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A PRELIMINARY STUDY OF GROWTH HORMONE IN THE TREATMENT OF DILATED CARDIOMYOPATHY

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Abstract Background. Cardiac hypertrophy is a physiologic response that allows the heart to adapt to an excess hemodynamic load. We hypothesized that inducing cardiac hypertrophy with recombinant human growth hormone might be an effective approach to the treatment of idiopathic dilated cardiomyopathy, a condition in which compensatory cardiac hypertrophy is believed to be deficient.

Methods. Seven patients with idiopathic dilated cardiomyopathy and moderate-to-severe heart failure were studied at base line, after three months of therapy with human growth hormone, and three months after the discontinuation of growth hormone. Standard therapy for heart failure was continued throughout the study. Cardiac function was evaluated with Doppler echocardiography, right-heart catheterization, and exercise testing.

Results. When administered at a dose of 14 IU per week, growth hormone doubled the serum concentrations of insulin-like growth factor I. Growth hormone increased left-ventricular-wall thickness and reduced chamber size significantly. Consequently, end-systolic wall stress (a function of both wall thickness and chamber size) fell

markedly (from a mean [\pm SE] of 144 ± 11 to 85 ± 8 dyn per square centimeter, $P < 0.001$). Growth hormone improved cardiac output, particularly during exercise (from 7.4 ± 0.7 to 9.7 ± 0.9 liters per minute, $P = 0.003$), and enhanced ventricular work, despite reductions in myocardial oxygen consumption (from 56 ± 6 to 39 ± 5 ml per minute, $P = 0.005$) and energy production (from 1014 ± 100 to 701 ± 80 J per minute, $P = 0.002$). Thus, ventricular mechanical efficiency rose from 9 ± 2 to 21 ± 5 percent ($P = 0.006$). Growth hormone also improved clinical symptoms, exercise capacity, and the patients' quality of life. The changes in cardiac size and shape, systolic function, and exercise tolerance were partially reversed three months after growth hormone was discontinued.

Conclusions. Recombinant human growth hormone administered for three months to patients with idiopathic dilated cardiomyopathy increased myocardial mass and reduced the size of the left ventricular chamber, resulting in improvement in hemodynamics, myocardial energy metabolism, and clinical status. (N Engl J Med 1996; 334:809-14.)

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IDIOPATHIC dilated cardiomyopathy is a common cause of cardiac dysfunction.^{1,2} It is characterized by progressive dilatation of the left ventricle (and sometimes the right ventricle as well), unaccompanied by compensatory wall thickening. This accounts for the marked elevation of left ventricular systolic wall stress, which is a function of both wall thickness and chamber size.³ There is no specific therapy for dilated cardiomyopathy. Medical treatment is aimed at alleviating the symptoms of heart failure, and only cardiac transplantation offers lasting benefit to patients with this condition.

Evidence is accumulating that growth hormone is a physiologic regulator of myocardial growth and performance.^{4,5} In patients with congenital deficiency of growth hormone, cardiac growth and function are im-

paired.^{6,7} Administering growth hormone to such patients increases wall thickness and normalizes cardiac performance.^{7,8} Conversely, a long-term excess of growth hormone causes cardiac hypertrophy and a hyperkinetic syndrome, with increased cardiac output and reduced vascular resistance.^{9,10} In an experimental model of heart failure, insulin-like growth factor I induced additional myocyte growth, which was associated with significant improvement of cardiac function.¹¹ More recently, growth hormone itself was shown to improve cardiac function in experimental heart failure.¹²

These observations provide a rationale for testing the effect of growth hormone in patients with heart failure due to dilated cardiomyopathy. Growth hormone activates cardiac cell growth, without changing the collagen content of the myocardium or the capillary density.¹¹⁻¹³ It also induces physiologic ventricular remodeling, in which the growth response is not detrimental but instead is associated with enhanced contractile performance.^{11,12} In addition, in models of long-term excess of

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growth hormone the force of cardiac contraction is increased despite a redistribution of the myosin heavy-chain isoforms toward the V_3 isoform, one that is characterized by a low shortening velocity and ATPase activity.^{14,15} This finding has led to the hypothesis that by reducing the energy cost, growth hormone may improve the thermodynamic efficiency of the contractile apparatus.¹⁴ Consequently, growth hormone may be effective in the treatment of dilated cardiomyopathy, in which the high-energy phosphate reserve is depleted^{16,17} and the ability to convert metabolic energy to mechanical work is impaired.¹⁸⁻²⁰

In this preliminary study, we examined the effect of therapy with recombinant human growth hormone in seven patients with idiopathic dilated cardiomyopathy.

METHODS

Study Patients

The study involved seven patients — five men and two women — with chronic heart failure caused by dilated cardiomyopathy. The mean (\pm SD) clinical duration of their condition was 3.5 ± 1.5 years, and their mean age was 46 ± 9 years (range, 36 to 57). The criteria for enrollment in the study were clinical evidence of heart failure despite conventional therapy; a left ventricular end-diastolic dimension greater than 60 mm, as measured by M-mode echocardiography; a left ventricular ejection fraction below 40 percent, as assessed by two-dimensional echocardiography; the ability to exercise for at least five minutes on a bicycle ergometer at 75 percent of the maximal capacity; a stable hemodynamic condition for the previous six months, as indicated by the absence of changes in the left ventricular ejection fraction of more than 5 percent; and a normal sinus rhythm. The exclusion criteria were the presence of active myocarditis, substantial coronary-artery stenosis, valvular heart disease (except mild mitral regurgitation), systemic hypertension, hypertrophic cardiomyopathy, diabetes mellitus, and chronic alcoholism. Heart failure was treated with digoxin, an angiotensin-converting-enzyme inhibitor (2.5 mg of ramipril per day), and a diuretic. During this therapeutic regimen, five patients were in New York Heart Association functional class III and two were in class II. Written informed consent was obtained from each patient, and the study protocol was approved by the Ethics Committee of the University of Naples Federico II.

Study Protocol

All the patients were studied at three times: at base line, immediately after a three-month course of treatment with recombinant human growth hormone (Genotropin [potency, 3 IU per milligram], Pharmacia, Stockholm, Sweden), and three months after treatment was discontinued. Growth hormone was administered subcutaneously at a dose of 4 IU every other day (0.15 to 0.20 IU per kilogram of body weight per week), which is a low replacement dose for patients with growth hormone deficiency.³ Standard medical therapy for heart failure was continued throughout the study. Patients were observed closely during the first week of therapy because of the potential sodium-retaining effect of growth hormone, which could aggravate congestive heart failure.²¹

Procedures

M-mode, two-dimensional, and Doppler echocardiographic measurements were performed with an ultrasonographic system equipped with a 3.5-MHz transducer (Apogee Cx, Interspec, Ambler, Pa.), according to the recommendations of the American Society of Echocardiography.²² Details of the procedure and variability coefficients of the measurements are reported elsewhere.²³ Left ventricular end-systolic stress, calculated according to Reichek et al.,²⁴ served as an index of afterload. The patients' maximal exercise capacity was determined before and after growth hormone treatment by upright bicycle ergometry, beginning with a workload of 25 watts, which was increased by

25 watts every two minutes. The test was stopped when severe fatigue or dyspnea developed. The effect of growth hormone treatment on the quality of the patients' lives was assessed on the Patient's Self-Rating Scale.²⁵

Right-heart catheterization was performed in the morning after the patients had fasted overnight and had received no therapy for 24 hours; no premedication was given. Pulmonary-artery and pulmonary-capillary wedge pressures were measured with a Swan-Ganz catheter introduced through the right jugular vein. Cardiac output was determined in triplicate by the thermodilution technique with the use of the same catheter. The coronary sinus was cannulated with a double-thermistor catheter (Wilton-Webster Laboratories, Baldwin Park, Calif.), introduced through the brachial vein. This catheter was used to measure coronary blood flow by the constant-infusion thermodilution technique²⁶ and to obtain blood samples from the coronary sinus. The possibility of substantial coronary-sinus reflux was excluded by monitoring the coronary blood temperature after injecting cold saline into the right atrium. A brachial artery was cannulated percutaneously with an 18-g catheter to record arterial blood pressure and to obtain arterial blood samples. After a stabilization period of 20 to 30 minutes, the resting hemodynamic measurements were taken, and two consecutive pairs of blood samples from the artery and from the coronary sinus were withdrawn simultaneously. The patients then performed submaximal physical exercise with a bicycle ergometer that was attached to the catheterization table. The workload was gradually increased to a level corresponding to 75 percent of the peak workload reached in the maximal-exercise test at base line. This workload was kept constant to allow the various measurements to be taken under similar conditions before and after growth hormone treatment. After at least five minutes of exercise at the final workload level, two pairs of arterial and coronary-sinus blood samples were withdrawn for the assay of blood gases, and the hemodynamic measurements were repeated. Blood oxygen and carbon dioxide were measured by an automated blood gas analyzer (ABL 520, Radiometer, Copenhagen, Denmark). Serum growth hormone, insulin-like growth factor I, thyroid hormone, and thyrotropin were measured before and during growth hormone treatment with the use of commercially available radioimmunoassay kits.

Calculations

Systemic vascular resistance ($\text{dyn} \cdot \text{sec} \cdot \text{cm}^{-5}$) was calculated with the following formula: $80 \times (\text{mean arterial pressure} - \text{right atrial pressure}) \div \text{cardiac output}$. Pulmonary vascular resistance was calculated as follows: $80 \times (\text{mean pulmonary pressure} - \text{capillary wedge pressure}) \div \text{cardiac output}$. Left ventricular mechanical work (LVW, measured in kilogram-meters per minute) was calculated as follows: $\text{cardiac output} \times (\text{mean systolic pressure} - \text{pulmonary wedge pressure}) \times 0.0136$, in which 0.0136 is a factor used to convert units of pressure and volume to kilogram-meters.

Myocardial oxygen uptake (MVO_2) and carbon-dioxide production (MVCO_2) were calculated as the product of coronary blood flow and the arterial-coronary-sinus blood-concentration gradient of each gas. The myocardial respiratory quotient was calculated as $\text{MVCO}_2 \div \text{MVO}_2$. Myocardial energy production (MEP, measured in joules per minute) was calculated as $0.33 \text{ MVO}_2 + 0.14 \text{ MVCO}_2$.²⁷ The oxidation rates of carbohydrates and lipids were calculated with classic calorimetric equations²⁷ and expressed as percent contributions to total energy production. Ventricular mechanical efficiency, defined as the fraction of chemical energy that is converted to external mechanical work, was calculated in two ways: by the equation $\text{LVW} \div (\text{MVO}_2 \times 2.059)$, in which 2.059 is the conversion factor representing the energy equivalent per unit of oxygen metabolized (1 ml of oxygen = 20.18 J), under the assumption that the metabolic substrates are oxidized by the myocardium in a fixed ratio; and by the equation $\text{LVW} \div \text{MEP}$, taking into account that 1 kg-m = 9.8 J. The latter approach is based on actual metabolic energy generated in the myocardium and takes into account any shift that may occur in the oxidative pattern of metabolic substrates as a consequence of physical exercise, growth hormone treatment, or both. Both measures of mechanical efficiency are dimensionless and are expressed as percentages.

All data are presented as means \pm SE. The effects of growth hor-

hormone on hemodynamic and metabolic measures were evaluated by the paired t-test or the two-way analysis of variance with Duncan's multiple-range test²⁸ when the comparison included the effects of discontinuing growth hormone therapy.

RESULTS

Clinical Effects of Growth Hormone Therapy

All the patients completed the three-month course of growth hormone treatment with no reported side effects. The clinical effects of the treatment are shown in Table 1. During growth hormone treatment, the patients reported a feeling of well-being and an improved quality of life. The patients' maximal exercise capacity increased after they received growth hormone, as shown by the significantly greater duration of exercise and peak workload than at base line. Arterial blood pressure was not affected by the treatment. Heart rates were lower at rest and slightly higher during peak exercise after treatment with growth hormone. The clinical improvement, although attenuated, persisted, in terms of both symptoms and maximal exercise capacity, three months after growth hormone treatment had been discontinued.

Left Ventricular Size and Shape

Doppler echocardiographic data are shown in Table 2. Growth hormone induced a significant increase in left ventricular mass and wall thickness. Despite the increased myocardial mass, both end-systolic and end-diastolic left ventricular dimensions were significantly reduced by growth hormone treatment. Overall, growth hormone improved left ventricular dimensions, as reflected in the significant increase in relative wall thickness (wall thickness ÷ ventricular radius). Cardiac mass and wall thickness were still significantly increased three months after the completion of growth hormone therapy, although there was a partial reversal of the effect of growth hormone on these variables.

Growth hormone consistently improved the indexes of systolic performance at rest — that is, ejection fraction, shortening velocity, and aortic acceleration (Table 2). The fall in the end-systolic wall stress was especially pronounced, probably as a consequence of the changes in left ventricular size and shape since arterial blood pressure did not change. Growth hormone also im-

proved the isovolumic relaxation time. The other diastolic indexes were only marginally affected; therefore, the ratio of early to late diastolic-flow velocity was slightly but not significantly increased. The beneficial effect of growth hormone on the systolic performance was reduced but still significant three months after the withdrawal of therapy, whereas the relaxation time returned to base-line levels.

Hemodynamic Variables

The effects of growth hormone treatment on hemodynamic variables measured invasively are shown in Table 3. After treatment, the mean pulmonary arterial and capillary wedge pressures decreased significantly, both when the patient was at rest and in response to physical exercise, whereas pulmonary vascular resistance was slightly but not significantly lower. Growth hormone significantly increased cardiac output at rest

Table 1. Clinical Variables and Maximal Exercise Capacity before, Immediately after, and Three Months after Growth Hormone Treatment.*

VARIABLE	AT BASE LINE	IMMEDIATELY AFTER THERAPY	P VALUE	3 MONTHS AFTER THERAPY	P VALUE
Weight (kg)	79±4	78±3		78±4	
New York Heart Association functional class	2.7±0.2	1.6±0.2	<0.001	2.3±0.3	0.03
Patient's Self-Rating Scale score†	19.3±3	11.6±2	<0.001	15.4±2	<0.001
Heart rate (beats/min)					
At rest	86±5	75±4	0.01	76±4	0.08
During exercise	144±7	151±5	NS	139±8	NS
Systolic blood pressure (mm Hg)					
At rest	121±5	126±5	NS	124±5	NS
During exercise	174±6	184±7	NS	181±7	NS
Exercise duration (min)	6.5±0.5	8.9±0.9	<0.001	7.9±0.8	0.005
Peak workload (watts)	89±5	118±13	<0.001	107±9	0.02

*Plus-minus values are means ±SE. P values are for comparisons with base-line values. NS denotes P>0.05.

†See Tandon et al.²⁵ for an explanation of this score.

Table 2. Doppler Echocardiographic Data before, Immediately after, and Three Months after Growth Hormone Treatment.*

VARIABLE	AT BASE LINE	IMMEDIATELY AFTER THERAPY	P VALUE	3 MONTHS AFTER THERAPY	P VALUE
Cardiac size and shape					
Left ventricular end-diastolic dimension (mm)	65±1	61±1	<0.001	63±1	0.05
Left ventricular end-systolic dimension (mm)	52±1	46±1	<0.001	49±1	0.004
Posterior wall thickness (mm)	10.0±0.6	12.9±0.8	<0.001	11.4±0.8	0.02
Relative wall thickness	0.31±0.01	0.41±0.02	<0.001	0.35±0.01	0.006
Left ventricular mass (g)	275±11	326±12	0.007	304±12	0.03
Systolic function					
Ejection fraction (%)	34±1.5	47±1.9	<0.001	40±2.4	0.02
Shortening velocity (circ/sec)†	0.68±0.03	0.90±0.06	<0.001	0.79±0.06	0.002
Mean aortic acceleration (m/sec ²)	7.8±0.6	10.9±1	0.009	8.2±0.6	NS
End-systolic wall stress (dyn/cm ²)	144±11	85±8	<0.001	107±10	<0.001
Diastolic function					
Isovolumic relaxation time (msec)	121±9	99±5	0.02	113±6	NS
Ratio of early to late filling velocity	1.17±0.25	1.27±0.21	NS	1.07±0.14	NS

*Plus-minus values are means ±SE. P values are for comparisons with base-line values. NS denotes P>0.05.

†Circ/sec denotes circumferences per second.

Table 3. Effects of Growth Hormone on Hemodynamic Variables Measured Invasively with the Patient at Rest and during Submaximal Exercise.*

VARIABLE	AT BASE LINE	IMMEDIATELY AFTER THERAPY	P VALUE
Pulmonary arterial pressure (mm Hg)			
At rest	21±3	15±1.5	0.03
During exercise	39±7	31±6	0.02
Pulmonary-capillary wedge pressure (mm Hg)			
At rest	14±3	8±1	0.05
During exercise	24±5	18±4	0.003
Pulmonary vascular resistance (dyn·sec·cm ⁻⁵)			
At rest	118±16	107±26	NS
During exercise	170±45	132±34	NS
Cardiac output (liters/min)			
At rest	4.9±0.4	5.7±0.6	0.04
During exercise	7.4±0.7	9.7±0.9	0.003
Systemic vascular resistance (dyn·sec·cm ⁻⁵)			
At rest	1666±136	1466±152	NS
During exercise	1270±125	988±98	0.05
Ventricular mechanical work (kg·m/min)			
At rest	5.4±0.6	6.7±0.8	0.03
During exercise	9.2±1.2	13.7±1.8	0.008
Coronary blood flow (ml/min)			
At rest	153±18	140±14	NS
During exercise	421±42	297±36	0.01

*Plus-minus values are means ±SE. NS denotes P>0.05.

and improved its response to physical exercise. Stroke volume increased from 62±6 to 72±8 ml per minute at rest (P=0.05) and from 61±8 to 79±9 ml per minute during exercise (P=0.004). Similarly, growth hormone increased the resting values of cardiac work and potentiated its response to physical exercise. Systemic vascular resistance was slightly lower at rest after growth hormone treatment. The decrease was more pronounced and statistically significant during physical exercise. The measurement of coronary blood flow was technically inadequate in one patient, and the data for coronary blood flow and myocardial energy were therefore derived from six patients. Growth hormone did not modify the resting coronary blood flow. During physical exercise, however, coronary blood flow increased to a significantly lesser extent after growth hormone treatment.

Myocardial Energy Metabolism

The effects of growth hormone treatment on myocardial energy metabolism are shown in Table 4. In the base-line study, myocardial oxygen consumption increased threefold in response to physical exercise. After treatment with growth hormone, the increase in oxygen consumption was significantly reduced. The difference between arterial and coronary-sinus oxygen volume content did not change during exercise, either at base line or after growth hormone treatment. Myocardial energy production paralleled oxygen consumption: the resting values were the same before and after growth hormone treatment, whereas the exercise values were greatly reduced after treatment. The myocardial respiratory quotient increased during exercise, indicating that the myocardial reliance on fatty-acid oxidation shifted to a reliance on carbohydrate oxidation. Accordingly, the ratio of the carbohydrate component of energy production to the lipid component rose to values above

1 during exercise, both before and after growth hormone treatment. Overall, growth hormone induced beneficial changes in myocardial energy metabolism, without, however, altering the substrate partitioning in the oxidative pathway.

In the base-line study, left ventricular mechanical efficiency (calculated from oxygen uptake) fell significantly during exercise (from 15±3 to 9±2 percent, P=0.05) (Fig. 1). Growth hormone increased mechanical efficiency at rest and prevented the decrease observed in the base-line study during exercise. Therefore, after treatment with growth hormone, the values for mechanical efficiency during exercise were more than twice as high as the corresponding values before treatment. Virtually identical results were obtained when mechanical efficiency was calculated

from energy produced (before treatment, 18±4 percent at rest and 11±3 percent during exercise; after treatment, 23±4 percent at rest [P=0.04] and 23±5 percent during exercise [P=0.006]).

Hormone Measurements

The serum concentrations of growth hormone, measured the day after injection, were not significantly different from pretreatment values (0.8±0.1 vs. 1.0±0.1 ng per milliliter), whereas the concentrations of insulin-like growth factor I were doubled (406±15 vs. 198±14 ng per milliliter, P<0.001; normal range, 90 to 210). Serum thyroid hormone and thyrotropin concentrations did not change significantly after growth hormone therapy.

DISCUSSION

Cardiac hypertrophy is an important physiologic adaptation to an excess hemodynamic load on the heart. In this study, we attempted to induce cardiac hypertrophy with recombinant human growth hormone in an effort to improve cardiac function in patients with idiopathic dilated cardiomyopathy. Our preliminary data demonstrated that growth hormone increased myocardial mass and improved cardiac function and exercise performance. Although these effects tended to wane three months after growth hormone was discontinued, significant improvement in most indexes of cardiac size, shape, and function and in maximal exercise tolerance was still found. Our patients had moderately severe heart failure. Whether growth hormone may be beneficial in patients with more severe heart failure remains to be determined.

Left ventricular remodeling induced by growth hormone was characterized by increased wall thickness and reduced chamber size. This change in ventricular size and shape may benefit patients with a disorder such as

Table 4. Effects of Growth Hormone on Myocardial Energy Metabolism.*

VARIABLE	AT BASE LINE	IMMEDIATELY AFTER THERAPY	P VALUE
Oxygen consumption (ml/min)			
At rest	19±3	18±3	NS
During exercise	56±6	39±5	0.005
Myocardial oxygen difference (vol %)			
At rest	12.5±0.9	13.1±1.3	NS
During exercise	13.2±0.4	13.2±0.6	NS
Energy production (J/min)			
At rest	330±42	317±40	NS
During exercise	1014±100	701±80	0.002
Respiratory quotient			
At rest	0.72±0.04	0.73±0.05	NS
During exercise	0.87±0.02	0.86±0.02	NS
Percent contribution to energy production (oxidation rate of carbohydrate/lipid)			
At rest	10/90	9/91	NS
During exercise	57/43	57/43	NS

*Plus-minus values are means ±SE. NS denotes P>0.05.

dilated cardiomyopathy, in which progressive dilatation of the ventricles is not accompanied by compensatory wall thickening. Indeed, growth hormone produced a decrease in systolic wall stress, which was probably responsible for most of the improvement in ventricular mechanics. Growth hormone also reduced peripheral vascular resistance, which allowed cardiac output to rise, particularly during physical exercise.

Growth hormone did not have a deleterious effect on diastolic ventricular function. Some diastolic properties in fact improved during the administration of growth hormone, particularly the isovolumic relaxation time, which worsened again after the withdrawal of growth hormone. This finding is reassuring, given the considerable increase in wall thickness, which could have adversely affected diastolic function. It is also consistent with reports that the growth-promoting action of growth hormone, at least in the short term, involves primarily myocytes.^{11,13,29} Had the increase in cardiac mass been due to the proliferation of interstitial cells, diastolic function should not have improved and might have deteriorated.

This study provides insights into the way growth hormone affects cardiac performance. In dilated, failing hearts, there is an imbalance between energy supply and demand, the energy reserve being depleted and the demand increased.^{17,30,31} This energy mismatch may limit myocardial performance, particularly under conditions of stress.^{16,32} Another problem with the failing myocardium is the reduced mechanical efficiency—that is, the process whereby metabolic energy is converted to external work.¹⁸⁻²⁰ Our estimate of mechanical efficiency at rest in dilated cardiomyopathy (15 percent) agrees with previous reports. Our data also show that the defect in energy conversion becomes more pronounced during physical exercise. In our patients, a threefold increase in energy production during exercise was accompanied by a disproportionately lower increase in cardiac work (from 5.4 to 9.2 kg-m per minute). This contrasts with the physiologic response of healthy hu-

man subjects, in whom supine exercise increases ventricular mechanical efficiency.^{33,34} A similar pattern was recently found in studies in animals with the use of the elastance model.³⁵ Growth hormone treatment induced substantial changes in myocardial energy metabolism in our patients, particularly during physical exercise, in which the heart generates more mechanical work with lower oxygen consumption and energy production, thus accounting for a remarkable increase in mechanical efficiency (from 9 to 21 percent). This oxygen-sparing effect of growth hormone during physical exercise may prove particularly beneficial in patients with heart failure due to ischemic heart disease.

The mechanism (or mechanisms) by which growth hormone allows the failing myocardium to work at a lower energy cost does not appear to have a metabolic basis. After growth hormone treatment, there was no change in the preferred metabolic substrates, as expressed by the myocardial respiratory quotient. In addition, the magnitude of the gain in efficiency induced by growth hormone exceeded the maximal theoretical contribution of metabolic mechanisms (10 to 15 percent).³⁶ It is conceivable that growth hormone improved myocardial energy metabolism indirectly through its growth effect and the consequent reduction in wall stress. Indeed, wall stress is a major determinant of myocardial oxygen consumption and energy demand. In patients with dilated cardiomyopathy and heart failure, myocardial oxygen consumption is increased^{37,38} and correlates with the increment in wall stress.³⁷ Consequently, it is likely that the decrease in oxygen consumption and energy production observed after growth hormone treatment was causally related to the decrease in wall stress.

A limitation of this study is the lack of a placebo control group. A placebo effect cannot be entirely ruled out in the interpretation of some of the data, in particular those concerning the quality of life and exercise capacity. However, given the magnitude and consistency of

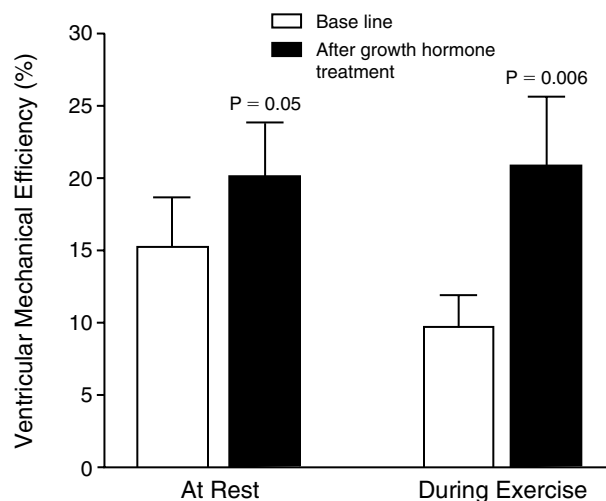


Figure 1. Effect of Growth Hormone on Ventricular Mechanical Efficiency at Rest and during Submaximal Bicycle Exercise in Patients with Idiopathic Dilated Cardiomyopathy.

the changes in a wide range of hemodynamic and metabolic variables after treatment with growth hormone, it is unlikely that the overall clinical improvement was spontaneous and not specifically related to growth hormone. In addition, our patients were in a stable hemodynamic condition before the study. It is possible that the clinical improvement was mediated in part by indirect, extracardiac mechanisms. For example, growth hormone may increase skeletal-muscle mass and strength, particularly in the elderly.³⁹

In conclusion, administration of recombinant human growth hormone to patients with dilated cardiomyopathy and heart failure activated myocardial growth, enhanced contractile performance, reduced the myocardial oxygen requirement, and improved exercise capacity. These preliminary findings should encourage the planning of larger clinical trials of longer duration to assess the long-term effect of growth hormone in patients with dilated cardiomyopathy and other forms of heart failure.

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