Growth hormone for the failing heart

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Idiopathic dilated cardiomyopathy is a common cause of heart failure. Despite advances in treatment, this disease has a mean survival time of 5 years (1). Currently, the only effective treatment for end-stage dilated cardiomyopathy is heart transplantation. However, additional, more conservative treatment options are being explored to prolong survival until an organ becomes available or even to obviate the necessity for transplantation. Left ventricular assist devices or partial left ventriculectomy, infusions of catecholamine analogs, and phosphodiesterase inhibitors are among some of the treatment options which are being experimentally evaluated (1 and references therein). In addition to these, growth hormone (GH) has emerged as a candidate for increasing cardiac performance, and thus possibly survival, in patients with failing hearts (2, 3).

The rationale for exploring GH as a therapeutic option in idiopathic dilated cardiomyopathy builds on a large body of experimental data (2, 3). Evidence has accumulated that GH is a physiological regulator of myocardial growth and performance. In patients with congenital deficiency of GH, cardiac growth and function are impaired; GH administration in such patients increases wall thickness and normalizes cardiac performance which reverses after treatment is stopped (4–7). Furthermore, in a patient with GH deficiency and cardiomyopathy, GH treatment has been reported to increase myocardial contractility and cardiac performance (8). However, not all reports demonstrate a substantial effect of GH on cardiac function. A double-blind, placebo-controlled crossover study of 4 months of GH treatment in GH-deficient adults did not alter echocardiographic wall mass of the left ventricle, whilst resting and exercise-induced heart rate was increased during GH treatment as compared with placebo. The exercise-induced increment in maximum heart rate may be reflecting the anabolic effects of GH on skeletal muscle mass and its increased exercise performance, thus requiring increased cardiac performance (9, 10). In an additional study, which was also randomized and placebo-controlled, six months of GH treatment in GH-deficient adults revealed an increase in left ventricular myocardial mass (5%, which was comparable with increases in thigh muscle and lean body mass), increased left ventricular end-diastolic dimension and stroke volume (11). These changes were interpreted as being due to activation of the renin-aldosterone system and sodium retention during GH treatment, leading to small increases in left ventricular preload and myocardial hypertrophy; without changes in mean arterial pressure reflecting anabolic actions of GH on the myocardium (11). An increase in cardiac stroke volume has previously been reported. In addition to increased preload, enhanced myocardial contractility may also underlie improved cardiac performance. Indeed, increases in myocardial shortening have been reported in some patients with acromegaly (12, 13), in normal subjects treated with human GH for 2 weeks (14) and in one patient with GH deficiency and cardiomyopathy (8).

On the other hand, an excess of GH is accompanied by cardiac dysfunction. Most acromegalic patients present with cardiac hypertrophy, increased cardiac output, and decreased systemic vascular resistance, all of which are characteristic of a hyperkinetic heart syndrome (15–18). Some patients, however, develop congestive heart failure with dilated cardiomyopathy and/or ventricular dysrythmias (16–19). Treatment of acromegaly can lead to an improvement of both the hyperkinetic and dilative forms of acromegalic cardiomyopathy (20–22). Cardiac hypertrophy has been observed in rats bearing GH-secreting transplantable tumors (23) or in rats repeatedly treated with GH injections (24). Reports on the hemodynamic effects of chronic GH excess in rats are conflicting in that a hyperkinetic heart syndrome (23) and depressed indices of cardiac pump function have both been observed (25). A third study found no change in the ratio of ventricular weight:body weight in rats bearing a GH secreting tumor for 18 weeks (26). However, the latter study reported a pattern of myocardial adaptation which allowed the muscle to improve its contractile performance and economy simultaneously, as assessed by myosin phenoconversion and increase in myosin ATPase enzymatic sites (26).

The effects of GH appear, in part, to be mediated by insulin-like growth factor-I (IGF-I). There is experimental evidence that IGF-I enhances ventricular hypertrophy and function during the onset of experimental cardiac failure in mice with increased end-diastolic volume and stroke volume (27). IGF-I stimulates myofibril development and decreases smooth muscle α-actin of adult cardiomyocytes, suggesting that IGF-I may be involved in stress-induced changes of cardiomyocytes (28). IGF-I has been shown to stimulate cardiomyocyte contractility in vitro (29). In rats, administration of either GH or IGF-I alone, or both in combination (for 4 weeks) increased left ventricular muscle mass, increased cardiac index and reduced systemic vascular resistance. Each of the single treatments led to increased in vivo and in vitro cardiac function parameters, whereas the combination
treatment revealed a blunted effect. Growth hormone alone induced a concentric growth pattern of the left ventricular wall (30). It is hypothesized that IGF-I may induce proliferation of and/or inhibit apoptosis of damaged cardiomyocytes. Furthermore, a single subcutaneous dose of IGF-I in humans increased stroke volume and cardiac output by 14 and 18%, respectively. The ejection fraction increased by 9% (31).

On the basis of these findings it is conceivable that GH may have a beneficial role in the treatment of certain forms of cardiac failure. In addition, in a study performed in rats with experimentally induced cardiac failure, GH treatment achieved improved cardiac performance (32), suggesting that GH may also be of use in humans suffering from cardiac failure. Two recent publications on the pharmacological treatment with growth hormone of patients with idiopathic dilated cardiomyopathy have stirred some controversy on the usefulness of GH as a therapeutic agent in the failing heart. In both studies the standard therapy for heart failure was continued. In the first study (33), where GH was administered for 3 months at a dose of 14 IU per week (4 IU every other day; corresponds to a low replacement dose for patients with GH deficiency) GH increased total IGF-I levels from 198 ± 14 to 406 ± 14 (normal range, 90–210 ng/ml). The subjects were studied at baseline immediately before treatment, then after 3 months of treatment, and finally 3 months after treatment was discontinued. GH increased left ventricular wall thickness and reduced chamber size significantly. End-systolic wall stress fell markedly. At rest, GH consistently improved the indices of systolic performance (i.e. ejection fraction, shortening velocity, and aortic acceleration), whereas diastolic indices were marginally affected. Cardiac output was improved (4.9 ± 0.4 to 5.7 ± 0.6 l/min), particularly during exercise (7.4 ± 0.7 to 9.7 ± 0.9 l/min). GH enhanced ventricular work despite reduced myocardial oxygen consumption and energy production. These results suggest an improved ventricular mechanical efficiency. During GH, myocardial respiratory quotient increased during exercise suggesting a shift from lipid to increased carbohydrate oxidation. Growth hormone also reduced basal heart rate (121 ± 5 to 75 ± 4 beats/min) at rest which, however, did not differ during exercise. Exercise duration and peak workload increased (6.5 ± 0.5 to 8.9 ± 0.9 min and 89 ± 5 to 118 ± 13 watts respectively). Improved clinical symptoms (New York Heart Association (NYHA) functional class 2.7 ± 0.2 to 1.6 ± 0.2) were also found at clinical evaluation of the patients. The changes were partially reversed three months after discontinuation of GH therapy. In brief, although this study was performed without a placebo control - as the authors discuss - beneficial effects of GH in idiopathic dilated cardiomyopathy during short-term treatment was suggested. The second study (34) was designed in a double-blind, randomized, placebo-controlled fashion. The number of studied subjects was determined after analysis of the study discussed above in order to have sufficient numbers for calculating statistical differences. GH or placebo was injected daily subcutaneously (2 IU) for at least 3 months. The studied groups were similar in their baseline characteristics. In contrast to the study discussed above, no significant changes were found in body weight, NYHA class, walking test or any hemodynamic parameters. Septal wall thickness and calculated ventricular mass increased in the GH group. A significant relation between ventricular mass and serum IGF-I concentrations was found in all patients. There was no relation between changes in left ventricular wall stress and vascular resistance or ejection fraction.

Is there a role for GH in the pharmacological treatment of idiopathic dilated cardiomyopathy? There is a large body of experimental data from in vitro and in vivo experiments which would suggest that GH treatment could be a potential benefit for patients. However, the last study strongly argues against GH treatment for dilated cardiomyopathy. Although the power of the study with a randomized, double-blind, placebo-controlled design is maximal there are some limitations to the study: first, the study patients are slightly older than in the first study (54 ± 10 years, range 36–57 vs 46 ± 9 years, range 25–70) leaving the possibility that duration of disease and age of patients may influence the effects of GH, and secondly, the study duration, although the same in both studies, is relatively short. Cardiovascular effects of GH replacement in patients with GH deficiency are in some studies only significant after 6 months of treatment (35–37), and therefore a short duration of GH treatment may conceal significant cardiac defects. A longer treatment period with GH in selected patients with dilated cardiomyopathy in a double-blind, randomized, placebo-controlled design would be conclusive. At the doses used, GH did not appear to increase morbidity or mortality. Additional endpoints such as mortality, morbidity to other conditions and rate of survival time until successful cardiac transplantation as well as performance after transplantation would be required in a longer term study. Until such data is available, treatment of a patient with idiopathic dilated cardiomyopathy should be carried out in specialized centers under careful monitoring and within study protocols.

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References
478 Highlight

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