Cardiovascular effects of growth hormone replacement therapy in hypopituitary adults

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In the present study the effects of replacement with biosynthetic human growth hormone (GH) in a large group of hypopituitary adults on cardiac structure and function were investigated. Thirty-six GH-deficient, hypopituitary patients (17 males and 19 females; aged 19–67 years) on conventional replacement therapy without GH were studied. Twenty-nine of the patients had acquired hypopituitarism in adult life, mainly due to pituitary tumours. The design of the study was a prospective, randomized, double-blind placebo-controlled trial for 6 months. Growth hormone (17 patients) was given in a daily dose of 0.02–0.05 IU/kg body wt sc (or a placebo. 19 patients) according to the patients’ tolerance. Other pituitary replacement treatment was unchanged. Resting and exercise electrocardiography using the Bruce protocol, two-dimensional echocardiography, Doppler ultrasound scanning and serum insulin-like growth factor I (IGF-I) were assessed at 0 and 6 months. Resting blood pressure was measured at 0, 1, 3 and 6 months. Serum IGF-I increased significantly on GH treatment (mean ± SD) GH: 293 ± 197 vs placebo: 82 ± 40 µg/l; p < 0.0001 at 6 months). Exercise time increased significantly on GH but not on placebo (GH: 8.45 ± 3.16 to 9.38 ± 2.42 min. sec, p < 0.01; placebo 9.08 ± 4.35 to 9.50 ± 4.14 min. sec, NS), although the change was not significantly different between the two. There was no change in the heart rate or the blood pressure either at rest or at the peak of exercise. No significant changes were observed in the left ventricular mass index, the left ventricular posterior wall thickness, the interventricular septal thickness, the ejection fraction or the cardiac output. Isovolumic relaxation time, a measure of the left ventricular diastolic function, decreased significantly on GH but not on placebo (GH: 98 ± 18 to 89 ± 11 ms, p = 0.03; placebo: 93 ± 17 to 89 ± 14 ms, NS), although again the change on GH was not significantly different from that on placebo. There was no significant change in the left ventricular filling. No significant changes were observed in plasma levels of urea, electrolytes or creatinine on either GH or placebo. In conclusion, six months of GH replacement therapy in hypopituitary adults had favourable cardiovascular effects, including increased exercise tolerance and improved diastolic function.

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Hypopituitarism is associated with increased morbidity and mortality (1, 2). Hypopituitary adults are treated conventionally using thyroxine, adrenal steroid and sex hormone replacement where appropriate, but growth hormone (GH) is not usually replaced (3, 4). Growth hormone deficiency is, however, common in pituitary disease at presentation or following treatment by surgery or radiotherapy (5). Growth hormone is a major anabolic hormone and its role in adult life has received much attention in recent years (6, 7). We have reported previously that hypopituitary patients on conventional replacement have impaired myocardial function. In particular, they have reduced exercise tolerance, electrocardiographic abnormalities on exercise and abnormal left ventricular diastolic function (8). We have observed also a relationship between circulating insulin-like growth factor I (IGF-I) concentration and the left ventricular mass and cardiac work on exercise, suggesting a physiological role for GH in the maintenance of cardiac structure and function in adults (8). A causal relationship has been suggested between GH deficiency and the increased vascular morbidity and mortality in hypopituitary adults (1, 2), but this relation is still not clear (9).

The aim of this study was to investigate the cardiovascular effects of replacement therapy in a large group of hypopituitary patients of mainly adult onset using the methods of two-dimensional echocardiography, Doppler ultrasound scanning and a standard exercise electrocardiography protocol. This work was
presented in part at the British Cardiac Society, Harrogate, UK, 1992 (10).

Patients and methods

Criteria for selection of patients

Patients recruited for this study were adults with GH deficiency acquired during adult life or patients who were treated with GH during childhood. Growth hormone deficiency was defined biochemically as a serum GH response of less than 6 mU/l to insulin-induced hypoglycaemia (blood glucose < 2.2 mmol/l) or to oral clonidine (50 µg). Age was limited between 18 and 70 years. Patients were required to have a blood pressure of less than 160/90 mmHg, either spontaneously or controlled, and stable to this level on monotherapy. They were stable on thyroxine and cortisol replacement where appropriate. No stipulation was made as to whether patients were or were not taking sex steroids provided that they did not start or stop the treatment or change the dose during the course of the study or in the preceding 6 months. Patients were excluded if they had GH treatment in the preceding year, had an original diagnosis of acromegaly, suffered from diabetes mellitus or another chronic disease or had any condition with increased risk of leukaemia.

Characteristics of the study population

Out of 40 adult hypopituitary patients participating in a randomized double-blind placebo-controlled trial, 36 patients (17 male and 19 females) were available for the cardiac investigations before and after GH treatment. Patients were recruited from the Endocrine Clinics at St. Mary's and adjacent hospitals in London. Seven patients had suffered from hypopituitarism since childhood and 29 acquired the condition during their adult life. Hypopituitarism resulted mostly from pituitary and parapituitary tumours treated medically and by surgery and/or radiotherapy. Patients had replacement therapy with cortisol and thyroxine and, when appropriate, with sex steroids (Table 1). The study protocol was approved by the ethical committee of Parkside Health Authority and patients gave written informed consent. Data on some of the patients at baseline, before GH or placebo, have been published in previous communications (8, 9).

Design of the study

The study was performed between December 1989 and March 1992. Following baseline assessments, patients were entered in a randomized double-blind placebo-controlled trial of either GH or a placebo for 6 months. Resting blood pressure was measured at baseline and after 1, 3 and 6 months of treatment. Exercise tolerance, echocardiography and Doppler studies were performed at 0 and 6 months. Plasma urea, electrolytes and creatinine were measured using standard routine methods. Serum IGF-I was measured by radioimmunoassay after acid–ethanol extraction as described previously (11). The normal serum IGF-I level (mean ± sd) in our laboratory is 171 ± 80 µg/l.

Growth hormone treatment regimen

Biosynthetic hGH (Norditropin®, Novo Nordisk, Denmark) was given subcutaneously in a daily dose of 0.02–0.05 IU/kg body wt injected at bed time (or a placebo). The starting daily dose was 0.05 IU/kg (to a maximal of 4 IU/day) and was adjusted according to the patients' tolerance. Growth Hormone was supplied by Novo Nordisk in vials containing 12 IU. The placebo consisted of freeze-dried carrier, sterile glycin, sodium bicarbonate and mannitol. Growth hormone and placebo were presented identically and reconstituted by patients, after appropriate training, in 3 ml of 0.9% benzyl alcohol. Randomization was by the GH manufacturer, men and women were randomized separately and the code was broken after completion of the study.
Resting blood pressure

Blood pressure (BP) measurements were performed by the same observer (SAB) using a conventional mercury sphygmomanometer (Accuson, UK) with the subject in the sitting position and after resting for 30 min.

Exercise electrocardiography

A 12-lead electrocardiogram was performed at rest. Then a symptom-limited, graded, multistage treadmill test using Bruce’s standard protocol of seven 3-min stages was performed (12). The test was performed in a temperature- and humidity-controlled environment with standard safety precautions. Heart rate and blood pressure were obtained at the end of each stage of the protocol and exercise was terminated when the patient showed symptoms such as leg weakness, shortness of breath or exhaustion.

Echocardiography

Each subject underwent two-dimensional and Doppler echocardiography using a phased array sector scanner (General Electric Pass 11, 3.5-MHz transducer) with the patient examined in the left lateral supine position using a standardized examination protocol (13). The left ventricular septal, the posterior wall thickness and cavity dimensions were measured from the parasternal left ventricular short axis projections at the chordae and papillary muscle junction using two-dimensionally guided M-mode echocardiography. The left ventricular mass was determined using an area × length method, which has been validated previously in man (14) with all measurements taken at end-diastole and at end-expiration. Two echocardiographic views are required to make this calculation: a parasternal short axis view of the left ventricle at the papillary muscle tip level to determine the area of the myocardium and an apical four-chamber view that maximizes the distance from the mitral valve annulus to the left ventricular apex to determine the length of the ventricle. The following algorithm is then used to calculate the left ventricular (LV) mass: LV mass = 1.04 (5/6 A₁ × l₁ − 5/6 A₂ × l₂), where A₁ and A₂ represent the epicardial and endocardial areas planimetered, respectively, and l₁ and l₂ represent the length of the left ventricle from mitral annulus to epicardial and endocardial borders, respectively. The left ventricular mass index is then determined by dividing the left ventricular mass by the patient’s body surface area.

Doppler scanning

Pulsed Doppler examination of transmittal flow was recorded from the apical four-chamber view with reference to the two-dimensional echocardiographic image. The sample volume was positioned between the mitral annulus and the tips of the mitral leaflets, with the position adjusted to maintain the sample volume at an angle as near parallel to transmittal flow as possible by using the audible signal and spectral velocity display. When the maximum transmittal velocity for the early filling wave was detected, the velocity profile was recorded at 50 mm/s with the patient in passive end-expiration. The peak flow velocity of the early and atrial waves were measured from the three consecutive cardiac cycles displaying the highest measurable velocity profiles. The isovolumic relaxation time was measured from the apical five-chamber view by placing the continuous wave Doppler beam between the mitral and aortic valve junction. The time interval between the end of the aortic velocity envelope and the onset of the early filling wave was taken to represent the isovolumic relaxation time (15) (Fig. 1). Abnormal left ventricular diastolic function is defined as follows: isovolumic relaxation time (IVRT) > 82 ms and early filling velocity/atrial filling velocity (E/A) < 1.5 for ages 20–29 years: IVRT > 92 ms and E/A ratio < 1.4 for ages 30–49 years; and IVRT > 100 ms and E/A ratio < 0.8 for ages 50–72 years (16).

![Early Flow Velocity](image)

Fig. 1. An actual sample of a Doppler recording from the apical five-chamber view used for assessment of the isovolumic relaxation time (top) and a schematic representation (bottom). See text for details.
Table 2. Resting blood pressure in hypopituitary adults before and during growth hormone (GH) replacement therapy or placebo.8

<table>
<thead>
<tr>
<th></th>
<th>Duration of treatment</th>
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<tbody>
<tr>
<td></td>
<td>0 months</td>
</tr>
<tr>
<td><strong>Systolic blood pressure (mmHg)</strong></td>
<td></td>
</tr>
<tr>
<td>GH</td>
<td>114 ± 4</td>
</tr>
<tr>
<td>Placebo</td>
<td>124 ± 4</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure (mmHg)</strong></td>
<td></td>
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<tr>
<td>GH</td>
<td>72 ± 2</td>
</tr>
<tr>
<td>Placebo</td>
<td>80 ± 2</td>
</tr>
</tbody>
</table>

8Values are means ± sd.

Variability of left ventricular mass and Doppler filling measurements

All echocardiographic and Doppler assessments before and after GH treatment and placebo were performed by the same observer (MS). The intra-observer and temporal variation in the calculation of left ventricular mass were determined in the following fashion. Five subjects underwent an echocardiographic study on two separate occasions approximately 5 days apart. Measurements were made on all the echocardiographs by one observer on the two occasions. The 95% confidence limits for each measurement, which accounted for both intra-observer and temporal variability, are as follows: septum: ±0.1 cm (8.7%); posterior wall thickness ±0.2 cm (17%); left ventricular internal diameter: ±0.4 cm (8.7%); LVMI: ±8.1 g/m² (6.1%); E/A ratio: ±0.13 (9.5%); isovolumic relaxation time: ±8.1 ms (8.8%).

Statistical analysis

All data are presented as mean ± sd or mean (range). Growth hormone and placebo were compared using Student’s unpaired t-test and results before and after treatment or placebo were compared using Student’s paired t-test for normally distributed data. In the case of non-normally distributed data, the Mann-Whitney U test and the Wilcoxon rank sum test were used for unpaired and paired comparisons, respectively.

Results

Study progress and clinical evaluation

Thirty-six patients (17 on GH and 19 on placebo) completed the 6-month study period. Seven patients on GH needed dose reduction because of side-effects, mainly fluid retention. The GH dose was reduced by 25% in four patients and by 50% in three patients. There was no significant change in body weight. None of the patients developed chest pain or shortness of breath. Fluid retention was not associated with clinical signs of heart failure. Resting blood pressure did not change after 1, 3 or 6 months on either GH or placebo (Table 2). Resting electrocardiography showed no

Table 3. The effect of growth hormone replacement in hypopituitary adults on physiological parameters during exercise.8

<table>
<thead>
<tr>
<th></th>
<th>Growth hormone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 months</td>
<td>6 months</td>
</tr>
<tr>
<td>Exercise time (minutes, seconds)</td>
<td>8.45 ± 3.16</td>
<td>9.38 ± 2.42*</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>76 ± 11</td>
<td>81 ± 13</td>
</tr>
<tr>
<td>Maximal</td>
<td>170 ± 21</td>
<td>170 ± 22</td>
</tr>
<tr>
<td>Mean arterial BP (mmHg)</td>
<td>123 ± 16</td>
<td>127 ± 18</td>
</tr>
<tr>
<td>Starting</td>
<td>182 ± 37</td>
<td>181 ± 27</td>
</tr>
<tr>
<td>Maximal × HR product (mmHg × beats/min × 1000)</td>
<td>29.7 ± 7.0</td>
<td>29.9 ± 6.2</td>
</tr>
<tr>
<td>ST - Maximal depression (mm)</td>
<td>1.4(0.2-1.9)</td>
<td>1.1(0.2-2.7)</td>
</tr>
</tbody>
</table>

8Values are mean ± sd or median (range); *p < 0.01 (Wilcoxon rank sum test). BP: blood pressure; HR: heart rate.
abnormalities of cardiac rhythm, intraventricular conduction or evidence of left ventricular hypertrophy in any patient on GH or placebo.

**Exercise electrocardiography**

The exercise tolerance test was terminated because of shortness of breath, exhaustion, leg weakness, fatigue and, in only one patient, because of marked asymptomatic ST segment changes. None of the patients developed chest pain. Exercise time (min) increased on GH but not on placebo (GH: 8.45 ± 3.16 to 9.38 ± 2.42 min, sec, p < 0.01; placebo: 9.08 ± 4.35 to 9.50 ± 4.14 min, sec, NS), although the change was not significantly different between the two. There was no change in the maximal heart rate and blood pressure during exercise (Table 3) and nor was there any significant change in the rate × pressure product. The median maximal ST segment depression was no different before or after GH and placebo (Table 3). At 6 months, marked asymptomatic ST segment depression occurred in two patients (one on GH and one on placebo) and warranted stopping the exercise test in the former. Subsequent coronary angiography showed normal coronary arteries in both patients.

**Echocardiography and Doppler data**

The results of echocardiographic and Doppler assessments are detailed in Table 4. There was no significant change in left ventricular (LV) mass, LV mass index, LV internal diameter, posterior wall thickness or interventricular septal thickness on either treatment. The ejection fraction tended to increase on both GH and placebo but the changes were not statistically significant (Table 4). Isovolumic relaxation time (an index of left ventricular diastolic function) improved significantly in the GH group but not in the placebo group. However, at 6 months, the isovolumic relaxation time was no different on GH or on placebo. There was no significant change in the left ventricular filling, measured by the E/A ratio, on either GH or placebo.

To evaluate possible factors influencing changes in different echocardiographic variables, we correlated the changes to their pretreatment values and with changes in serum IGF-I using Spearman’s correlation coefficient (r). The changes on both GH treatment and placebo correlated negatively with the corresponding pretreatment values for both the isovolumic relaxation time (GH: r = -0.81, p = 0.001; placebo: r = -0.59, p < 0.02) and the ejection fraction (GH: r = -0.69, p = 0.01; placebo: r = -0.82, p = 0.0005). The changes in left ventricular mass index tended to correlate negatively with the pretreatment value in the GH treatment group (r = -0.45, p = 0.07) but not in the placebo group (r = -0.33, p < 0.16). The change in left ventricular internal diameter tended to correlate positively with its corresponding pretreatment value again in the GH treatment group (r = 0.45, p = 0.06) but not in the placebo group (r = -0.04, p = 0.80). There was no significant correlation between changes in the echocardiographic and Doppler parameters and in serum IGF-I on GH treatment.

**Serum IGF-I response and renal function**

Serum IGF-I increased significantly on GH treatment but not on placebo (mean ± SD) (GH: 92 ± 40 to 293 ± 197 (range 67–673) µg/l, p < 0.001; placebo: 92 ± 55 to 82 ± 40 (range 23–226) µg/l, NS). There

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**Table 4.** Echocardiographic and Doppler scanning data before and after growth hormone replacement in hypopituitary adults.

<table>
<thead>
<tr>
<th></th>
<th>Growth hormone</th>
<th>Placebo</th>
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<tbody>
<tr>
<td></td>
<td>0 months</td>
<td>6 months</td>
</tr>
<tr>
<td>Septum (cm)</td>
<td>0.75 ± 0.20</td>
<td>0.73 ± 0.10</td>
</tr>
<tr>
<td>PW (cm)</td>
<td>0.80 ± 0.17</td>
<td>0.83 ± 0.13</td>
</tr>
<tr>
<td>LVID (cm)</td>
<td>4.83 ± 0.47</td>
<td>4.85 ± 0.62</td>
</tr>
<tr>
<td>LVM (g)</td>
<td>169 ± 69</td>
<td>166 ± 66</td>
</tr>
<tr>
<td>LVM (g/m²)</td>
<td>89 ± 24</td>
<td>87.3 ± 22.2</td>
</tr>
<tr>
<td>EF (%)</td>
<td>69.7 ± 7.8</td>
<td>72.4 ± 4.3</td>
</tr>
<tr>
<td>E (cm/s)</td>
<td>69 ± 12</td>
<td>68 ± 10</td>
</tr>
<tr>
<td>E FVI</td>
<td>8.2 ± 2.0</td>
<td>8.6 ± 2.0</td>
</tr>
<tr>
<td>A (cm/s)</td>
<td>59 ± 14</td>
<td>59 ± 15</td>
</tr>
<tr>
<td>A FVI</td>
<td>4.8 ± 1.7</td>
<td>4.6 ± 1.5</td>
</tr>
<tr>
<td>E/A</td>
<td>1.2 ± 0.4</td>
<td>1.2 ± 0.3</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>98.1 ± 17.6</td>
<td>89.2 ± 11.5*</td>
</tr>
<tr>
<td>Aortic (cm/s)</td>
<td>114 ± 18</td>
<td>119 ± 25</td>
</tr>
<tr>
<td>Aortic FVI</td>
<td>21.1 ± 4.3</td>
<td>22.2 ± 4.1</td>
</tr>
</tbody>
</table>

*Values are means ± SD; *p < 0.05 (post-treatment vs pretreatment). Septum: interventricular septal thickness; PW: posterior wall thickness; LVID: left ventricular internal diameter; LVM: left ventricular mass index (LVM/LV/m²); EF: ejection fraction; IVRT: isovolumic relaxation time; Aortic: peak aortic velocity; Aortic FVI: flow velocity integral under A wave; A: atrial filling velocity; A FVI: flow velocity integral under A wave; E/A: E/A ratio; 4.14 min, sec, NS)
was no change in plasma urea, sodium, potassium or creatinine levels on either GH treatment or placebo.

Discussion

In this study we investigated the effects of 6 months of GH replacement therapy on cardiac structure and function in hypopituitary adults. Cardiac death due to myocardial infarction and heart failure has been shown to occur more commonly than normal in retrospective studies (1). During life, we have demonstrated previously an abnormal diastolic function and exercise induced-electrocardiographic abnormalities in symptom-free hypopituitary adults (8). Arterial wall abnormalities and an increased number of atheromatous carotid plaques also have been demonstrated (17). In the present study, we have used established methods to assess cardiac structure and function and a high workload treadmill protocol to assess exercise tolerance before and after GH treatment. Four months of GH treatment has been shown previously to be sufficient to demonstrate the anabolic action of GH (18). Although the GH dose in the present study was lower than in some previous studies, the mean serum IGF-I on GH increased significantly to the physiological range (and, in some cases, to the supraphysiological range). The patients in the present study were older than groups studied previously (18, 19).

There are two principal findings in this study. Firstly 6 months of GH treatment significantly increased the isovolumic relaxation time, reflecting an improvement in the diastolic function; secondly, exercise tolerance measured as exercise time significantly improved on GH treatment.

In experimental animals, the sizes of visceral organs, including the heart, are reduced after hypophysectomy (20) and increase with GH administration. In acromegaly, visceral organs are abnormally large (21, 22) and there is increased total body lean tissue mass (23). However, administration of physiological amounts of GH did not increase body weight in our GH-deficient subjects, in keeping with other studies (18, 24–27). However, GH has a potent effect on body composition, with a decrease in fat and an increase in lean tissue, including muscle (18, 24–28). Earlier experiments in rats (20, 29) had suggested this anabolic effect and that it might involve the heart as well as skeletal muscle. However, we found no evidence for anabolic effects on the myocardium because there was no change in the left ventricle mass. This is in agreement with the findings of Jorgensen et al. (18), who also showed no change in ventricular mass, but contrasts with the study by Cuneo et al. (19), who demonstrated a 5% increase in left ventricular mass. The reported increase in left ventricular mass was due to an increase of left ventricular dimension. In neither of the studies (18, 19) was there an increase in left ventricular wall thickness, and the increased mass was explained solely by increased ventricular cavity dimension. We could not confirm this finding in our larger group of patients. A possible explanation for this difference is that our patients started with a normal left ventricular mass and thus the potential for increase might have been limited. This may be supported by the trend of a negative correlation between the change in the left ventricular mass index and the corresponding pretreatment values.

In addition to a direct anabolic effect, the increased cardiac dimensions reported by other workers might reflect an increase in cardiac output secondary to increased heart rate, or an increase in stroke volume with a secondary increase in left ventricular dimensions. In the present study we found no significant changes either in heart rate or in stroke volume. Therefore, cardiac output did not increase on GH treatment. Previous studies demonstrated an increase in heart rate on GH therapy (18). In the present study, heart rate was slightly elevated in both GH and placebo groups before treatment and this may have prevented any further increase on GH. Why these patients had an elevated heart rate prior to treatment is not clear. Our patients received conventional thyroxine replacement therapy (Table 1) and they had no clinical or biochemical evidence of thyroxine over-replacement. Additionally, none of our patients had a clinical history of angina pectoris. However, two patients developed significant ST segment depression during exercise but subsequent coronary angiography was normal (8). The change in ejection fraction on GH correlated negatively with pretreatment ejection fraction values, suggesting that although the overall change was not statistically significant a greater increase occurred in those with a relatively lower ejection fraction and less change affected those with relatively normal ejection fraction. Although, a significant increase in myocardial contractility was reported following short-term high-dose GH treatment (9.6 U/day) in normal adult subjects (30), the authors suggested that their findings were secondary to increased peripheral blood flow. In addition, GH treatment in GH-deficient children (31) and in children with idiopathic short stature (32) was not associated with changes in echocardiographic parameters of left ventricular size and function when corrected for changes in body size.

The growth of cardiac muscle fibres is stimulated by GH and may be a direct action of GH or be mediated via IGF-I (33). Growth factors influence maturation of the normal cardiovascular system and also may be important for the structural changes in hypertension (34) and myocardial infarction (35). In two separate case reports, marked beneficial effects of GH treatment in severe cases of congestive heart failure were demonstrated. Cuneo et al. (36) reported that the administration of GH produced a major clinical improvement and an increase in peripheral circulation, as well as myocardial contractility in a patient.
with hypophysectomy due to Cushing’s disease who had resistant congestive heart failure. In another case report, a woman with Sheehan’s syndrome and severe dilated cardiomyopathy had a dramatic clinical, haemodynamic and histological improvement on GH administration and deteriorated after withdrawal of GH treatment (37).

Diastolic left ventricular function has not been evaluated in previous fully published studies (19, 24–27). In our study, the left ventricular relaxation improved, as judged from the isovolumic relaxation time. The significant negative correlation of the change in isovolumic relaxation time with the pretreatment values suggests that the improvement was greater in those with relatively abnormal diastolic function. Such a correlation was observed in patients both on GH treatment and on placebo, the difference being statistically significant only in the GH therapy group and these changes cannot be explained solely by the phenomenon of regression to the mean. The exact clinical significance of impaired left ventricular diastolic function is not known. A significant proportion of patients with congestive failure have normal systolic function (38). It has been suggested that abnormal diastolic function is a precursor of abnormal left ventricular diastolic function (38–40). These findings may be of particular importance because congestive heart failure was shown to be a frequent cause of cardiac morbidity and mortality in hypopituitarism (1). The earliest abnormality of left ventricular diastolic function is usually the prolonged isovolumic relaxation time followed by changes in left ventricular filling. In the present study, an improvement in isovolumic relaxation time was observed only in the GH treatment group and therefore it is suggested that more prolonged treatment may be required to observe changes in left ventricular filling (i.e. E/A ratio).

Improved exercise capacity could result from improved cardiac output or improved muscle strength or mass. Improved exercise capacity after 4–6 months of GH treatment has been demonstrated in previous studies (18, 25, 41). In only one study was a significant increase in isometric muscle strength observed in one muscle group (hip flexion) (42). In the present study there was no significant concomitant change in isometric muscle strength in any of five muscle groups (43). Although it has been suggested that the muscle strength-testing methods employed may have not been suitable for this population (42), the mechanism by which exercise tolerance improved remains uncertain.

No adverse effects of GH replacement on the cardiovascular system were seen. In particular, no increase in resting blood pressure was observed and there were no changes in cardiac rhythm.

We conclude that 6 months of GH replacement therapy in hypopituitary adults had some favourable cardiovascular effects, including a significant increase in exercise tolerance and improved left ventricular diastolic function without demonstrable changes in left ventricular mass, cardiac output or peripheral resistance. These beneficial haemodynamic responses may have implications for the future prognosis of hypopituitary adult patients on GH replacement therapy.

Acknowledgments. We are indebted to Professor H Jacob for the gift of human growth hormone.

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