of evidence have suggested that the cardiovascular abnormalities can be partially reversed by suppressing GH and IGF-I levels in acromegaly or after GH replacement therapy in GHD patients.

Recently, much attention has been focussed on the ability of GH to increase cardiac mass suggesting its possible use in the treatment of chronic non-endocrine heart failure. In fact, GH administration can induce an improvement in haemodynamic and clinical status in some patients. Although these data need to be confirmed in more extensive studies, such promising results seem to open new perspectives for GH treatment in humans.

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Introduction

GH and insulin-like growth factor I (IGF-I) are multifunctional growth factors primarily known as regulators of longitudinal bone growth. GH works as an endocrine promoter of hepatic production of IGF-I, which ultimately mediates GH action on peripheral tissues. These hormones elicit primary regulatory activities both in the developmental growth of the heart and in the maintenance of its structure, but autocrine and paracrine mechanisms exerted by IGF and their binding peptides might also be involved (Isgaard *et al*., 1989; Toyozaki *et al*., 1993; Delafontaine, 1995). After cessation of body growth, GH still has a physiological role in the human body. It is evident that GH plays a positive effect on body composition, muscle strength, bone mineral density, reproductive capacity, skin properties and metabolic functions (De Boer *et al*., 1995). Interestingly, the existence of a relationship between GH/IGF-I and the cardiovascular system has long been suggested (Huchard, 1895), and an increased risk for cardiovascular morbidity and mortality has been documented both in GH excess and deficiency (Wright *et al*., 1970; Nabarro, 1987; Rosén & Bengtsson, 1990; Bates *et al*., 1993, 1996; Rajasoorya *et al*., 1994; Saccà *et al*., 1994; Bulöw *et al*., 1997; Bengtsson *et al*., 1998; Orme *et al*., 1998). Changes of plasma volume also occur both in GH excess and deficiency. In fact, GH causes fluid retention in patients with acromegaly (Ikkos *et al*., 1954) while patients with GH deficiency have decreased extracellular volume and plasma volume which is restored by GH replacement (Møller *et al*., 1997). The alteration of body fluids play a concomitant role in the impairment of the cardiac performance in these patients.

The aim of this study is to review some of the most recent experimental and clinical evidence concerning the interaction of GH and IGF-I with cardiovascular function. Cardiac consequences of GH excess and deficiency in humans and their possible reversibility after medical treatment are also discussed together with the potential indication for GH treatment in patients with heart failure.

Effect of GH on the heart: the experimental basis

Cardiomyocytes are almost unequivocally considered as

terminally differentiated cells unable to proliferate. They respond to biomechanical stress, like pressure and volume overload, by remodelling and hypertrophy, and re-expressing fetal cytoskeletal and myofibrillar proteins (Reiss *et al*., 1994). From a physiological point of view, several components of the IGF family can be expressed in an autocrine/paracrine fashion within the heart. Both the epicardium and the coronary vessel of the human fetus express IGF-I mRNA (Han *et al*., 1987). In the neonatal rat, the ventricles preferentially express IGF-II mRNA transcripts and contain both IGF-I receptor type 1 and 2 (Engelmann *et al*., 1989). In the adult rat, cardiac IGF-I transcription and IGF-I receptor expression is partly blunted (Anversa *et al*., 1986; Toyozaki *et al*., 1993; Delafontaine, 1995; Le Roith *et al*., 1995). In addition, increased IGF-I immunoreactivity has been found in the inner layers of the left ventricle (Wahlander *et al*., 1992) where both tension and wall stress are high, with a gradual decline towards the epicardial surface (Mirsky, 1979). No elevation of IGF-I expression has been observed in the right ventricle (Isgaard *et al*., 1999). Interestingly, the onset of IGF-I expression preceded or paralleled the development of left ventricular hypertrophy (Wahlander *et al*., 1992; Guron *et al*., 1996).

The involvement of the IGF system in rat experimental cardiopathy suggests that co-ordinated gene expression is activated (Delafontaine, 1995), and that IGF-I, IGF receptors and IGF binding proteins (IGFBPs) can take part to the response to increased workload (Guron *et al*., 1996), inflammation-linked angiogenesis (Schaper *et al*., 1994; Kluge *et al*., 1997) and repair processes following ischaemic events (Dean *et al*., 1999). The expression of IGF-I mRNA and IGF receptors is increased in both ventricles following pressure and volume overload (Komuro & Yazaki, 1993; Donohue *et al*., 1994), experimental infarction and cardiac hypertrophy (Donohue *et al*., 1994). Post-ischaemic heart failure is associated with a higher expression of IGFBP-3, 4, 5 and 6 in the infarct/peri-infarct area of the left ventricle (Kluge *et al*., 1997; Dean *et al*., 1999). The activation of genes essential to DNA synthesis is supposed to act in a pathological context as a repair mechanism for the reconstitution of damaged cardiac tissue (Reiss *et al*., 1994). Despite this evidence, it is still difficult to understand the real importance of IGF-I in prenatal life, as far as development of the heart is concerned. An increase of IGF-I mRNA was found in rat myocardium after pressure overload secondary to either banding of the ascending aorta, aorto-caval shunting, myocardial infarction secondary to experimental renal hypertension and induction of pulmonary hypertension (Wahlander *et al*., 1992; Hanson *et al*., 1993; Russel-Jones *et al*., 1993; Isgaard *et al*., 1994; Reiss *et al*., 1994). In fact, newborns of knock-out mice for the IGF-I gene show a reduced body size as compared to control litter-mates, but the heart size is generally unaffected (Wang *et al*., 1999). Similarly, when hepatic IGF-I synthesis is knocked-out with the Cre/loxP recombination system, no negative effect on the postnatal cardiac size can be detected (Sjogren *et al*., 1999).

Otherwise, several lines of evidence suggest that the rate of GH secretion has a prominent role in postnatal cardiac development. Rats subjected to pituitary excision show decreased cardiac expression of IGF-I mRNA, which can be restored by exogenous rGH administration (Flyvbjerg *et al*., 1991). GH-secreting tumours implanted in rats induce cardiac hypertrophy, enhance contractile performance and induce the action potential of cardiac fibres (Courville & Mason, 1938; Hunter & Chien, 1999). The exogenous administration of GH and IGF-I in normal adult rats induced a cardiac hypertrophic response without development of significant fibrosis (Cittadini *et al*., 1996). Furthermore, IGF-I increases intracellular calcium content and enhances the calcium sensitivity of myofilaments in cardiomyocytes (Xu & Best, 1991; Freestone *et al*., 1996; Cittadini *et al*., 1998). GH and IGF-I stimulation of the cardiac fibre is associated with a low-energy conformational feature, through the myosin pheno-conversion from the isoform V3 to a low ATPase activity isoform (Rubin *et al*., 1990; Xu & Best, 1991). GH and IGF-I also play a direct effect on myocardial contractility. Increased contractility was shown in preparations of cardiac tissue from animal models of chronic GH excess (Timsit *et al*., 1990), or in cardiomyocytes from neonatal rats (Vetter *et al*., 1988), likely due to increased calcium responsiveness of myofilaments (Strömer *et al*., 1996).

However, it is hard to separate the effects elicited by GH from those directly due to IGF-I. In humans, the acute intravenous infusion or subcutaneous administration of recombinant IGF-I to healthy subjects has been reported to increase cardiac performance, as assessed by impedance cardiography or echocardiography (Russell-Jones *et al*., 1995; Donath *et al*., 1996). Systemic side-effects with metabolic changes were induced by the intravenous infusion of 60 μg/kg of IGF-I over 3 h (Russell-Jones *et al*., 1995), but not when the same dose was given subcutaneously (Donath *et al*., 1996). In this study, glucose levels were unchanged while insulin levels and the GH response to physical exercise were inhibited (Donath *et al*., 1996). Moreover, subcutaneous injection of 20 μg/kg of IGF-I was demonstrated to enhance cardiac inotropism in healthy subjects (Bisi *et al*., 1999a). The IGF-I-induced increase in the LV ejection fraction could be due not only to a direct cardiac action but also to a secondary vasodilatation. In fact, IGF-I displays vasodilator effects in forearm muscles and kidneys (Guler *et al*., 1989; Hirschberg & Kopple, 1989; Copeland & Sreekuran, 1994). An alternative explanation might involve cathecolamine release, although the results reported by Bisi *et al*. (1999a) did not show changes in epinephrine or norepinephrine secretion after rIGF-I administration.

Cardiovascular effects of GH excess

In humans, chronic excess of GH and IGF-I secretion is able to affect heart morphology and performance (Wright *et al*., 1970; McGuffin *et al*., 1974). Cardiac involvement in the theoretical absence of other cardiac disease can define acromegalic cardiomyopathy, which most commonly features concentric hypertrophy (McGuffin *et al*., 1974). Cardiac walls are thickened, but cardiac chambers are rarely enlarged, an event resulting from the relative increase in cardiac myocyte width, due to the parallel assembly of new contractile-protein units (Hunter & Chien, 1999). Biopsy and autopsy studies have shown that interstitial fibrosis constitutes the main histological abnormality and it gradually impairs the organ architecture (Courville & Mason, 1938; Hejtmancik *et al*., 1951; Lie & Grossman, 1980; Hayward *et al*., 1987). Extracellular deposition of collagen is increased and coexists with myofibrillar derangement, areas of monocyte necrosis and lympho-mononuclear infiltration, thus resembling a pattern of myocarditis (Hejtmancik *et al*., 1951; Lie & Grossman, 1980; Hayward *et al*., 1987). *In vivo* examination of biopsy specimens, obtained during heart catheterization, showed increased apoptosis in cardiac myocytes and interstitial fibroblasts, found to be inversely correlated to the output rate (Frustaci *et al*., 1999).

From a clinical perspective, heart hypertrophy is the most widely described feature of the cardiac involvement in acromegaly (Wright *et al*., 1970; McGuffin *et al*., 1974; Savage *et al*., 1979; Smallridge *et al*., 1979; Hayward *et al*., 1987; Morvan *et al*., 1991; Fazio *et al*., 1993; Colao *et al*. 2000a). Although the hypertrophy of the left ventricle is prominent, evidence has been provided that the right ventricle can be equally involved (Fazio *et al*., 1993). Ageing and long duration of acromegaly are main determinants of heart derangement and results collected *in vivo* and postmortem show a cardiac hypertrophy rate higher than 90% in patients with a long disease duration (Hejtmancik *et al*., 1951; Lie & Grossman, 1980). More recent surveys suggest that structural changes of the heart can even occur in patients after short-term exposure to GH hypersecretion (Colao *et al*., 1997a; Fazio *et al*. 2000), and at least 20% of normotensive patients aged under 30 years have been found to have cardiac hypertrophy (Minniti *et al*., 1998). Functionally, in the early phase of acromegaly, and thus in young patients with a short disease duration, high heart rate and increased systolic output configure the hyperkinetic syndrome (Thuesen *et al*., 1988). In a review of our series, the left ventricular (LV) mass index (LVMi) was found to be significantly increased in patients with active acromegaly aged below 40 years and estimated disease duration between 3 and 7 years, as compared to age-matched controls, and 54·5% of them had clear-cut echocardiographic signs of LV hypertrophy (defined as LVMi ≥ 110 g/m^2 in women and ≥ 135 g/m^2 in men) (Fig. 1). In active acromegalic patients aged 41–60 years and with estimated disease duration of 5–15 years, the LVMi was significantly higher than in age-matched controls, and 72·2% of them had LV hypertrophy (Fig. 1). This finding confirmed data obtained in another cohort of patients (Colao *et al*., 1997a), suggesting that cardiac hypertrophy can be an early sign of acromegaly, which is worsened as long as GH/IGF-I hypersecretion is left untreated.

Other factors can potentially contribute to the cardiac derangement in acromegaly. Arterial hypertension affects at least one-third of patients and it can accelerate the development of cardiac hypertrophy (López-Velasco *et al*., 1997). A survey performed on a large number of acromegalic patients studied at their diagnosis (Colao *et al*. 2000a), allowed us to observe that hypertension and, additionally, glucose intolerance can significantly increase the impact of cardiac hypertrophy, that was documented in 51% of the cases included in this series. The prevalence of hypertrophy was found to be significantly higher both in hypertensive and diabetic patients, and multivariate analysis showed that the diastolic blood pressure could better predict the presence of cardiac hypertrophy (Colao *et al*. 2000a). The concomitant development of thyrotoxicosis, which has been reported to represent a rare complication of acromegaly, can also induce a significant impairment of both cardiac mass and performance (Marzullo *et al*. 2000). However, other components of the cardiovascular system can be involved in the progression of cardiomyopathy. Lie & Grossman (1980) documented the presence of mitral and aortic abnormalities in 19% of their autopsy series; ring fragility and leaflets disarray has also been described (Ohtsuka *et al*., 1997), accompanied functionally by regurgitation and stenosis. In such conditions, when the functional complication requires therapeutic intervention, replacement surgery seems to assure a better result than valve plasty, thus improving long-term results (Ohtsuka *et al*., 1997).

Abnormalities of cardiac rhythm have also been documented, both with electrocardiography studies and Holter recordings. The frequency of supraventricular premature complexes in acromegaly is not significantly higher as compared to the normal population (Surawicz & Mangiardi, 1977). Conversely, 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 and are reported to increase during physical exercise (Rodrigues *et al*., 1989; Kahaly *et al*., 1992). Up to 41% of patients can suffer from conduction disorders and recovery from acromegaly does not significantly improve this rate (Rodrigues *et al*., 1989).

The haemodynamics of coronary perfusion have not been

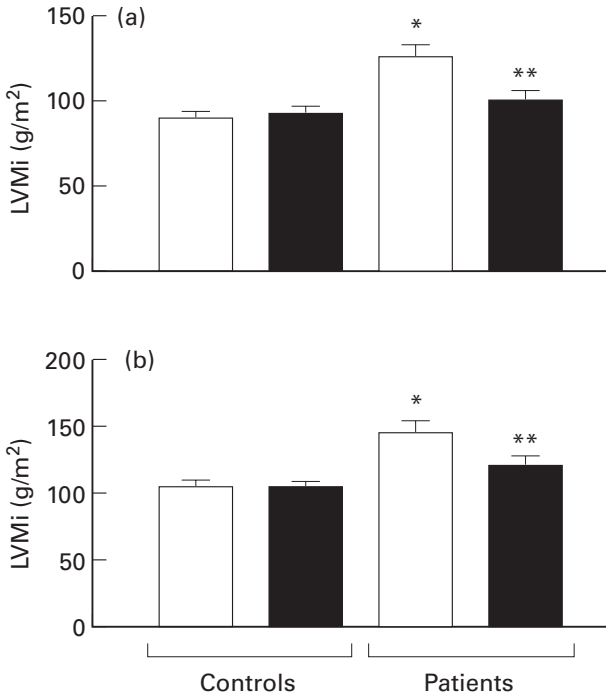

Fig. 1 Left ventricular mass index (LVMi) measured by echocardiography in acromegalic patients aged (a) < 40 years or (b) between 40 and 60 years in comparison to sex- and age-matched control subjects. Measurement of LVMi at baseline (□) was repeated in both groups after 6 months (■), without any drug administration in controls and after lanreotide (60–90 mg/month) or octreotide-LAR (20–30 mg/month) in acromegalic patients. *$P < 0{\cdot}01$ *vs.* controls; **$P < 0{\cdot}05$ *vs.* baseline.

subjected to extensive study, but a prevalence of coronaropathy of between 3 and 37% of cases has been reported in different studies (reviewed by Harrison *et al*., 1978). Postmortem and heart-catheterization studies showed a prominent involvement of small vessels, and thickening of intramural vessels has been described in up to 22% of cases (Courville & Mason, 1938; Hejtmancik *et al*., 1951; Lie & Grossman, 1980). Proximal arteries are generally normal, but they can be either enlarged and tortuous or, rarely, stenotic (Lie & Grossman, 1980). Finally, episodes of angina pectoris are seldom reported, but the presence of chronic myocardial ischaemia cannot be excluded.

From a functional perspective, the most striking cardiac disorder of early acromegalic cardiomyopathy is inadequate filling capacity. Doppler ultrasonography documented that both the diastolic filling wave and the early to late mitral and tricuspid velocity ratio are generally decreased (Saccà *et al*., 1994), whereas limited elasticity of myocardial fibres can cause prolongation of the isovolumic relaxation time (Colao *et al*. 2000a). This disorder can be asymptomatic for years before clinical signs of cardiac involvement are experienced. In the presence of diastolic impairment, the incomplete recovery of an adequate preload can affect systolic parameters during physical effort (Sicolo *et al*., 1993). In fact, the LV ejection fraction and diastolic filling were found to be impaired in 19% and 28% of 130 untreated acromegalic patients, respectively (Colao *et al*. 2000a). In the advanced stage of untreated disease, systolic disorders become more relevant when the association with respiratory disorders, arterial hypertension, metabolic diseases, arrhythmogenic phenomena and coronaropathy can arise.

The application of equilibrium radionuclide angiography seems to provide more accurate information on cardiac performance not only in resting conditions but also at peak exercise. Being operator independent, it allows measurement of the ejection fraction from end-diastolic and end-systolic counts; furthermore, filling and ejection rate can be normalized to the end-diastolic heart rate (Bonow *et al*., 1981, 1985, 1988; Cuocolo *et al*., 1995). Radionuclide studies have confirmed that decreased diastolic filling capacities and impairment of the ejection fraction after exercise can be recorded in 73% of patients (Fazio *et al*., 1994). According to age stratification, in a group of nonhypertensive patients we have observed a decline in the ejection fraction response to physical exercise in 40% of those aged under 40 years and in 95% of older patients (Colao *et al*., 1999a).

It should not be disregarded, however, that the coexistence of other potential risk factors can play a negative role in the progression of this sequence of events. Arterial hypertension and metabolic complications have been already mentioned as determinant factors in the setting of cardiovascular disorders in acromegaly. In addition, cigarette smoking, and hereditary disorders have been recognized as cardiovascular risk factors in the normal population, whereas the occurrence of elevated levels of lipoprotein-a, homocysteine, fibrinogen and triglycerides have been associated with increased cardiovascular morbidity (Harjai, 1999). A limited number of reports have recently suggested that untreated acromegaly is associated with elevated levels of triglycerides, apolipoprotein A-I and apolipoprotein-E, fibrinogen, plasminogen activator inhibitor activity and tissue plasminogen activator (Colao *et al*., 1997b; Landin-Wilhelmsen *et al*., 1997; Wildbrett *et al*., 1997). Understanding their role in this multifactorial mosaic could help to better define the individual progression of cardiovascular complications in these patients.

Few data are currently available on vascular involvement in acromegaly. A heterogeneous distribution of cardiac output has recently been demonstrated in patients with active acromegaly: the direct measurement of brachial artery haemodynamics showed a lower regional blood flow and an increased local resistance (Chanson *et al*., 1998). Morphological alterations in the peripheral microcirculation have been

also documented (Schiavon *et al*., 1999). We recently found a significant increase of the carotid intima-media thickness (IMT) in 30 active acromegalic patients (Colao *et al*. 2001) and in 15 patients cured from acromegaly. Although such data indicate that even long-term GH/IGF-I suppression was not able to reverse intimal thickening, it should be noted that the prevalence of well-defined atherosclerotic plaques was not higher than in control subjects (Colao *et al*. 2001). On the other hand, the prevalence of glucose tolerance alterations, hypertension, unfavourable lipid profile and increased fibrinogen levels was found to be slightly higher in the group of cured acromegalic patients than in controls (Colao *et al*. 2001). The adaptive increase of IMT has been suggested as a compensatory response of the vessels to the changes in blood flow or vascular tone (Bots *et al*., 1997). In fact, in our 75 subjects age was one of the strongest predictors of IMT followed by GH level (Colao *et al*. 2001). Furthermore, acromegalic patients have an increase in insulin levels which are known to be directly correlated with IMT (Kahn *et al*., 1993; Sowers *et al*., 1993; Wu *et al*., 1994), that has been suggested to act as a risk factor for myocardial infarction in adults (O'Leary *et al*., 1999).

The effect of GH and IGF-I suppression on acromegalic cardiomyopathy

A number of investigations (Table 1) have consistently suggested that the progression of cardiac disorders can be arrested by achieving therapeutic control of the disease. Cardiovascular mortality in acromegaly mainly depends on the estimated disease duration, patient's age and the presence, at diagnosis, of cardiovascular disease and arterial hypertension (Wright *et al*., 1970; Bates *et al*., 1993; Rajasoorya *et al*., 1994). The last known GH value seems to better predict life-threatening complications (Orme *et al*., 1998; Swearingen *et al*., 1998). Mortality from cardiovascular accidents, in fact, is significantly increased in the presence of uncontrolled disease and long exposure to elevated hormone levels (Orme *et al*., 1998). The suppression of GH concentration below 5–7·5 mU/l (equal to 2·5 μg/l) and the inhibition of IGF-I-values to the age-adjusted normal range reduce the cardiovascular mortality to that of the general population rate (Orme *et al*., 1998; Swearingen *et al*., 1998). Based on this viewpoint, therapeutic success can consistently reduce both cardiovascular mortality and morbidity in acromegaly. Adenomectomy has been reported to improve the mortality rate in patients achieving either complete tumour removal or biochemical control during medical therapy postsurgically (Swearingen *et al*., 1998). The radio-therapeutic approach presents some major limitations, including partial/delayed effectiveness and high incidence of pituitary deficiency (Ferone *et al*. 2000). Electrocardiographic and echocardiographic abnormalities have been reported to worsen during long-term follow-up in irradiated patients (Baldwin *et al*., 1985). Therefore, both surgery and radiotherapy, when unsuccessful, cannot significantly blunt the progression of cardiovascular complications.

In such circumstances, an adjunctive or substitutive medical approach seems to exert a beneficial effect on cardiac mass and structure. Due to their scant therapeutic effectiveness, dopamine-agonists cannot adequately control the progression of acromegaly, with few exceptions (Colao *et al*., 1997c; Abs *et al*., 1998; Cozzi *et al*., 1998). Although there have been reports of improvement of cardiac hypertrophy during long-term treatment with bromocriptine (Luboshitzky & Barzilai, 1980), the lack of more extensive investigations limits any conclusion. On the contrary, the extended use of somatostatin analogues in the therapeutic management of acromegalic patients has shown that suppression GH and IGF-I can be obtained at least in 60% and 70% of cases, respectively (Lamberts *et al*., 1996). Both short-lasting and long-lasting formulations have been reported to successfully improve cardiovascular indexes. Treatment with short-lasting s.c. octreotide has been shown to reduce LV posterior wall and interventricular septum thickness as early as 3 months (Tokgözoglu *et al*., 1994), and a more significant effect is achieved with long-term treatment (Thuesen *et al*., 1989; Pereira *et al*., 1991; Merola *et al*., 1993a). We reported a significant reduction of indexed cardiac mass after 6 months of therapy, and the prevalence of hypertrophy decreased from 72% to 27% (Merola *et al*., 1993a). Diastolic and systolic improvement is more evident in patients obtaining GH suppression and IGF-I normalization. A significant improvement in LV ejection fraction was recorded in 13 patients achieving biochemical control of the disease, out of 30 patients subjected to a 1-year treatment with s.c. octreotide (Colao *et al*., 1999b). A positive response to octreotide has been reported also in acromegalic patients suffering from congestive heart failure, who gained a significant improvement of cardiac hypertrophy and an increase in cardiac output (Chanson *et al*., 1989, 1990). Similarly, cardiopulmonary performance, impaired in acromegalic patients when compared to controls, was acutely improved by continuous infusion of s.c. octreotide for 24 h (Giustina *et al*., 1995). Depot formulations of somatostatin analogues, namely slow-release lanreotide and long-acting release octreotide (octreotide-LAR), allow more effective and sustained biochemical control of the disease, improving patients' compliance (Caron *et al*., 1997; Gillis *et al*., 1997; Colao & Lombardi, 1998; Lancranjan & Atkinson, 1999). Lanreotide has been shown to induce a significant and progressive reduction in LVMi and isovolumic relaxation time after 3, 6 and 12 months of therapy (Baldelli *et al*., 1999), allowing a consistent improvement of diastolic filling

Table 1 Overview of the effect of different treatments on cardiac parameters in patients with acromegaly

Author	Total patients	Treatment	Follow-up	Methods	Results
Baldwin *et al*., 1985	11	RT	3–17 years	ECG,ECHO	Increased prevalence of cardiovascular events.
Hayward *et al*., 1987	10	Surgery + RT	1–11 years	X-ray, ECG	Two of six cured improved, three not cured died.
Thuesen *et al*., 1989	9	Octreotide	12 months	ECHO	Decreased blood pressure and LV mass.
Pereira *et al*., 1991	5	Octreotide	6 months	ECHO	Significantly decreased IVST, improved diastolic filling.
Lim *et al*., 1992	16	Octreotide	2 months	ECHO	Rapid decrease of the LV mass in patients with hypertrophy but not in those without hypertrophy.
Merola *et al*. 1993a	11	Octreotide	6 months	ECG, ECHO	Significantly decreased LVM, improved diastolic filling, unchanged blood pressure and ejection fraction.
Tokgözoglu *et al*., 1994	6	Octreotide	6 months	ECG, ECHO	Significantly decreased LVM, increased time in treadmill exercise, uchanged blood pressure and ejection fraction.
Colao *et al*., 1999	30	Octreotide	12 months	ERA	Significantly decreased heart rate, and increased ejection fraction in controlled patients, significantly increased blood pressure and decreased ejection fraction in noncontrolled patients.
Baldelli *et al*., 1999	13	Lanreotide	12 months	ECHO	Significantly decreased LVM, improved diastolic filling, unchanged blood pressure and ejection fraction.
Hradec *et al*., 1999	13	Lanreotide	12 months	ECHO	Significantly decreased LVM, unchanged blood pressure,
Colao *et al*. 2000c	15	Octreotide-LAR	6 months	ECHO, ERA	diastolic filling, and ejection fraction. Significantly decreased LVM in all patients, significantly increased ejection fraction at rest and at peak exercise in controlled patients but not in noncontrolled patients.

RT, radiotherapy; ECG, elecrocardiogram; ECHO, echocardiogram; ERA, equilibrium radionuclide angiography; X-ray, radiography; LV, left ventricle; IVST, interventricular septum thickness; LVM, left ventricular mass.

capacities. This observation has been confirmed in another study, where a correlation between the reduction of the cardiac mass and the suppression of GH levels was suggested (Hradec *et al*., 1999). Preliminary data on three patients treated for 18 months with octreotide-LAR has similarly shown a significant reduction in cardiac mass (Colao *et al*., 1997a). These data were confirmed in another series of previously untreated acromegalic patients after 6 months of octreotide-LAR treatment (Colao *et al*. 2000b). In particular, a significant decrease in the left ventricular mass ranging 5·2–35·2% was observed in all patients (Fig. 2), while an increase in the response of the LV ejection fraction at peak exercise was found only in patients achieving disease control (Fig. 2). Despite these results, it is still debatable whether the cardiac benefit achieved after effective therapy for acromegaly could restore the heart features to a predisease condition. The overall reduction of cardiac mass after treatment appears to be close to 20% of basal values, and the incidence of complete normalization of cardiac structure and performance difficult to assess, due to the short duration of follow-ups so far reported. Interestingly, young patients with short disease duration showed average LVMi values comparable to age-matched controls 6 months after treatment either with lanreotide and octreotide-LAR (Fig. 1), and 50% of the entire patient group with cardiac hypertrophy regained a normal LVMi (unpublished data).

It is thus conceivable that more extensive data will shed new light on this question when prolonged follow-up results will be reported.

Cardiovascular involvement in GH deficiency

Whereas the cardiac involvement in acromegaly had already been described at the end of the 19th century (Huchard, 1895), the evidence that GH deficiency (GHD) can cause cardiovascular impairment has only recently been described. Beyond their growth and differentiation effect on whole body organs and tissues as their metabolic role in glucose uptake, glycogen synthesis and amino-acid transport, GH and IGF-I were also demonstrated to display relevant effects on cardiac development and performance. Long-standing GHD in adult subjects is associated with changes in bone turnover and body composition, impairment in lipid profile, reduction in exercise capacity and abnormalities in cardiac function (De Boer *et al*., 1995; Carrol & Christ, 1998; Vance & Mauras, 1999). The attention of several investigators has focussed on this life-threatening complication. In fact, epidemiological data suggest that adults with hypopituitarism have reduced life expectancy compared with healthy controls, with a greater than twofold increase mortality for cardiovascular disease (Rosén & Bengtsson, 1990). These epidemiological findings were confirmed in

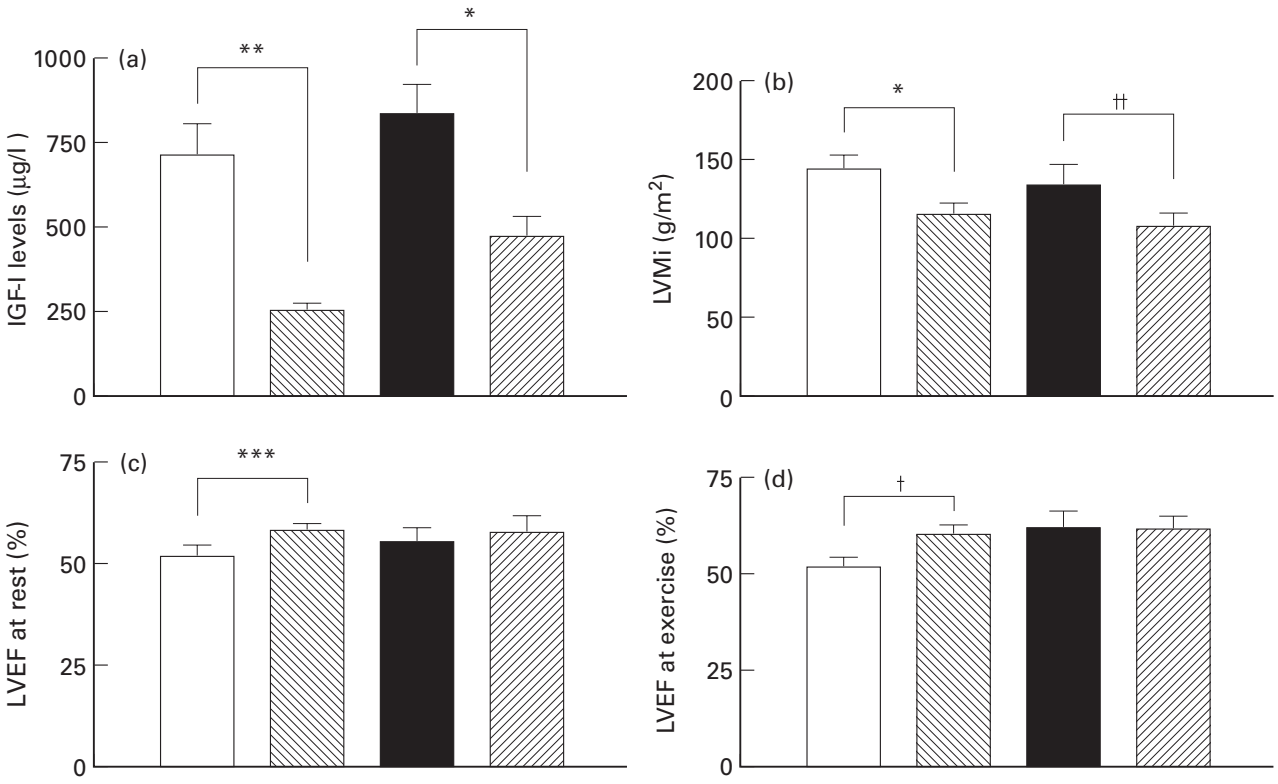

Fig. 2 Effect of treatment with octreotide-LAR for 6 months on IGF-I levels (a) left ventricular mass index (LVMi) (b), ejection fraction at rest (c) and at peak exercise (d) in nine acromegalic patients achieving disease control (basal: □; 6 months: ▨) and in six acromegalic patients not achieving disease control (basal: ■; 6 months: ▨). *$P < 0{\cdot}001$; **$P = 0{\cdot}02$; ***$P = 0{\cdot}05$; †$P = 0{\cdot}002$; ††$P = 0{\cdot}01$ *vs.* basal values.

another study demonstrating a standardized mortality ratio of 1·74 for cardiovascular disease among 344 patients with hypopituitarism (Bulöw *et al*., 1997; Erfurth & Hagmar, 1998). All these reports suggested that the factor responsible for the increased mortality was the GHD. A direct effect of GH deficiency on the heart is highly reliable, although the possibility that gonadal steroid under-replacement and glucocorticoid over-replacement can also negatively affect the cardiovascular system cannot be ruled out. Overall, the negative effect of GHD on cardiovascular functions seems to be due not only to a direct effect played by GH and IGF-I (see experimental basis) but also to an indirect mechanism exerted by unfavourable lipid profile, hypercoagulability and atherosclerosis, as well as decreased muscle performance, pulmonary capacity and endothelial function (reviewed by Beshyah & Johnston, 1999).

A decrease in cardiac size following hypophysectomy, which was reversed by GH administration, was first demonstrated in experimental models (Beznak, 1954; Hjalmarson *et al*., 1969), whereas abnormalities in cardiac structure and function in humans have only recently been demonstrated. Using Doppler ultrasonography, a decrease in the thickness of the LV posterior wall and of the interventricular septum, together with a decrease in the LV internal diameter, was reported in childhood-onset GHD patients (Amato *et al*., 1993; Merola *et al*., 1993b). In particular, a decrease in the thickness of the LV posterior wall and the interventricular septum was, respectively, found in 22% and 33% of adult patients with childhood-onset GHD with an average decrease in cardiac size of 36% (Merola *et al*., 1993b). A significant decrease of 14% of the LV ejection fraction was also observed (Merola *et al*., 1993b). In one study, GHD patients were reported to have a decrease in LV posterior wall and interventricular septum thickness, although no difference of the LVMi, LV internal diameter and systolic function evaluated as LV ejection fraction between patients and controls was noted (Beshyah *et al*., 1995). Contrastingly, other studies on adult patients both with childhood-and adulthood-onset GHD, have shown no difference in the morphological and functional parameters of the LV between patients and controls (Thuesen *et al*., 1994; Beshyah *et al*., 1995; Dunne *et al*., 1995; Valcavi *et al*., 1995). Normal values of LV geometry were also found in GHD patients by Nass *et al*. (1995), although no control subjects were studied. Serum IGF-I levels were found to be correlated

with the LVM and the total fat-free mass in hypopituitary subjects (Beshyah *et al*., 1995; Shahi *et al*., 1992), suggesting that GH can affect cardiac size and body composition to the same extent. Although both patients with childhood-onset and adulthood-onset GHD show decreased vitality, energy, and physical mobility together with several psychological symptoms, the former were shown to present more severe symptoms than the latter (Attanasio *et al*., 1997). No report has compared cardiac characteristics in patients with childhood-onset and adulthood-onset disease so far except for one study, where cardiac performance was evaluated by equilibrium radionuclide angiography in a group of patients younger than 40 years of age. Although no data on cardiac geometry were available, decreased LV ejection fraction at rest (of 17%) and at peak exercise (of 29%) as compared to sex- and age-matched controls was found in both childhood-and adulthood-onset GHD patients without any difference between them (Longobardi *et al*., 1998).

To further evaluate the influence of GHD during adult age, cardiac performance was investigated in a large cohort divided in young patients aged < 40 years, and middle-aged patients aged between 41 and 60 years. Diastolic filling abnormalities and impaired response of LV ejection fraction at peak exercise were found in as many as 65·4% of patients with GHD acquired in adulthood, regardless the age of onset of the disease (Colao *et al*., 2000c). The impairment of LV performance can be due either to a cardiac muscle disease directly caused by the deficiency of GH and IGF-I themselves or to altered haemodynamic conditions, low heart rate and blood pressure indirectly caused by GH and IGF-I deficiency, or both. A characteristic *hypokinetic syndrome* of GHD was, however, only found in young patients, indicating that the age of onset play a relevant role in determining the severity of cardiac impairment in GHD patients (Colao *et al*., 2000c). As in the young patients, elderly patients with GHD also seem to present a specific clinical and biochemical syndrome (Toogood *et al*., 1996a, 1996b). In fact, bone mineral density was reported either to be normal (Toogood *et al*., 1997) or reduced (Colao *et al*., 1998b), whereas body composition was consistently reported to be altered in these patients (Toogood *et al*., 1996b; Colao *et al*., 1998b). Scant data are available on cardiac size and performance in elderly GHD patients. We have recently reported in 11 GHD patients aged over 60 years that cardiac mass was similar to that observed in age- and sex-matched controls (LVMi 97·6 ± 1·8 *vs.* 99·9 ± 1·5 g/m^2) while the LV ejection fraction at peak exercise was markedly depressed in patients compared to controls (51 ± 2·5% *vs.* 73·3 ± 3%, $P < 0{\cdot}001$) (Colao *et al*., 1999c). A normal response of LV ejection fraction at peak exercise was found in eight controls (72·7%) and in two out of 11 patients (18·2%) (Colao *et al*., 1999c), giving a result that was similar to that observed in younger patients (Cittadini *et al*., 1994; Cuocolo *et al*., 1996; Longobardi *et al*., 1998; Colao *et al*. 2000c).

Another point that should not be disregarded is the presence of endothelial dysfunction in GHD. Circulating IGF-I levels seem to play a role on endothelial properties. Endothelial cells possess high-affinity binding sites for IGF-I (Delafontaine *et al*., 1991) and IGF-I was demonstrated to increase nitric oxide (NO) production in *in vitro* experimental procedures (Walsh *et al*., 1996), so contributing to the regulation of vascular tone (Guler *et al*., 1989; Hirshberg *et al*., 1993; Copeland & Sreekuran, 1994; Tsukahara *et al*., 1994; Böger *et al*., 1996). It should be considered that a decreased NO activity is associated with impaired arterial vasodilator capacity, increased platelet aggregability and intimal thickening (Böger *et al*., 1996). An inverse relationship between free IGF-I levels and intima-media thickness (IMT) has been recently reported in healthy elderly subjects (Janssen *et al*., 1998). Moreover, IGF-I may potentially be an important regulator of regional blood flow: IGF-I was demonstrated to possess a direct impact on the vasculature and to attenuate contractility in rat arteries, an effect related to NO production itself (Gryglewski *et al*., 1986). Finally, the infusion of recombinant human IGF-I increases renal blood flow and decreases local vascular resistance both in humans and rats (Guler *et al*., 1989; Hirshberg *et al*., 1993). As IGF-I is not only secreted by vascular smooth muscle cells but also stimulates vascular NO production, it has been suggested that this hormone might play a significant paracrine/autocrine role in the regulation of local blood flow (Delafontaine *et al*., 1991). It is therefore likely that patients affected with GHD might diplay both a specific disarray of cardiomyocytes, leading to impairment of cardiac performance, and an alteration at the vascular level. Less distensibility of aorta (Lehmann *et al*., 1993) and endothelial dysfunction (Evans *et al*., 1999) together with a significant increase in IMT at the level of both common carotid arteries (Markussis *et al*., 1992; Capaldo *et al*., 1997; Borson-Chazot *et al*., 1999; Pfeifer *et al*., 1999) were demonstrated in patients with GHD developing either during childhood or adulthood. These patients also had intense sympathetic nerve activity, likely of central origin, which may be another important mechanism of increased cardiovascular mortality (Sverrisdottir *et al*., 1998).

On this basis, a careful cardiological and vascular assessment of adult patients with GHD could be helpful both in diagnostic strategies and in therapeutic monitoring of the early stages of cardiac failure and atherosclerosis.

The effect of GH replacement therapy on cardiac size and performance

Although the administration of GH to GHD adults reverses

many of the changes in body composition, bone mineral density, exercise capacity and strength, and improves the lipid profile (reviewed by Carrol & Christ, 1998; Beshyah & Johnston, 1999; Vance & Mauras, 1999), little is known about the ultimate efficacy of GH treatment in reversing the cardiovascular risk. The analysis of the results is further complicated by the fact that the doses of GH employed have gradually been reduced during the last decade and have ranged from 6 to 26 μg/kg body weight in different studies. GH was reported to increase cardiac mass in some short-term studies (Amato *et al*., 1993; Caidahl *et al*., 1994; Valcavi *et al*., 1995; Johansson *et al*., 1996) but not in others (Beshyah *et al*., 1995; Thuesen *et al*., 1994; Nass *et al*., 1995). In one study (Amato *et al*., 1993), a 26% increase of the LVMi and a 12% increase in the LV ejection fraction followed GH replacement treatment: these effects disappeared after 6 months of GH discontinuation. An increase in cardiac mass was found either with higher (Johansson *et al*., 1996) or lower GH replacement dosages (Valcavi *et al*., 1995). Interestingly, a significant increase in cardiac mass was reported by Ter Maaten *et al*. (1999) during the first year of GH replacement at supraphysiological doses. However, the hypertrophic effect of GH replacement subsided during treatment and was not detectable 2 years after therapy continuation; cardiac mass was similar to pretreatment values after 10-years' replacement (Ter Maaten *et al*., 1999). No difference in cardiac size between baseline and GH treatment data was reported also by Gibney *et al*. (1999) in another 10-year follow-up study. No change in cardiac function by echocardiography was reported by Nass *et al*. (1995) while improvement both in the diastolic filling and systolic function was observed by radionuclide angiography after 6 months of GH replacement in small series of childhood-onset GHD adults (Cittadini *et al*., 1994; Cuocolo *et al*., 1996). Similarly, a significant increase in stroke volume was observed during the first year of GH therapy in men with childhood-onset GHD (Ter Maaten *et al*., 1999). The increase in stroke volume was attributed to fluid retention on the basis of an increased preload, as indicated by the concomitant rise in LV end-diastolic volume (Ter Maaten *et al*., 1999). However, a direct cardiac inotropic effect of GH can not be ruled out (Valcavi *et al*., 1995). During the 10-year follow-up Ter Maaten *et al*. (1999) also reported a noteable increase in the cardiac index together with an increase in heart rate over time. The improved cardiac performance was also sustained by a remarkable increase in exercise performance. In a recent review of a cohort of young GHD patients, we observed a significant increase of the LV ejection fraction at peak exercise during a 12 month GH replacement course (unpublished data, Fig. 3). However, the exercise-induced changes of LV ejection fraction remained significantly lower than controls after treatment (Fig. 3). In 20 GHD adults aged below 40 years, no difference both of LV ejection fraction and diastolic filling was found between childhood-onset and adulthood-onset patients (unpublished data, Fig. 3). In line with previous reports (reviewed by Carrol & Christ, 1998; Beshyah & Johnston, 1999; Vance & Mauras, 1999), we found a remarkable increase both in exercise capacity (from 84·2 ± 3·4 to 98·7 ± 4 watts, $P = 0{\cdot}002$; controls 100·0 ± 4·1 watts) and duration (from 7·3 ± 0·4 to 8·9 ± 0·4 minutes, $P = 0{\cdot}0003$; controls, 9·6 ± 0·2 minutes).

A beneficial effect of GH replacement on the vascular abnormalities of GHD has also recently been demonstrated. GH treatment in hypopituitary GHD men reversed early morphological and functional atherosclerotic changes in major arteries (Pfeifer *et al*., 1999). The reduction in IMT observed in GH treated GHD patients occurred without a consensual improvement of cardiovascular risk factor parameters, as only a transient 10% decrease in LDL-cholesterol levels was found after 6 months (Borson-Chazot *et al*., 1999). These findings suggested a direct effect of GH on the arterial wall (Bots *et al*., 1997). In fact, blood flow responses to acetylcholine and nitroprusside were significantly greater after GH replacement (Christ *et al*., 1999).

However, no data are available on the effect of GH replacement on cardiovascular-related morbidity and mortality.

Perspectives in the treatment of heart failure with GH

The rationale for exploring GH as a therapeutic agent in idiopathic dilated cardiomyopathy relies on a large body of experimental data. GH and/or IGF-I showed beneficial effects in experimental models of heart failure (Duerr *et al*., 1995; Yang *et al*., 1995; Duerr *et al*., 1996). In rats with experimental heart failure due to coronary artery ligation, myocyte growth was obtained in the residual healthy myocardium and was associated with a significant functional improvement after treatment with IGF-I (Duerr *et al*., 1995). Moreover, in rats with LV failure, GH and IGF-I administration 1 month after experimental myocardial infarction was associated with increased cardiac output and decreased systemic vascular resistance (Duerr *et al*., 1996). Improvement of cardiac function in rats with experimental heart failure was shown after administering GH alone (Yang *et al*., 1995), and after pretreatment with angiotensin-converting enzyme inhibitors (Jin *et al*., 1995). In a few patients with GHD and heart failure due to dilated cardiomyopathy, a prompt recovery of cardiac performance was described after GH replacement had been started (Cuneo *et al*., 1989; Frustaci *et al*., 1992; Fazio *et al*., 1996a). Based on this evidence, GH was suggested in the treatment of idiopathic dilated cardiomyopathy, a condition in which compensatory cardiac hypertrophy is believed to be deficient. A pilot study performed in a small series of patients

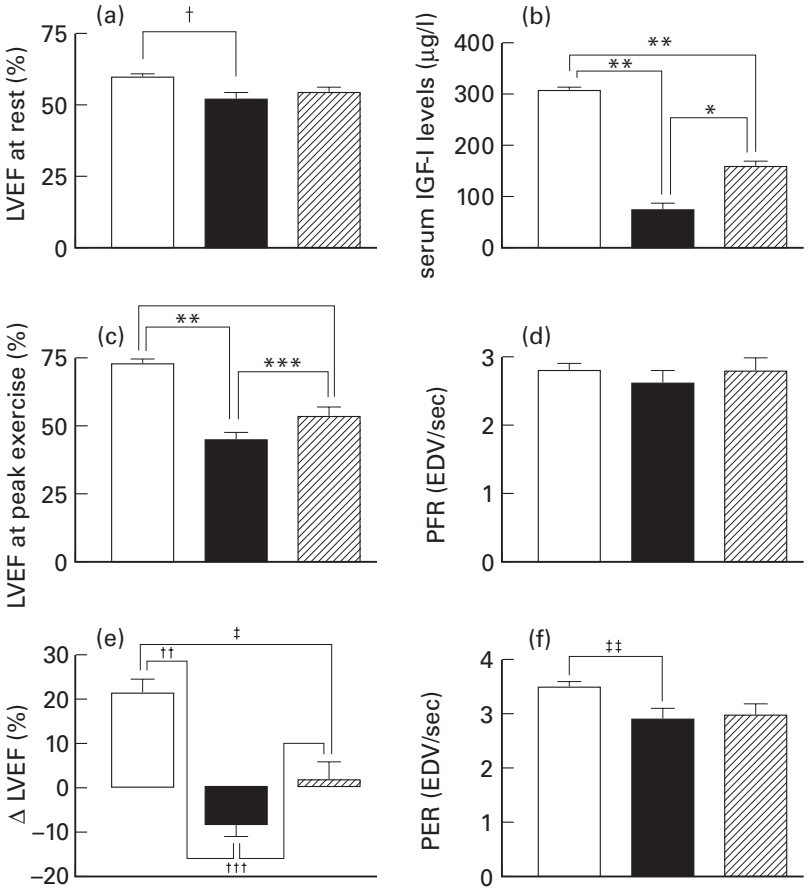

Fig. 3 Effect of GH replacement treatment for 12 months in 20 patients with GH deficiency and age below 40 years (before: ■ and after: ▨ GH treatment) as compared to sex- and age-matched control subjects (□). From top to bottom are shown the left ventricular ejection fraction at rest (a), at peak exercise (c), and the exercise-induced changes of ejection fraction (e), IGF-I levels (b), the peak filling rate (PFR; d) and the peak ejection rate (PER; f). Cardiac parameters were assessed by radionuclide angiography. $*P < 0{\cdot}001$; $**P < 0{\cdot}0001$; $***P = 0{\cdot}001$ $\dagger P = 0{\cdot}02$; $\dagger\dagger P = 0{\cdot}0001$; $\dagger\dagger\dagger P = 0{\cdot}03$; $\ddagger P = 0{\cdot}0005$; $\ddagger\ddagger P = 0{\cdot}004$.

with idiopathic dilated cardiomyopathy and heart failure demonstrated that the administration of GH for 3 months induced myocardial growth, improved contractility, reduced myocardial oxygen consumption and, finally, improved exercise tolerance (Fazio *et al*., 1996b). In another study, however, GH or placebo was injected subcutaneously for 3 months and no significant changes in body weight, walking test, haemodynamic parameters or in the New York Heart Association class were found (Osterziel *et al*., 1998). However, GH treated patients had an increase in ventricular mass (Osterziel *et al*., 1998). Volterrani *et al*. (1997) also demonstrated beneficial effects in patients with chronic heart failure due to either ischaemic or idiopathic dilated cardiomyopathy, with improvement in haemodynamics when GH was added as a short-term infusion. On the other hand, alterations in the GH/IGF-I axis have been reported in patients with idiopathic dilated cardiomyopathy, as low IGF-I levels (Broglio *et al*., 1999), subnormal spontaneous GH secretion (Giustina *et al*., 1996), and low responsiveness of GH after GHRH alone or combined with arginine (Broglio *et al*. 2000) have been reported in these patients. Despite the low IGF-I levels, the sensitivity to exogenous GH administration was reported to be normal (Broglio *et al*., 1999), thus potentially adding another endocrine rationale to the GH treatment in these patients. However, GH treatment in these patients was accompanied by side-effects either related to the increase in circulating IGF-I levels to supra-physiologic levels (Turner & Wass, 1996) and to the risk of dysrhythmia (Frustaci *et al*., 1996). Furthermore, in a placebo-controlled 3-month study, GH treatment of patients with chronic heart failure of various aetiologies did not significantly improve their cardiac function, although it was safe and well tolerated without serious adverse effects (Isgaard *et al*., 1998). However, a dose-dependent increase in IGF-I and IGFBP3 levels was observed during GH treatment in 20 clinically stable patients with moderate heart failure, and the increase in IGF-I induced by 10 μg/kg/day of GH correlated positively with the LV ejection fraction and inversely with the LV end-diastolic and end-systolic dimensions (Osterziel *et al*., 2000). This finding suggested that individual dose adjustments are a basic requisite for the success of GH therapy in heart failure. An overview of the effects of GH treatment in heart failure is shown in Table 2.

GH secretagogues (GHSs) and the heart

The pathophysiology of the GH/IGF-I axis, and more generally, of pituitary secretion has been recently re-evaluated after the introduction of GHSs (Casanueva & Dieguez, 1999). GHS are synthetic compounds developed to release GH *in vitro*, acting though specific receptors different from those of GHRH (Bowers *et al*., 1991). GHSs mimic an endogenous factor activating the GHS receptor at the pituitary and hypothalamus (Casanueva & Dieguez, 1999). The GHS receptor was recently cloned (Howard, 1996), so demonstrating that GHS is a new physiological system regulating GH secretion together with GHRH and somatostatin (Casanueva & Dieguez, 1999). Beyond the effects on GH secretion, GHSs seem to display specific actions on the heart. In particular, hexarelin (HEX), an hexapeptide GHS, possesses specific receptors on cardiomyocytes at partial variance with other GHSs (Bodart *et al*., 1999). Protective actions of HEX on the heart were demonstrated in a model of aged rats with induced postischaemic ventricular dysfunction (Rossoni *et al*., 1998). Similarly, beneficial effects of HEX on cardiac performance were reported in rats after experimental myocardial infarction (Tivesten *et al*. 2000) and in perfused hearts from GHD rats (De Gennaro Colonna *et al*., 1997). In another study, HEX treatment for 7 days at the dose of 80 μg/kg s.c. prevented the exacerbation of the ischaemia-reperfusion damage induced by hypophysectomy in the rat (Locatelli *et al*., 1999). In this model HEX prevented increases in LV end-diastolic pressure, coronary perfusion pressure, reactivity of the coronary vasculature to angiotensin II and release of creatinine kinase in the heart perfusate (Locatelli *et al*., 1999).

A single i.v. injection of HEX was recently demonstrated to increase the LV ejection fraction, without any change in mean blood pressure or heart rate in healthy men (Bisi *et al*., 1999b). No such result was obtained with a single GH administration (Bisi *et al*., 1999b). In addition, HEX increased LV ejection fraction in patients with GHD (Bisi *et al*., 1999c). Whether the cardiac actions of HEX directly involve the activation of specific receptors or occur indirectly through stimulation of the GH/IGF-I axis remains unknown.

Conclusions

From the first observations of Huchard in 1895, describing cardiovascular abnormalities in acromegaly, to the evidence of premature mortality from cardiovascular disease in hypopituitarism (Rosén & Bengtsson, 1990; Bates *et al*., 1996; Bülow *et al*., 1997), great efforts have been made to understand the pathophysiology of the GH/IGF-I axis in cardiac development and function. Theoretically, the impairment in cardiac performance could be due to a large number of factors, including a direct reduced pump function, increased vascular resistance and reduction of pulmonary function and/or muscle strength. Generally, patients with GH excess and deficiency have varying degree of cardiovascular impairment at different levels. In the management of patients with acromegaly and GHD, careful evaluation of cardiac function at diagnosis and during follow-up seems, thus, to be mandatory. However, it should be pointed out that no data are available on the reversibility of cardiovascular mortality after GH replacement in GHD patients, and the actual role of GH levels on the cardiovascular mortality in nonhypopituitary patients is still questioned (Maison *et al*., 1998). Conversely, additional endpoints such as mortality, morbidity and survival time until successful cardiac transplantation as well as performance after transplantation would be required in long-term studies, in order to define the role, the mechanism of action and the clinical applicability of GH in heart failure.

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Table 2 Overview of the effect of GH treatment in chronic heart failure

Author	Total patients	Follow-up	GH dose (IU)	Study design	Clinical benefits	IGF-I change
Cuneo *et al*., 1989	1	3 months	12/day	Open	Yes	n.g.
Fazio *et al*., 1996	7	3 months	4, on alternate days	Open	Yes	+ 100%
Frustaci *et al*., 1996	5	3 months	4/day	Open	No	n.g.
Volterrani *et al*., 1997	12	24 h	0·1/kg/24 h	Open	Yes	+ 47%
O'Driscoll *et al*., 1997	2	1 + 6 weeks	10 + 14/day	Open	Yes	n.g.
Osterziel *et al*., 1998	25	3 months	2/day	Randomised/placebo controlled	No	+ 57·5%
Isgaard *et al*., 1998	22	3 months	2·6/day	Randomised/placebo controlled	No	+ 143%
Spallarossa *et al*., 1999	10	6 months	0·02/kg/day	Open	Yes	n.g.

n.g., not given.

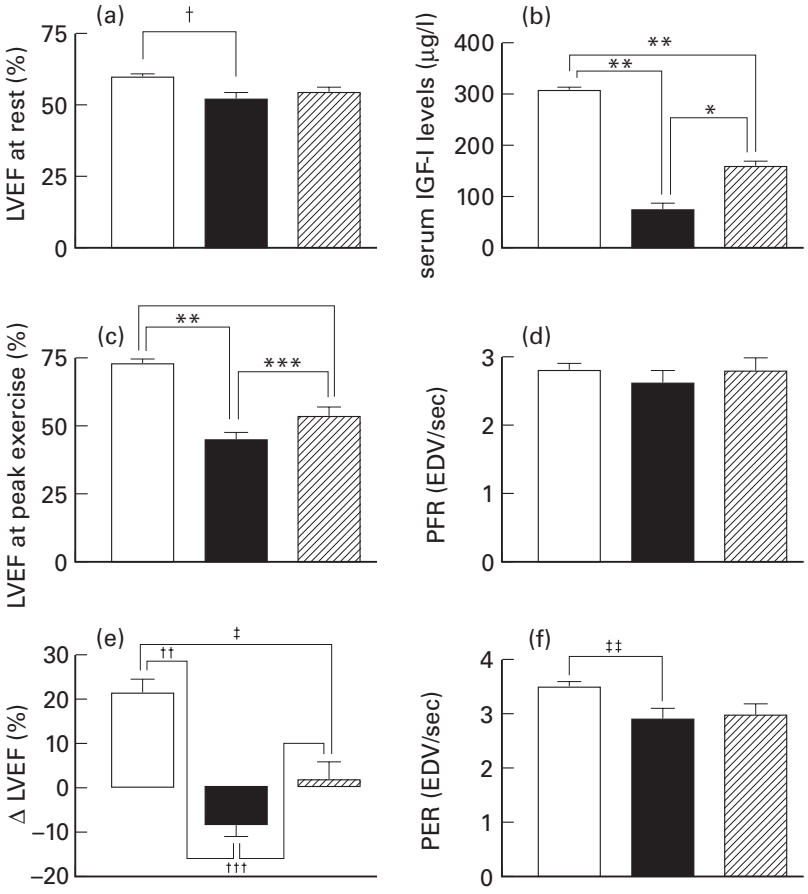

Fig. 3 Effect of GH replacement treatment for 12 months in 20 patients with GH deficiency and age below 40 years (before: ■ and after: ▨ GH treatment) as compared to sex- and age-matched control subjects (□). From top to bottom are shown the left ventricular ejection fraction at rest (a), at peak exercise (c), and the exercise-induced changes of ejection fraction (e), IGF-I levels (b), the peak filling rate (PFR; d) and the peak ejection rate (PER; f). Cardiac parameters were assessed by radionuclide angiography. $*P < 0{\cdot}001$; $**P < 0{\cdot}0001$; $***P = 0{\cdot}001$ $\dagger P = 0{\cdot}02$; $\dagger\dagger P = 0{\cdot}0001$; $\dagger\dagger\dagger P = 0{\cdot}03$; $\ddagger P = 0{\cdot}0005$; $\ddagger\ddagger P = 0{\cdot}004$.

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