Endocrine, *vol. 12, no. 2, 153–161, April 2000* 0969–711X/00/12:153–161/$12.25

Cardiovascular Effects of Growth Hormone

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Introduction

In addition to growth hormone's stimulatory effects on longitudinal bone growth, growth hormone (GH) has direct and indirect effects on many other organs. Over the past decade the effects of growth hormone on the heart have begun to be elucidated. In addition to growth hormone's endocrine action, evidence suggests that growth hormone and/or insulin-like growth factor-I (IGF-I) work in a paracrine and/or autocrine fashion to regulate cardiac size and function.

Growth hormone therapy has been available for almost four decades. However, the advent of recombinant growth hormone in the 1980s has led to widespread use of growth hormone in children with growth hormone deficiency as well as other conditions. Experience in adults is also increasing. Despite this experience, many questions remain regarding the long-term effects of growth hormone therapy upon cardiac anatomy and function. Yet its potential cardiac benefits have led to growth hormone's increasing use in growth hormone deficiency and experimental use in cardiac disorders.

To begin, this paper reviews in vitro and in vivo laboratory studies on the effect of GH and/or IGF-I on cardiac structure and function. Cardiac abnormalities associated with growth hormone deficiency or excess in humans are explored. The use of growth hormone in cardiac disorders, such as cardiomyopathy and myocardial infarction, is investigated as well. Finally, we summarize the experience of growth hormone therapy and subsequent adverse cardiac effects in children with and without underlying cardiac disease.

Basic Physiology

In 1989, Mathews et al. reported the presence of growth hormone receptors in myocardium *(1)*. In addition, IGF-I and IGF-I receptors have been found in ventricular myocytes *(2)*. Varying expression of IGF-I and insulin-like growth factor-II (IGF-II) mRNA in the ovine fetus argues for a regulatory role of these growth factors in cardiac development *(3)*. Several lines of evidence support the hypothesis that the cardiac actions of growth hormone are mediated through IGF-I. When hypophysectomized rats are given growth hormone, cardiac IGF-I content and IGF-I mRNA expression increase *(4)*. In addition, Wistar-Furth rats implanted with a growth hormone secreting GH3 cell line are found to have increased cardiac IGF-I and IGF-II compared to controls *(5)*. What is not clear, however, is why Butler and colleagues found no change in cardiac IGF-I mRNA when GH deficient dwarf rats (dw/dw) had been given growth hormone *(6)*.

In addition, IGF-I has been found to increase myocardial protein synthesis. In rats implanted with the growth hormone secreting cell line GH3, the more energy efficient V3 myosin isoform is increased with a decrease in V1 isoforms *(7)*. However when administered to cultured cardiac myocytes, IGF-I, not GH, has been associated with cell enlargement and increases in cardiac protein mRNA *(8)*. As with the inotropic effects of IGF-I, addition of insulin-like growth factor binding protein-3 (IGFBP-3) blocks IGF-I mediated myocyte hypertrophy and protein synthesis *(9)*.

The findings of in vitro experiments are supported further by in vivo experiments. Several groups have looked at the relationship of cardiac IGF-I to ventricular hypertrophy, induced by pressure or fluid overload. Hansen et al. in 1993 found that rats that had banding of the ascending aorta had increased IGF-I mRNA compared to controls *(10)*. In an extensive study, Donohue et al. compared cardiac IGF-I mRNA in rats with induced low, moderate, and high renin hypertension. In each case there was a transient increase in IGF-I mRNA and stable translation of IGF-I receptor mRNA *(4)*. These findings have been repeated by others who have found that left ventricular IGF-I mRNA as well as IGF-I protein have increased in association with increased wall stress *(11,12)*. In fluid overload, increase in IGF-I is again coupled to increased wall stress. However, in the face of volume overload, right ventricular growth

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homone receptor mRNA and IGF-I mRNA expression is increased *(13)*. Donohue et al. confirmed his early findings of the association of hypertrophy and IGF-I by giving antihypertensive medications to spontaneously hypertensive rats. With therapy and subsequent reductions in left ventricular (LV) hypertrophy, ventricular IGF-I mRNA was decreased *(14)*. These findings argue for the role of IGF-I in mediating the growth of cardiac tissue as seen in ventricular hypertrophy.

Several groups have studied the role of IGF-I in cardiac anatomy by giving recombinant growth hormone and/or IGF-I to rats and mice. Cittadini and colleagues found differential cardiac effects of growth hormone and/or IGF-I in the rat. Growth hormone, IGF-I, or a combination of both were given over a four week period. Each treatment group experienced LV hypertrophy, but the hypertrophy was concentric in the growth hormone alone group. In each case, no significant increase in fibrosis was noted. In addition, increased cardiac index and decreased systemic vascular resistance occurred in each group; however, the effect was blunted in the combination group *(15)*. Conversely, in mice receiving growth hormone, IGF-I, or the combination increases in LV hypertrophy, contractility, and heart rate were only seen in the combination group *(16)*. The contradiction in these results is not well-explained, but may be due to length of therapy, dose, or intrinsic differences in the model. Tachycardia was noted in the mice, but not commented on in the rat experiments. The beta-adrenergic pathway does not seem to be involved in growth hormone's effects on the heart because growth hormone reverses the cardiac abnormalities of growth-deficient rats even in the presence of propranolol *(17)*.

Physiologic findings argue that growth hormone and IGF-I, alone or in combination, lead to an increase in cardiac contractility. In search of the mechanism of this action, Stromer et al. have found with chronic growth hormone, IGF-I, or the combination, systolic cardiac performance is improved and can be explained by increased calcium responsiveness *(18)*. In this situation however, each treatment therapy is also associated with hypertrophy. In order to separate the influence of hypertrophy on the improvement of cardiac function, Cittadini et al. evaluated the acute effects of growth hormone and IGF-I. They found that IGF-I, but not GH, displays positive inotropic properties by sensitizing the myofilaments to calcium *(19)*. Interestingly, the inotropic effects of IGF-I were blocked by the addition of IGFBP-3.

IGF-I administration has also been shown to be involved in selective potassium channel expression of cultured neonatal rat ventricular myocytes in association with myocyte enlargement *(20)*. Seventy-two hours of IGF-I exposure has been found to upregulate the expression of certain potassium channels. The meaning of this differential expression is not clear, but may relate to changes in contractility seen with IGF-I.

At the cellular level, GH and IGF-I appear to stimulate multiple signal transduction pathways. GH stimulates tyrosine kinase activity of JAK2, insulin receptor substrate-1 (IRS-1), insulin receptor substrate-2 (IRS-2), and Shc in fasted rat cardiac tissue *(21)*. Foncea et al. found that when IGF-I is bound to its receptor, the IGF-I receptor undergoes autophosphorylation which is followed by increased phosphorylation of extracellular signal-regulated kinases (ERKs), IRS-1, phospholipase C-1, and phosphatidylinositol 3-kinase *(22)*. Activation of the ERK cascade specifically may be associated with cardiac myocyte hypertrophy *(23)*.

What is especially interesting is the role of IGF-I in the regulation of apoptosis, since apoptosis has recently been found to be involved in the development of cardiomyopathy and ventricular remodeling. Wang and colleagues found that addition of IGF-I to primary cardiomyocytes inhibited apoptosis, presumably by inhibiting Bax induction and caspase 3 activation *(24)*. In fact, IGF-I given to rats one hour prior to ischemia, followed by reperfusion, attenuated myocyte apoptosis as well as polymorphonuclear leukocyte-induced cardiac necrosis *(25)*. Surprisingly, Frustaci et al. found that myocardial samples from patients with acromegalic cardiomyopathy showed increased evidence of apoptosis of myocytes and interstitial cells *(26)*.

The roles of GH and IGF-I in the therapy of myocardial infarction (MI) and/or cardiomyopathy has been studied in animals in vivo. Growth hormone and/or IGF-I increases cardiac function and decreases systemic vascular resistance (SVR) when used in rats post MI. GH (2 mg/kg/d × 15 d), given 4 wk after induced-MI in rats, increases cardiac function apparently by increasing myocardial contractility and decreasing peripheral vascular resistance *(27)*. When given one day after induction of MI, hypertrophy of noninfarcted myocardium as well as improved cardiac function are noted *(28)*. In rats that received IGF-I, 2 d after induced-MI, again hypertrophy is noted with some evidence suggestive of improved cardiac function *(29)*. Finally when IGF-I and GH is given to rats 4 wk post-induced myocardial infarction, increased body growth, decreased systemic vascular resistance, and increased cardiac output are observed *(30)*.

The growth hormone-induced hypertrophy seen post-myocardial infarction appears to be concentric *(28)*. Increases in cardiomyocyte width and decreases in collagen accumulation are observed *(31)*. The mechanisms of increased myocardial contractility in post-infarction rats are currently being elucidated. In rats with post-infarction heart failure, peak systolic calcium concentrations and myocyte fractional shortening are lower than controls. Giving growth hormone 4 wk after induced-MI for 2 wk, increases the peak systolic calcium concentration and the myocyte fractional shortening to values comparable to controls *(32)*. In addition, in hypertrophic cardiomyopathic

hamsters, adminstrating growth hormone preserves the density of cardiac sarcoplasmic reticulum calcium release channels, leading to enhanced cellular function *(33)*.

From pathophysiologic experiments we have learned that GH and IGF-I play a role in fetal cardiac development, in mediating growth of cardiac myocytes associated with cardiac hypertrophy, in increasing cardiac contractility, and in stimulating protein synthesis. Evidence is building that suggests the actions of GH and/or IGF-I are mediated through activation of specific signal transduction pathways, and IGF-I may play a regulatory role in apoptosis.

Adult Growth Hormone Deficiency

An increase in cardiovascular mortality due to human growth hormone deficiency was suggested in a study by Rosen and Bengtsson *(34)*. Of 333 Swedish adults who were diagnosed with hypopituitarism between 1956 and 1987 and treated with hormonal replacement, except for growth hormone, there were 61 deaths—double what would have been expected for the general population. The relationship between growth hormone deficiency and cardiovascular morbidity and mortality is difficult to elucidate because of the frequent presence of concomitant cardiovascular risk factors. With increasing use of growth hormone in GH-deficient adults, experience has provided a better understanding of the cardiac effects of growth hormone.

In terms of cardiac structure and function, left ventricular wall thickness and left ventricular mass index are decreased in growth hormone-deficient (GHD) adults compared to controls *(35)*. Some studies involving mainly acquired growth hormone-deficient adults, show no difference in LV wall thickness or LV mass index *(36,37)*. These differences may be a function of duration of GH deficiency. Abnormalities in systolic function with decreased cardiac index and ejection fraction are found at rest and with exercise in both adult-onset and childhood-onset growth hormone deficiency *(35,37,38)*. The reduced cardiac index that is seen in some GHD adults has been termed the "hypokinetic syndrome." Diastolic, as well as systolic, abnormalities are reported at rest *(37)*. In addition, ischemic-like ST segment changes are found in adults with GHD without coronary artery disease during exercise *(37)*.

Growth hormone improves cardiac structure and function in adults with GH deficiency. In a 4-mo crossover study, GHD patients received GH at 2 IU/m^2 *(39)*. Heart rate at rest and with exercise rose significantly; however, LV mass and blood pressure did not change. However, when 24 GHD patients were given GH or a placebo for 6 mo (0.07 U/kg/d), maximal heart rates did not change with exercise, but maximal oxygen intake did rise significantly, suggesting improved exercise performance *(40)*. In another study, growth hormone therapy (0.01 mg/kg 3x/wk for 6 mo) normalized the left ventricular mass index and systolic function *(41)*. The ability of growth hormone to reverse the cardiac impairment seen in GH deficiency, was again demonstrated in a study by Cittadini et al. *(38)*. There was a small sample size, but all 11 patients had childhood-onset GH deficiency. With growth hormone therapy (0.05 U/kg/d for 6 mo) cardiac index at rest and with exercise improved. In addition stroke volume decreased, without changes in arterial pressure, suggesting a decrease in the systemic vascular resistance. Similarly, improvements in cardiac performance were noted by Valcavi et al.; however, his patients had normal systolic function and LV mass at baseline, without therapy *(36)*. Even with long-term growth hormone therapy (0.25 IU/kg/wk for 42 mo) left ventricular function improved and approached that of controls *(42)*. Interestingly, 38 adult males with childhood-onset growth hormone deficiency, who were treated with growth hormone for 3–5 yr, showed a transient increase in left ventricular hypertrophy, but a sustained increase in LV performance over time *(43)*.

Discrepancies in the literature exist, but overall, it appears that childhood-onset growth hormone-deficient adults have more severe cardiac abnormalities than adult-onset individuals. Whether this is related to the duration of the growth hormone-deficient state or to the lack of growth hormone during crucial periods of cardiac development remains unanswered.

It has been suggested that hypertension is a risk factor for cardiovascular disease in patients with GH deficiency. One study by Rosen et al. found that more patients with GH deficiency than controls are receiving treatment for hypertension *(44)*. The increase in treated hypertension may reflect the increased medical care adults with panhypopituitarism receive relative to a healthy population. Conversely, baseline blood pressure of growth hormone-deficient adults was found to be lower than that of the control group. After 6 mo of GH therapy no change was seen in blood pressure, but after 42 mo of GH therapy the initially lower blood pressure of the growth hormone-deficient group was similar to that of the control group *(42)*. Short-term growth hormone therapy of 6 mo duration produced no significant change in two other studies *(36,45)*, and in one of those studies there was no significant difference in blood pressure compared to normals *(36)*.

Adults with growth hormone deficiency have increased body weight and body mass index (BMI). Rosen et al. found the increased body weight was due to an increase in body fat *(44,46)*. Many of these patients had central obesity with increased waist/hip ratios *(47,48)*. Dyslipidemias have been noted in GHD patients, with increased triglycerides *(48)*, decreased HDL cholesterol *(44,49)*, and increased LDL cholesterol *(49,50)*. Most recently, Cummings et al. further defined the dyslipidemia found in GHD-patients as consisting of increased hepatic secretion rate of VLDL apoB and decreased catabolism of VLDL apoB *(51)*.

Abnormal body composition and dyslipidemias improve with growth hormone therapy. Most studies evaluated growth hormone use for 6 mo *(49,52,53)*, with a recent one by Cuneo et al. looking at the effects of 12 mo of growth hormone therapy *(48)*. Growth hormone therapy causes a significant increase in lean body mass *(52,53)*, a decrease in truncal obesity *(48,52)*, a decrease in total cholesterol *(48,49,53,54)*, a decrease in LDL cholesterol *(48,51,54)*, a decrease in apo B *(49,54)*, and a variable trend towards an increase in HDL cholesterol *(49)*.

Using high-resolution ultrasonography to examine carotid intima-media thickness, Markussiss et al. studied premature atherosclerosis as a risk factor for cardiovascular morbidity in asymptomatic GHD-patients *(50)*. He found an increase in intima-media thickness (IMT), which is suggestive of premature atherosclerosis, in GHD-adults. In this study no difference in fibrinogen, another risk factor for vascular disease, was found between controls and GHD-adults. However, Johannson et al. found an increase in fibrinogen and plasma activator inhibitor in their set of 20 GHD-adults *(47)*. In adults who have acquired GH deficiency, one cannot exclude prior vascular disease as contributing to the atherosclerosis. Therefore Capaldo et al., studied 14 childhood-onset GHD-patients who had been treated with growth hormone for 2–16 yr and had been off growth hormone for at least 3 yr as well as 14 age, sex, and BMI matched controls. They found that IMT was significantly greater in the growth hormone-deficient group. Few other metabolic abnormalities were found in the GHD group. LDL triglycerides were significantly increased, but no difference in LDL cholesterol, total triglycerides, or fibrinogen were noted. Whether the increase in IMT noted in growth hormone-deficient adults is associated with the same risk for premature atherosclerosis as seen in the general population is unknown.

Diabetes mellitus (DM) is also a risk factor for cardiovascular disease, but few studies have explored the relationship between DM and GH deficiency. Rosen et al. found no increase in diabetes in the GHD group *(44)*. However, Johansson et al. found significantly lower fasting glucose concentrations *(47)*. In contrast, glucose intolerance was noted in one set of patients with GH deficiency and hypopituitarism *(50)*. Again recently, GHD subjects and control subjects had similar glucose and insulin concentrations fasting and after an oral glucose load *(55)*.

In the general population, decreased nitric oxide (NO) biologic activity has also been associated with atherosclerosis. Interestingly, Boger and colleagues found adults with acquired GH deficiency had decreased NO formation, as measured by urinary nitrate and cyclic GMP *(56)*. Markers of NO formation improved with growth hormone therapy.

Experience suggests that growth hormone-deficient adults do have cardiac abnormalities that may be worsened due to concomitant cardiovascular risk factors. The increased cardiovascular risk due to body composition abnormalities and dyslipidemias in growth hormone-deficient adults is convincing. On the other hand, hypertension and diabetes mellitus as cardiovascular risk factors in the growth hormone-deficient population have not been convincingly established. However, it remains to be determined, if long-term GH therapy will lead to a significant decrease in cardiac mortality and morbidity.

Growth Hormone Excess: Acromegaly

In contrast to GH deficiency, acromegaly has long been associated with increased cardiovascular morbidity and mortality *(57,58)*. In fact, cardiomyopathy has been a known part of acromegaly since its description in 1895 by Huchard *(59)*. Initially, the cardiac disease was thought to be due to other risk factors, but then, repeated reports of cardiomyopathy in the absence of other risk factors has led some to use the term "acromegalic cardiomyopathy" for the cardiac disease resulting directly from growth hormone excess.

The types of cardiac disease reported in acromegaly include hypertension, valvular disease, ventricular arrhythmias, aortic root dilatation, coronary artery disease, and congestive heart failure. Initial studies investigating acromegalic cardiomyopathy date back to the mid- to late 1970s and early 1980s. The majority of acromegalic patients have increased left ventricular mass when indexed to body surface area and increased left ventricular wall thickness, fitting criteria for hypertrophy by echocardiography, most with concentric hypertrophy *(57,60–66)*. Importantly, many nonhypertensive acromegalics, some of whom may be asymptomatic, also have cardiac hypertrophy *(57,60–64)*.

In order to clarify the relationship of excess growth hormone secretion and hypertension, Lopez-Velasco et al., using dynamic echocardiography and doppler, compared cardiac structure and function in 39 patients with active or resolved acromegaly to 17 healthy controls and 16 patients with essential hypertension and no signs of cardiac disease. The acromegalic patients were divided into four groups: active nonhypertensives, hypertensives, as well as cured nonhypertensives, and hypertensives. Twenty-eight of the acromegalic subjects had repeat studies one year later. They found that acromegaly and hypertension were independently associated with increased LV mass. Five of ten patients, who initially had active acromegaly, had significant decreases in GH hypersecretion at the time of follow-up and showed significant improvement in cardiac abnormalities *(67)*.

Left ventricular diastolic function is abnormal in acromegalic patients in that they have impaired relaxation *(62,66)* even in the absence of other cardiovascular disease *(65)*. In a rigorous study, Fazio and colleagues found diastolic dysfunction of the right and left ventricle *(61,68)*. The question remains, however, whether the diastolic dysfunc-

tion is at least partly due to the hypertrophy, since hypertrophy is known to cause diastolic dysfunction. Because there is no correlation between left ventricular mass or thickness and diastolic dysfunction, Rodrigues et al. propose the diastolic dysfunction is secondary to the growth hormone excess *(62)*. Fazio et al. come to similar conclusions *(61,68)*. The direct role of GH/IGF-I hypersecretion in causing the cardiac abnormalities is further supported by a study by Minniti et al. *(69)*. Twenty acromegalic normotensive patients less than 30 years of age, with normal glucose tolerance, had an increased LV mass index and subclinical biventricular diastolic dysfunction when compared to controls.

Except for a rare patient with a decreased ejection fraction *(63,64)*, systolic function is thought to be normal in acromegalic patients despite cardiac hypertrophy. Fazio and his colleagues presented further evidence of this when patients were at rest *(68)*. However, during physical exercise, they found 73% of acromegalic patients were not able to increase their ejection fraction by 5% and developed shortness of breath after testing, fitting the criteria for impaired cardiac performance.

The presence and extent of cardiac disease has been associated with growth hormone concentration after therapy *(63)*. In one necropsy review, however, cardiac disease was related to disease duration *(57)*. Recently, Fazio and colleagues found that right ventricular free wall thickness correlated with duration of disease *(61)*. Similarly, Colao and colleagues found that worse LV performance was associated with longer duration of disease and older age *(70)*.

A clinically important question then is can therapy that decreases GH and IGF-I concentrations also reverse the cardiac manifestations of acromegaly? Accompanying cardiovascular disease as well as less stringent definitions of effective treatment for acromegaly complicates research in this area. In 1987, Hayward et al. reported that even with resolution of acromegaly (transsphenoidal surgery with or without radiation) limited improvement of cardiac function occurred *(71)*. However, without successful therapy, cardiac disease progressed and was often fatal. Specifically, interstitial fibrosis, lymphomononuclear infiltrates and myocyte necrosis (signs of myocarditis) are associated with acromegaly. Myocarditis may be an early stage of acromegalic cardiomyopathy and may, at least partially, be reversed with early therapeutic intervention. Fibrosis, however, may be irreversible and account for arrhythmias even after effective therapy.

Since the late 1980s, octreotide, a somatostatin analogue, which is a potent suppressor of growth hormone release and less potent suppressor of insulin is being used to treat acromegaly. Multiple studies, looking at octreotide use for 2 to 14 mo, have found improvements, but not normalization of left ventricular mass indexed to body surface and left ventricular wall thickness *(72–77)*. Chanson et al., however, did find a normalization of cardiac index with octreotide used for 2 mo to 2 yr *(78)*. The most rigorous study to date has recently been completed by Colao et al. Thirty acromegalic patients without latent coronary artery disease had left ventricular diastolic and systolic function evaluated at rest and during exercise by gated blood pool cardiac scintigraphy before and after one year of octreotide therapy. The estimated duration of disease before treatment ranged from 4 to 30 yr. They found that aggressive treatment with octreotide for one year, until basal or glucose-stimulated GH levels were <2.5 mg/L and 1 mg/L, respectively, led to significant improvements of LV ejection fractions at rest and with exercise *(79)*. No changes were noted in diastolic function. Those individuals not controlled well after one year, had worsening systolic blood pressure and cardiac performance. Reversal of cardiac abnormalities has also been found in patients treated with the depot form of octreotide *(80,81)*. These studies suggest that with prolonged octreotide therapy normalization of cardiac function might occur.

Growing evidence suggests cardiac abnormalities directly related to GH excess can account for some of the cardiovascular morbidity and mortality seen in acromegaly. Longer duration of GH excess is associated with increasing cardiac morbidity. But one must also consider other concomitant cardiovascular risk factors in this population. An increase of diabetes is known to occur in acromegaly, which brings its own cardiovascular abnormalities. In addition, the increase in hypertension seen in acromegaly also predisposes these patients to cardiovascular disease. There is some evidence to suggest an increase in coronary artery disease in acromegaly. However, this is not found consistently in the literature *(57,71)*.

Cardiomyopathy: Dilated and Ischemic

In the past decade there has been an increased interest in finding alternative therapies to cardiac transplantation for treatment of cardiomyopathy. Since dilated cardiomyopathy is characterized by ventricular dilatation without accompanying ventricular wall thickness, growth hormone has been suggested as a possible therapeutic agent. Recently, Lee et al. have found that a lower serum IGF-I concentration immediately after MI is associated with more ventricular dysfunction and a poorer clinical outcome *(82)*. This supports a protective role for endogenous IGF-I and, at least theoretically, a therapeutic role for recombinant GH or IGF-I. A case report of dilated cardiomyopathy in a growth hormone-deficient individual that improves with growth hormone therapy, gives further support to this hypothesis *(83)*.

Fazio et al. reported the results of one of the first studies using growth hormone in the treatment of dilated cardiomyopathy in seven patients *(84)*. After 3 mo of growth hormone therapy (4IU daily), improvements in myocar-

dial mass, cardiac function, and exercise performance were seen. In a placebo-controlled, double-blind study of recombinant GH in 50 patients with dilated cardiomyopathy and chronic heart failure *(85)*, growth hormone (2 IU daily for at least 12 wk) significantly increased left ventricular mass, but did not improve cardiac performance.

On the other hand, seven patients with ischemic cardiomyopathy treated with growth hormone (2 IU daily × 3 mo) had improvements in ventricular wall thickness, cardiac output, and exercise performance. Again no control group was used *(86)*.

Because the actions of growth hormone are at least partially mediated through IGF-I, recombinant IGF-I has also been tried as a therapeutic agent in cardiomyopathy. Donath et al. administered IGF-I to eight patients with cardiomyopathy (five dilated, three ischemic), and found an improvement in cardiac performance, at least partially, attributable to decreased systemic vascular resistance *(87)*.

On a theoretical basis, GH and/or IGF-I may be expected to have a role in cardiomyopathy and post-myocardial infarction therapy, but well-designed clinical trials are necessary to evaluate their clinical benefits.

Cardiac Effects in Children

Growth hormone use in the GH-deficient child has dramatic effects on longitudinal growth. However, the cardiovascular risks and benefits of growth hormone use in children are unknown. Replacement doses of growth hormone as given in GH-deficient children may have different effects on the heart than the pharmacologic doses used in children with short stature who are growth hormone sufficient. To complicate matters, some patients receiving growth hormone have genetic syndromes (i.e., Turner's and Noonan's syndromes), which have associated intrinsic cardiac defects.

Crepaz and colleagues studied growth hormone-deficient children, as defined by peak growth hormone concentrations less than 10 ng/mL in two stimulation tests *(88)*. Twenty-two children received growth hormone (0.95 ± 0.12 IU/kg/wk) for an average of 13 mo when echochardiagram studies were performed. Results were compared to a matched control group. No differences were seen in cardiac anatomy, left ventricular diastolic function, cardiac output, or systemic vascular resistance. In a similar study, cardiac size, wall thickness, and contractility were found to be within normal range for 16 children, who had received growth hormone (0.17 ± 0.04 IU/kg 3x/wk) for the previous 13–46 consecutive mo *(89)*. Thirteen of the 16 patients were growth hormone-deficient.

In children with short stature without growth hormone deficiency, a limited number of studies has looked at the cardiac effects of growth hormone therapy and different dosing regimens. Barton et al. investigated left ventricular size and function in 29 patients with idiopathic short stature, before, 6 mo into, and 12 mo into therapy *(90)*. Growth hormone was given in varying doses up to 40 IU/m^2/wk. An increase in the increments in wall thickness and left ventricular mass was greatest with the highest growth hormone dose, but this was fully explained by the accompanying increase in body size. Daubeney et al. found similar findings after long-term growth hormone therapy (30 IU/m^2/wk) in 15 normal patients with short stature and a mean age of 7.8 yr *(91)*. At the end of 4 yr there was a tendency toward increased left ventricular mass which disappeared when the data was indexed for body surface area and lean body mass.

Lampit recently studied cardiac abnormalities of 21 short normal children treated with growth hormone at 0.9mg/m^2/d for 3 yr *(23)*. Serial echocardiograms were performed prior to therapy and annually thereafter until 12 mo after cessation of growth hormone. During the three years of treatment no changes in cardiac parameters were noted. However, up to 12 mo after the discontinuation of therapy, cardiac size and output were decreased. Interestingly, the growth velocity the year after treatment ended was lower than the pretreatment growth velocity. Deceleration of growth lasted for as long as 18 mo. Cardiac studies were not available after the 12-mo post-therapy period.

Many children treated with GH have genetic syndromes that include cardiac disease. This is often the case in Turner's syndrome, in which the existence of cardiac abnormalities (left sided obstruction, dilatation, and others) has been reported to be as high as 60%. Saenger et al. found no increase in left ventricular hypertrophy or aortic dilatation in 12 patients with Turner's syndrome treated with growth hormone (0.375 mg/kg/wk) for at least 1 yr *(92)*. The majority of the patients, however, were studied more than four years after the cessation of growth hormone therapy. Cotterill et al. looked at the cardiac effect of growth hormone (4 IU/m^2/d) prospectively on 30 patients with Noonan's syndrome, which is associated with multiple cardiac anomalies, commonly pulmonary stenosis and hypertrophic cardiomyopathy *(93)*. However, all patients with hypertrophic cardiomyopathy were excluded from the study. They found that after growth hormone therapy for 12 mo, no child developed hypertrophic cardiomyopathy. The LV end-diastolic dimension increased, but all other cardiac parameters, including ventricular wall thickness were unchanged.

Since 1985, Genentech, Inc., has been monitoring the safety of GH as part of a large post-marketing surveillance program, the National Cooperative Growth Study (NCGS). More than 30,000 children have been enrolled in this observational study. Of all these children, there have been reports of serious cardiovascular adverse events in 55 children. However, these cardiovascular events are difficult to interpret because of concomitant disorders or illnesses. Of Turner's syndrome patients, three had aortic aneurysms that ruptured leading to death and three had hypertension.

Both aortic aneurysms and hypertension are known to occur more frequently in females with Turner's syndrome. Of four individuals with idiopathic growth hormone deficiency, one had Kawasaki disease, one had a stroke thought to be unrelated to GH, one had hypertension from excess mineralocorticoid of unclear etiology, and one had a ruptured descending aorta.

Short stature and cardiac disease are common features of Noonan's syndrome. Two hundred and fifty patients with Noonan's syndrome have been enrolled in NCGS, 48 of whom have prior heart disease. One patient developed increasing LV hypertrophy and new right ventricular hypertrophy after 15 mo of therapy. One patient was diagnosed with hypertrophic cardiomyopathy after 6 mo of therapy. A third patient was noted to have supravalvar aortic stenosis while on GH therapy. Since cardiac abnormalities are common to Noonan's syndrome it is difficult to assess the causal relationship between GH and these cardiac findings.

At least two cases of cardiac morbidity have been classified as "possibly" being caused by growth hormone therapy. Tachycardia developed in a 16-yr-old boy with GH deficiency and hypertrophic cardiomyopathy, and it appears to have worsened after he was given GH. In the second case, a 14-yr-old boy with GH deficiency developed a cardiac arrhythmia during treatment with GH and leuprolide.

Even with the cumulative experience of the NCGS, no severe, clinically obvious cardiovascular side effects of GH are apparent. This speaks against growth hormone causing cardiac morbidity in children, at least in the short term.

Many further questions remain unanswered in regards to growth hormone therapy in children. To date, the existence of the hypokinetic syndrome, as seen in GHD adults, has not been described in untreated, GH-deficient children. In addition, if the hypokinetic syndrome does exist in GHD children, the ability of growth hormone to restore normal cardiac structure and function remains unclear. Growth hormone is also being used at younger ages and for longer periods of time. We know that cardiac abnormalities are associated with longer duration of active acromegaly, but we do not know if duration of growth hormone therapy, especially in the GH-sufficient child, will actually lead to cardiac abnormalities. Fortunately, cardiac effects of GH therapy should, at least theoretically, be reversible when GH therapy is discontinued, since improvement in cardiac structure and function occurs when acromegaly is well-treated.

Conclusions

Growth hormone and IGF-1 play important roles in the development and maintenance of normal cardiac structure and function. Both extremes of growth hormone excess and growth hormone deficiency have been shown to lead to cardiac pathology that has minimal to severe clinical significance. Evidence continues to build suggesting increased cardiovascular mortality and morbidity in both conditions compared to individuals with normal growth hormone/IGF-1 regulation. Fortunately, growth hormone therapy in GHD adults reverses, at least partially, the many cardiac abnormalities of growth hormone deficiency. Theoretically overly aggressive treatment may put the GHD-patient at risk for the cardiovascular abnormalities seen in growth hormone excess. The risks of long-term GH replacement over decades or during the more advanced years of life have not been clearly defined.

Although the use of GH for the treatment of cardiovascular diseases, such as cardiomyopathy, is theoretically tempting, the data to date are not compelling for its widespread use. GH therapy in such cases should occur only under the rubric of well-designed clinical trials.

Still more questions relate to the treatment of children with growth hormone therapy, especially in those who are not growth hormone-deficient. Doses used for growth are often in excess of physiologic secretion and growth hormone is being given during cardiac development. The literature suggests that in the short term, growth hormone therapy does not cause cardiac abnormalities. However, no study has explored the cardiac ramifications of 10–15 yr of GH therapy in growth hormone-sufficient children with short stature. Further research is necessary to better understand the cardiovascular effects of growth hormone therapy in GH-deficient children, GH-sufficient children, and in those children with underlying cardiac anomalies.

Acknowledgments

We thank Marcy Premer, Pharm D and Kenneth O'Connelly for providing the National Cooperative Growth Study Data.

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