GH/IGF-1 and myocardial adaptation
3.1

Acromegaly and Heart Failure

“Revisions on the growth hormone (GH) / Insulin-like growth factor (IGF) axis in its relation with the cardiovascular system”

(review)
Many diseases in endocrinology are characterised by an increase in cardiovascular mortality. In this Current Perspective, we highlight the cardiovascular pathology in active acromegaly (circulating growth hormone excess) that is responsible for an increase in cardiovascular mortality, with recent developments in molecular endocrinology and cardiology. Afterwards, possible relationships between growth hormone (GH) / insulin-like growth factor (IGF) system and heart function in ischemic heart failure, in order to underline a concept of cardiovascular endocrinology, will be discussed.

**Cardiovascular Mortality in Acromegaly**

In patients with active acromegaly, clinical studies noted an increase in cardiovascular mortality, that is determined mostly by heart failure (1;2). Premature atherosclerosis, as a second contributor of the increased cardiovascular mortality in acromegaly, may be due to disturbances in lipoprotein remnant metabolism or other present cardiovascular risk factors (1;3).

Aggressive treatment of active acromegaly may be able to reverse cardiovascular pathology. A retrospective study by Orme et al reported a decrease in cardiovascular morbidity and mortality in acromegaly after lowering the plasma concentration of GH under 7.5 mU/l and of IGF compatible with reference levels that are age and gender related (4). In addition to observations, suggesting that ultimate levels of plasma GH and IGF determine the cardiovascular and consequently the clinical outcome, also the mode of treatment and the delay in obtaining “normal” GH and IGF levels are relevant. Neurosurgical treatment with total removal of the GH-producing adenoma, with supplementary drug treatment, will result in a reduction of cardiovascular mortality (5). The highest death rates are observed in acromegalic patients with aged over 60 years (75% of the total deceased patients) and with persistent acromegaly despite medical treatment (3.5 fold increase in relative mortality rate). During treatment with Octreotide retard * (Lanreotide) in postoperative persistent disease, an improvement of the diastolic left ventricular function (decrease of the isovolumetric relaxation time) and geometry (decrease of left ventricular mass) was found after 3 months’ treatment period (6). This improvement in left ventricle function was stable during a one year follow-up treatment, but the significance for life expectancy needs to be evaluated. Unfortunately, treatment with Octreotide alone lowers the plasma GH and IGF levels in only 70% of all treated acromegalic patients (7). In contradiction to supplementary medical therapy that lowers systemic plasma GH and IGF-1, pituitary radiotherapy alone deteriorated heart function (as measured by pulse-wave Doppler echocardiography and electrocardiography) over a 10 year follow-up treatment period (8). Probably, the consequence of radiotherapy on mortality may be explained by the observation that the threshold for plasma GH concentration was thought to be under 2.5 microgram/L to obtain similar cardiovascular mortality rates compared to a healthy unaffected population. However radiotherapy alone was able to decrease plasma GH concentrations to those threshold levels in about 20% of acromegalic patients after a 10-year treatment period (9).

To consider together, an active and postoperative persistent disease in acromegaly give rise to increased cardiovascular morbidity and mortality. Cardiovascular mortality in acromegaly could be reduced if the threshold for plasma GH under 2.5 microgram/L is reached and this limits treatment with a combination therapy or long acting Octreotide.

**Development of Cardiomyopathy in Acromegaly**

An untreated acromegaly or persistent postoperative disease results primarily in a concentric hypertrophic cardiomyopathy that develops over several years (for a short review (10)). The development of cardiomyopathy in active acromegaly is determined by several periods (figure 1).
The Hyperkinetic Hemodynamic Period

At an early phase in acromegaly, cardiovascular symptoms are explained by a high cardiac output that is caused by a low systemic resistance. Such dilation of the peripheral arterial system is probably due to elevated plasma levels of GH and IGF that are able to induce nitric oxide (NO) in endothelial cells; increased endothelial NO gives rise to significant vasodilatation (11). This initial period is called the hyperkinetic hemodynamic period. The fall in afterload is associated with an increase in the activation of both the renin-angiotensin-aldosteron system (RAAS) and the beta-adrenergic system. High plasma levels of angiotensin II, and also high plasma levels of aldosterone, have maladaptive effects on the heart muscle. Therefore, high circulating levels of angiotensin II and aldosterone may worsen the cardiac performance by an increase of myocardial hypertrophy and fibrosis (12). In addition to after load reduction, the condition of the cardiac muscle to respond properly may also be limited. In \textit{in vivo} models, GH is required for normal intrinsic function of cardiac muscle (reflected by its capacity to contract) by maintaining Ca(2+)- and beta-adrenergic responsiveness (13), although no relation was found in a different rat model (14). Moreover, in long standing acromegaly, no increased adrenergic activity was found (15).

In conclusion, the increased circulating GH and IGF-I, that induce high endothelial NO levels with vasodilation, result through systemic maladaptation in an increased workload of the heart muscle. Together with the trophic effect of the elevated plasma GH and IGF-1 levels on the myocardium, the heart chamber in acromegaly is characterised by a normal size with increased relative wall thickness (concentric remodelling).

The period of development of concentric hypertrophic cardiomyopathy

As a result of the increased left ventricular workload and the direct trophic effects of GH and IGF-1, concentric hypertrophic changes of the cardiac muscle occur (16). In parallel with concentric remodelling, local processes in the ventricular wall result in an increase of interstitial fibrosis, an influx of polymorphonuclear cells and a replacement of (functional) cardiomyocytes (17).
continuous deposition of interstitial fibrosis and ventricular hypertrophy in combination with the hyperkinetic haemodynamic period result in a left ventricular diastolic dysfunction, as determined by measurement of the isovolumetric relaxation time (prolonged) and an inversed ratio of the early (Ev) and late (Av) diastolic peak velocity (18). Long term persistence and inability to compensate the hemodynamic profile result in a transition from a compensated hypertrophy to heart failure (with ultimately an overt diastolic left ventricular incompetence with accompanying systolic failure)(10). Not only the left ventricular function may be affected, but also the right ventricular function could be involved in acromegalic cardiomyopathy (biventricular heart failure).

Pathophysiological Concept of Cardiomyopathy in Acromegaly

In-Vitro and Animal Studies

The heart, and its functional units the cardiomyocytes, is integrated in the body by several extrinsic pathways (such as by the endocrinological and neurological pathways) and by the circulation itself. Deprived of blood plasma in in-vitro experiments, cardiomyocytes demonstrated increased apoptosis that is prevented by addition of IGF-1, which inhibits apoptosis by activation of Bax induction and Caspase 3 activation (19). This action of IGF-1 further progresses the cardiomyocyte in the cell growth period. This in-vitro observation supports a relation of IGF with cell growth and cardiomyocyte hypertrophy. Indeed, cardiomyocytes possess large amounts of GH (GH-R) (20) and GH secretagogue receptors (GHS-R)(21). In a physiological state, the binding of systemically circulating plasma GH to the GH-R is a signal to the cardiomyocyte to produce and secrete local IGF in an autocrine and/or paracrine way. This autocrine / paracrine secreted IGF binds to IGF-receptors of cardiomyocytes and induces an increase of protein transcription (myofibrils) and growth of cardiomyocytes (17). Due to the systemic high levels of GH in acromegaly, local IGF is overexpressed with prevention of apoptosis, but with ventricular hypertrophy (22). Probably, this inverse relation between apoptosis and ventricular hypertrophy serves to protect the early cardiac adaptive system. Therefore, these previous results confirm that imbalances in systemic and local GH/IGF systems cause final damage to cardiomyocytes (23). This may explain the effects of systemic excess of GH (and IGF-1), occurring in active acromegaly (24). The contribution of IGF-I to unfavourable changes in cardiac performance in acromegaly can be indirectly confirmed in knock-out animal models for hepatic IGF-I production. With this model, no cardiac malfunction is observed, although plasma GH levels reach excessive levels (25). The marked contribution of IGF-1 in acromegaly, and not specifically GH, is once again proven with these experiments. In the development of hypertrophic cardiomyopathy, not only systemic IGF-1 but also locally produced IGF-I may play a role; in vitro experiments showed an increase in tissue expression of IGF-I receptor and IGF-I mRNA of cardiac muscle tissue in the case of an elevated pressure or volume load (25). Increase of left ventricular hypertrophy results in a decrease of wall compliance and subsequently to an increased end-diastolic left ventricular pressure. Consequently, local increase of IGF-I in cardiac muscle gives rise to further hypertrophic changes, but in addition to adaptive hypertrophic changes another factor need to be present to give rise to cardiomyopathy, such as a decreased property of muscle contraction. GH regulates the contractility of the heart muscle by its influence on Ca2+ dependent processes. But in vitro, Hexarelin (a synthetic GH secretagogue) had no significant effect on calcium transients and on the Ca flux measured in isolated ventricular cells (26). In line with this observation, acromegaly deteriorates the cardiac ventricular relaxation (diastolic phase) while it has no influence on contractility (systolic phase)(27), and the progression of cardiomyopathy. Also in concordance with strict lowering of both GH (because...
this will decrease local IGF-I) and IGF-I with aggressive octreotide therapy (such as Slow Release Lanreotide and Long-Acting Release Octreotide) that results in improvement of the end-diastolic pressure (after three months of therapy)(6).

In Humans
Most previous proposed pathophysiological mechanisms of the hypertrophic cardiomyopathy in acromegaly are constructed from several non-human models (such as animal models and in-vitro experiments). On the other hand, cardiomyocytes obtained from cardiac muscle biopsies from acromegalic patients, reveal an increase of apoptosis. Moreover, the increase of apoptosis is functionally related to a decrease in ejection fraction, but not related to plasma GH or plasma IGF-I levels (Fristaci et al 1999 Circulation). This observation is in contrast with results as described in animal models: IGF protects for cardiomyocyte apoptosis, while in GH deficiency an increased apoptosis and increased occurrence of enhanced heart performance is found (28). Possibly, this contradiction may partly be explained by a down-regulated GH-R, in case of GH excess because that may give rise to an increased apoptosis although high circulating GH and IGF levels exist. Therefore, we hypothesize that increased plasma levels of GH and IGF may exist, with a low local expression of GH-R on the cardiomyocyte, which give rise to a relatively low local biological activity of IGF-I. The decrease in GH-R results in a reduction of intracellular signal transmission towards intracellular production of IGF-I and, therefore, with few or no release of local and paracrine and autocrine active IGF-I. In addition, GH receptors on the surface of cardiomyocytes are regionally expressed in different amounts, mediated through the intracellular ubiquitin-proteasome (U-P) system (29). Increase of the U-P system activity results in a decrease of GH-R expression (such as occurs in cachectic patients with a malignant disease (30)) and by intervention with antagonists of the U-P system, GH resistance may be corrected. The coexisting excessive amounts of systemic IGF-1 are functional in the negative hypothalamic feedback route and not in local tissue effects. Hitherto, this analysis of IGF-1 in acromegaly and its effect on tissue level is still under study. More efforts need to be made in human models in order to evaluate the balance between local and systemic IGF-1 in cardiomyopathy during acromegaly.

To conclude, the pathophysiological concept of hypertrophic cardiomyopathy in acromegaly based on animal models and in vitro experiments needs to be reassessed with results that are derived from human studies. Completion of the pathophysiological basis of the cardiomyopathy by the rapid development of non-invasive techniques (such as metabolic studies with MRI of the heart) and the increase of knowledge of GH-R expression and apoptosis will be an impulse in the creation of future interventions.

New Insights in Heart Failure Pathophysiology: Role for GH/IGF-1 axis?

GH substitution and heart failure
Cardiomyopathy and subsequent heart failure, is mostly the consequence of ischemic heart disease (31). In a recent editorial written by Cuneo (32), the substitution of rhGH in patients with ischemic heart disease was favourable for cardiac performance, such as ejection fraction and wall kinetics. Especially its effect on trophic stimulation of the heart muscle and the subsequent increase of contractility is put forward to be principally important. One study showed an additional effect on ACE inhibition of GH in improving cardiac performance after mild cardiac ischemia (33). Although these positive effects on left ventricular function during rhGH substitution in short term intervention studies, there are no randomised placebo controlled studies that show a decrease in cardiovascular morbidity and mortality after rhGH substitution in patients with coronary artery disease (CAD).
Acquired GH insensitivity in heart failure

Besides substitution of rhGH in CAD patients to prevent the definite decrease in heart performance, subcutaneous substitution of GHrelin may be cautiously considered as another progress in the treatment of heart failure. GHrelin is an endogenous ligand of the growth hormone secretagogue receptor (GHS) (34) and in this way acts additionally in the GH/IGF-1 axis (35). In a rat model with ischemic heart failure, left ventricular dysfunction and cardiac cachexia ameliorated during long-term application of subcutaneous Ghrelin (36). In patients with chronic ischemic heart failure, Ghrelin administration improved cardiac function without a negative influence on renal function (21). In other studies, plasma Ghrelin levels were elevated in patients with congestive heart failure and cachexia, compared to patients with only congestive heart failure. These plasma levels of Ghrelin are significantly associated with plasma GH and TNF-alpha levels and body mass index (37). Elevated plasma GH, that suggests a decreased local GH sensitivity (38), and Ghrelin levels compensate for low expression of cardiomyocyte GH-R in order to increase intracellular IGF production. Increased secretion of IGF-1 will induce trophic changes that may sustain cardiac performance. Therefore, application of synthetic Ghrelin in a condition of a decreased cardiac performance due to ischemic heart disease, may correct simultaneously an acquired GH resistance state on the level of cardiac tissue. Anand et al (39) and Anker et al (40) who have shown an increase in plasma levels of GH and a decrease in GH-BP, IGF-1 and IGF-BP3 supported a GH resistant state in case of ischemic heart failure.

Oxidative stress

In vitro and animal studies, congestive heart failure is considered as a state of oxidative stress. GH has a direct protective effect on oxidative stress-induced apoptosis in cardiac myocytes and that the effect of GH is attributed at least in part to the activation of ERKs through Ras and PTKs including JAK2, Src, and EGF receptor tyrosine kinase(41). However, human studies do not support this oxidative state as the origin of congestive heart failure (42).

In conclusion

The GH axis/IGF system is related to hypertrophic cardiomyopathy (in acromegaly) and heart failure (in ischemic heart disease) in distinctive ways. Although several local processes in the cardiomyocyte play a role in the adaptation of heart function, similarities in coping are observed. Control of apoptosis appears to be a key factor, and that is partly related to GH/IGF balances in local heart tissue. Specific interventions (such as Ghrelin administration) may modulate these balances and give rise to a reversal of deranged coping mechanism of the heart. Our contribution aims to express the need for a multidisciplinary approach in cardiovascular disease, and its relation with hormonal balances: the concept of cardiovascular endocrinology (43).

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References


3.2
Significant improvement of acromegaly-induced cardiomyopathy after normalisation of GH levels
- A case report and review -

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Each year, approximately one hundred patients are candidates to be evaluated for a cardiac transplantation procedure in the Netherlands, and several thousand patients worldwide. In most patients, an underlying cardiomyopathy (in 40-74% the result of ischemic heart disease), is the major reason for transplantation (1). Although it is the leading cause, not only ischemic heart disease may be the reason of (severe) cardiomyopathy and an elaborate analysis of the cardiomyopathy may identify reversible causes. Cardiovascular morbidity and mortality has been associated with hormonal disturbances, such as occurs in subclinical hypothyroidism (2;3), subclinical hyperthyroidism (4) and adult-onset growth hormone (GH) deficiency (5-7). Although these hormonal disturbances are frequently observed in premature cardiovascular disease, a more rare but impressive effect of GH excess (acromegaly) on cardiac function is known. However, the clinical presentation and recognition of acromegaly and especially its relation with overt cardiovascular disease is not easy. In general, careful clinical observation is necessary to diagnose a possible hormonal disturbance that underlies cardiovascular disease, preferably at an early stage. With this case report, we focus on GH excess as a primary cause of overt and disabling cardiovascular disease. In addition, we will discuss the effects of the GH/IGF system on the cardiovascular system and its implication in our understanding of the development into end stage cardiomyopathy.

**Case**

A 49-years old woman was referred to our heart transplantation unit because of an idiopathic cardiomyopathy, first diagnosed one year before the referral. Two months before, she was hospitalized in a local hospital due to manifest cardiac failure that was treated with intravenous dehydration therapy in the acute period. She continued the medication she used before the heart failure period such as diuretics, Angiotensin-Converting-Enzyme (ACE) inhibitors, oral nitrates, selective antagonist of alpha 1 and alpha 2 receptors and lipid lowering medication. In parallel, she also developed diabetes, which had become insulin-dependent the moment of presentation. Before the observation of the cardiomyopathy, she had always been “in excellent health”. She had no other risk factors for cardiovascular disease besides diabetes. Routine laboratory tests were within normal limits. No definite cause for the cardiomyopathy was found at that time. Echocardiography...
showed poor left ventricular function and mild secondary regurgitation of the mitral and tricuspid valves. The angiographic procedure (performed in the local hospital) showed a severely dilated left ventricle with only poor contractions of the left ventricle. The coronary arteries were normal. The pressure in the right cardiac system was not increased.

At our heart transplantation unit, extensive investigations confirmed the dilated left ventricle with a low ejection fraction (figure 1, period A). Her body mass index was 34 kg/m² (height: 1,62 m; weight: 90 kg). Blood pressure was 110/65 mmHg. Glycosylated Hb was 9.7% with a fasting plasma glucose level of 16.6 mmol/l. Baseline fasting plasma cholesterol, HDL-cholesterol and triglycerides were 6.7 mmol/l, 1.02 mmol/l and 8.5 mmol/l, respectively. As a consequence of her stable clinical condition, no immediate measures were taken to prepare her for heart transplantation and consequently she was followed in the outpatient clinic. In this period life style measures, fluid restriction and optimisation of her medication improved further her clinical condition and exercise tolerance. From the cardiology department, she was referred to the department of endocrinology because of increasing dosages of insulin which were needed to correct the hyperglycemia.

At the endocrinology department, she complained of increased sweating and diminished sensitivity in both her feet and hands during the last year. Also, shoe size had increased during that time. She did not smoke or drink alcohol in large amounts (less than 2 units a day). Menses were regular and she had no (severe) headaches. At physical examination, she had an evident acromegalic appearance that consisted of manifestations of soft tissue swelling (thickened fingers and no fit of her rings) and acral overgrowth. In addition, she had a carpal tunnel syndrome. Previous ophthalmological evaluations had revealed visual disturbances that were thought to be related to the DM type 2; no retinal disease or visual field defects had been detected. In line with the clinical diagnosis of acromegaly, both the plasma levels of plasma insulin like growth factor-1 (IGF-1) and GH were increased (fig 1A). The MRI scan of the pituitary region showed an adenoma with a size of 1.5 cm, which was resected by transphenoidal surgery after pretreatment with Octreotide LAR (20 mg during 4 weeks). Histologic examination revealed a GH and prolactin secreting adenoma. Both the type 2 diabetes and the hyperlipidemia with which she initially presented, were considered to be part of the acromegaly syndrome.

Postoperative evaluation showed significant reduction but no normalisation of plasma GH and IGF-1 levels (fig 1B). MRI scanning of the pituitary region showed a contrast filling remnant adenoma tissue next to the left internal carotid artery. Octreotide LAR treatment was restarted and she underwent local radiotherapy (RT: rotation technique, 50 Gy in 25 fractions). In the year following RT, Octreotide LAR dosages had to be increased from 20 to 30 mg/weeks and additional cabergolin (1mg/wk) treatment was initiated (fig 1C) because of persisting remnant GH overproduction.

Echocardiography during the treatment of

![Figure 1. An overview of the several parameters measured in the patient with acromegaly during clinical follow-up (from A to B to C to D; in the upper part) in the cardiology and endocrinology department. Plasma levels of IGF-1 (left y-axis; closed boxes) and of GH (right axis; open triangles) are shown. The ejection fraction of the left ventricle is presented by a bar with an indication of its actual value (in percentage). Closed horizontal bars beneath the graph express the: Oct: Octreotide treatment, Cab: Cabergolin treatment.](image)
the acromegaly showed a dramatic improvement in left ventricular function. Initially, the left ventricle was severely dilated with an impaired function (ejection fraction at rest was 20%, fig 1 period [A]). No significant abnormalities of the right ventricle were observed. After one year, the left ventricle was less dilated in combination with a mild concentric hypertrophy and a moderate diffuse hypokinesia of the left ventricle. In the third year of evaluation the left ventricle size was within normal limits. Only slight concentric left ventricle hypertrophy and further reduction of global hypokinesia were observed. The ejection fraction of the left ventricle at rest increased to 45% (Fig 1 period [C]). The most recent evaluation (Fig 1 period [D]) showed a normalization of the left ventricle size and left ventricle wall thickness with only a slightly impaired left ventricular systolic function with an ejection fraction of 55%. Fractional shortening [defined as \[\frac{\text{Left Ventricular Intrinsic Diameter in diastole} - \text{Left Ventricular Intrinsic Diameter in systole}}{\text{Left Ventricular Intrinsic Diameter in diastole}} \times 100\%\]] was increased from 18% (period A) to 36% in period D (figure 2). The left atrium was mildly dilated during the first two years of evaluation, which was normalized at the third evaluation.

"Parasternal long axis M-mode echocardiographic recordings. Figure 2a depicts a severely dilated left ventricle with a global hypokinesia. Fig 2b demonstrates the normalization of the left ventricle size, with a slightly impaired left ventricular systolic function. In both ultrasound pictures (figure 2a and 2b), the left vertical white line indicates the left ventricular intrinsic diameter (LVID) in the diastolic period (d), and the right vertical white line the LVID in the systolic period (s)."
Discussion

Disturbances in the GH/IGF-1 axis, as in a deficient (GH deficiency) and excessive (acromegaly) state, are associated with disturbances in cardiovascular performance, in body composition and in lipoprotein remnant metabolism (8;9), with a consequent increased cardiovascular morbidity and mortality (10-12). Suppression of plasma GH levels below 5.0-7.5 mU/l and lowering of plasma IGF-1 levels to age and sex adjusted normal ranges reduce the cardiovascular morbidity and mortality to that of the general population (13).

In our patient, all three therapeutic options (neuro-surgery, radiotherapy and medication) were needed to control the increased activity of the plasma GH/IGF-1 axis. Despite aggressive therapeutic strategy, plasma IGF-1 levels could not be normalised, in contrast to the plasma GH levels. Limitations of the results of medical treatment after neuro-surgery and radiotherapy in acromegaly are well known. Octreotide therapy only reduces plasma IGF-1 levels in at least 60-70% of the total acromegalic population (14). Suppression of systemic levels of plasma IGF-1 and GH, such as with octreotide therapy (slow release lanreotide and long-acting release octreotide) result in improvement of diastolic function after 3 months of treatment (15).

In most cases, GH excess (acromegaly) results in a concentric hypertrophic cardiomyopathy (16) that slowly develops during several years. The origin of this cardiomyopathy results from a high cardiac output, due to an initially low systemic vascular resistance, together with a high diastolic capacity of the left ventricle, that is also described as a hyperkinetic hemodynamic syndrome (17). The decrease in afterload can be explained by the inductive effect of IGF-1 on the nitric oxide (NO) system in the arterial endothelium that results in a vasodilation (18). As a consequence of the high output state, the workload of the left ventricle is continuously elevated, resulting in hypertrophic changes. In addition, GH excess induces interstitial fibrosis of the ventricular myocardium (19). Finally, in chronic GH excess state, the impairment of diastolic competence accounts for the definite systolic dysfunction [16]. In our patient, both the severe impairment of the contractility (with an ejection fraction of 20 % at rest) and the increase in the left ventricle diameter in both the systolic and diastolic period indicate that similar processes in the development of left ventricle dysfunction took place. Although Fazio et al (20) reported a biventricular involvement in the cardiac dysfunction in acromegalic patients, no impairment of the right ventricle function could be observed in our patient. Both hypertension (especially elevated diastolic blood pressure)(21) and glucose intolerance (16) are aggravating factors in cardiac dysfunction in acromegaly. In our patient the insulin resistance progressively increased; this may have contributed to the severity of the impaired left ventricle function at admission. No hypertension was observed at that stage, probably due to severely impaired ejection fraction (20%) and GH-related peripheral vasodilation.

In order to explain in acromegaly the transition from the initial adaptive hypertrophy towards heart failure, recent observations show that local expression of distinctive growth factors increase the susceptibility of a failing myocardium. The cross-talk between these growth factors and the myocardium determine the definite response of the heart muscle on haemodynamic changes, with a different response in case of a volume or a pressure overload (22;23). Several local growth factors (such as IGF-I, endothelin-I and Angiotensin-II) are expressed in a closely coordinated and sequential order (24). In acromegaly, the early diastolic dysfunction (with a progressive increase in volume load and a subsequent overload) is compensated by hypertrophy of the left ventricle. In the process of adaptation in case of volume overload, the local expression of both the IGF-I mRNA and protein are necessary (25). After a certain level of wall stress (threshold) is
reached, the local expression of IGF-I will diminish. Reciprocally, with an increase in transmural tension the local tissue expression of Angiotensin-II will be upregulated with a subsequent harmful effect on the function of the cardiomyocyte (26). Apoptosis of cardiomyocytes and the development of myocardial fibrosis are positively associated with local tissue levels of this inducible Angiotensin-II (27;28). In line with the knowledge about local expression of growth factors in the heart, the transition towards heart failure in overt acromegaly could be related to the actual expression of the local IGF system. An adequate expression of local IGF-I in the cardiomyocyte prevent the cell from apoptosis (29;30). The capability to express the local IGF system may be intrinsically (such as polymorphisms for IGF-1 receptor) (31) or extrinsically (such as acquired GH insensitivity) (32) related. The non-availability of the GH receptor on the cardiomyocyte is indirectly suggested by positive effects on the heart function in heart failure after stimulation of the GH secretagogue receptors (GHS-R). These GHS-Rs are abundantly, and in parallel with the GH receptor, expressed on the myocardial surface (33). Stimulation of the GHS-R by the natural GHS ligand, ghrelin, improves left ventricle dysfunction in rats (34) and in humans in end stage heart failure (33;35). Therefore, in the final stage of heart failure not GH itself but the GHS ligand is able to transmit a positive signal directing maladaptation towards adaptation of the left ventricle, probably through local induction of IGF-I.

In conclusion, in case of severe non-ischemic cardiomyopathy reversible defects in the activity of hormonal systems (such as the GH/IGF system) need to be thoroughly investigated. The cardiac dysfunction as observed in acromegaly depends on the effect of the influence of systemic GH on the local GH/IGF balance in the cardiac tissue. Therefore, plasma GH levels may better reflect the consequences of acromegaly on the local equilibrium of the cardiac muscle than plasma IGF-1 does. Cardiovascular dysfunction is reversible after optimal lowering of the plasma GH levels, probably as a consequence of normalization of the local GH/IGF balance in the cardiac tissue.

References

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