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Impaired Cardiac Performance in Elderly Patients with Growth Hormone Deficiency

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ABSTRACT

Several evidences indicate that GH and/or insulin-like growth factor I (IGF-I) are involved in the regulation of cardiovascular function. In patients with childhood and adulthood-onset GH deficiency (GHD), the impairment of cardiac performance is manifest primarily as a reduction in the left ventricular (LV) mass (LVM), inadequacy of LV ejection fraction both at rest and at peak exercise, and abnormalities of LV diastolic filling. No study has been reported to date in elderly GHD patients that investigated cardiac function. In particular, it is unknown whether cardiac function is modified in accordance with patients' age as a physiological response to aging, as in normal subjects the rate and extent of LV filling are reduced with age. This study was designed to evaluate heart morphology and function, by echocardiography and equilibrium radionuclide angiography, respectively, in rigorously selected elderly patients with GHD but without evidence of other complications able to affect cardiac performance.

Eleven patients with hypopituitarism (6 men and 5 women, aged 60–72 yr) and 11 sex- age- and body mass index-matched healthy subjects entered this study. None of the patients and controls presented with or had previously suffered from other concomitant diseases, such as diabetes mellitus, coronary artery diseases, long-standing hypertension, and hyperthyroidism, which could affect cardiac function. All patients had been previously operated on via the transsphenoidal and/or transcranic route for nonfunctioning pituitary adenoma, meningioma, or craniopharyngioma, and 6 of them had been irradiated. Eight patients had FSH/LH insufficiency, 5 had TSH insufficiency, and 6 had ACTH insufficiency, appropriately replaced. All subjects were tested with the combined arginine plus GHRH test showing a GH response below 9 μg/L.

No significant difference was found in plasma IGF-I levels (49.2 ± 8.5 *vs.* 71.8 ± 7.5 μg/L) between patients and controls. However, IGF-I levels were lower than the normal range in 8 patients and 3 controls. Interventricular septum thickness (9.1 ± 0.2 *vs.* 9.1 ± 0.2 mm), LV posterior wall thickness (9.1 ± 0.2 *vs.* 9.0 ± 0.2 mm), and LVM after correction for body surface area (97.6 ± 1.8 *vs.* 99.9 ± 1.5 g/m^2) were similar in patients and controls. Similarly, the LV ejection fraction at rest was similar in patients and controls (57.1 ± 2% *vs.* 63.2 ± 2.5%; P = NS), and it was normal (≥50%) in all controls and in 10 of 11 patients. By contrast, the LV ejection fraction at peak exercise was markedly depressed in elderly GHD patients compared to age-matched controls (51 ± 2.5% *vs.* 73.3 ± 3%; $P < 0.001$). A normal response (≥5% increase compared to basal value) of LV ejection fraction at peak exercise was found in 8 controls (72.7%) and in 2 of 11 patients (18.2%). No difference was found in the peak rate of LV filling, whether peak filling rate was normalized to end-diastolic volume (2.5 ± 0.2 *vs.* 2.6 ± 0.2 end-diastolic volume/s) or stroke volume (4.3 ± 0.3 *vs.* 4.0 ± 0.3 stroke volume/s), between patients and controls. Finally, exercise duration was significantly shorter in elderly GHD patients than in age-matched controls (7.2 ± 2.1 *vs.* 9.1 ± 0.2 min; $P < 0.01$). In the patient group, the GH peak after arginine plus GHRH test was significantly correlated with the LV ejection fraction at rest (r = 0.822; $P < 0.01$), whereas IGF-I was significantly correlated with the peak rate of LV filling whether the peak filling rate was normalized to end-diastolic volume (r = −0.863; $P < 0.001$) or stroke volume (r = −0.616; $P < 0.05$) or expressed as the ratio of peak filling rate to peak ejection fraction rate (r = −0.736; $P < 0.01$). Disease duration was significantly correlated with heart rate at peak exercise (r = 0.614; $P < 0.05$) and with systolic and diastolic blood pressures both at rest (r = 0.745; $P < 0.01$ and r = 0.650; $P < 0.05$) and at peak exercise (r = 0.684; $P < 0.05$ and r = 0.617; $P < 0.05$).

The results of the present study demonstrated that, as in young and adult GHD patients, cardiac performance was impaired in elderly GHD patients, whereas cardiac mass was normal. These findings further support the potential usefulness of GH replacement in elderly hypopituitary patients. (*J Clin Endocrinol Metab* **84:** 3950–3955, 1999)

GH IS IMPLICATED not only in the somatic growth during childhood, but also in other physiological functions during adult age, such as the maintenance of muscle mass and strength, body composition, and energy metabolism (1, 2). In addition, several evidences indicate that GH and/or insulin-like growth factor I (IGF-I) are involved in the regulation of cardiovascular function (3–5). Adult subjects with GH deficiency (GHD) were shown to have increased cardiovascular risk factors, including abnormal levels of serum lipids and lipoproteins, decreased fibrinolytic activity, premature atherosclerosis, abnormal cardiac structure, impaired cardiac performance, and, ultimately, increased cardiovascular morbidity and mortality (6, 7). In patients with childhood and adulthood-onset GHD, the impairment of cardiac performance is manifest primarily as a reduction in the left ventricular (LV) mass (LVM), inadequacy of ejection fraction both at rest and during exercise, and abnormalities of LV diastolic filling (8–12). In these patients the impairment of the cardiovascular system is partially reverted after GH replacement therapy. In fact, GH

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replacement was found to increase cardiac output and LV ejection fraction and to improve other indexes of LV systolic and diastolic function (9–13).

As GH secretion physiologically declines with age, and in aging GH and IGF-I levels are low, the existence of a GHD syndrome in elderly patients is still debated. Although impairment of GH dynamics has been reported in elderly patients with GHD (14, 15), controversial data have been reported on the impairment of bone mass or body composition (16–18). No study has been reported to date in elderly GHD patients to investigate cardiac function. In particular, it is unknown whether LV function is modified in accordance with patients' age as a physiological response to aging, as in normal subjects a reduction of the rate and extent of LV filling has been reported (19–21).

This study was designed to evaluate heart morphology, by echocardiography, and function, by equilibrium radionuclide angiography, in a series of rigorously selected elderly patients with GHD but without evidence of other complications able to affect cardiac performance.

Subjects and Methods

Patients

Among 97 patients subjected to diagnostic screening for GHD after pituitary surgery, 20 patients were more than 60 yr of age, and 11 of them (6 men and 5 women, aged 60–72 yr) entered this study after their informed consent had been obtained. Eleven sex-, age-, and body mass index (BMI)-matched healthy subjects served as controls. None of the patients or controls presented with or had previously suffered from other concomitant diseases, such as diabetes mellitus, coronary artery diseases, long-standing hypertension, or hyperthyroidism, which could affect cardiac function. All patients and controls had a similar sedentary lifestyle; 2 patients and 2 controls were mild smokers (<10 cigarettes/day). None of the 22 subjects was obese (BMI, <30). Seven patients and 5 controls were moderately overweight (BMI, 25–30). Table 1 shows the patients' profile at study entry. All patients had been previously operated on via a transsphenoidal and/or transcranic route for nonfunctioning pituitary adenoma, meningioma, or craniopharyngioma, and 6 of them had been irradiated. Eight patients had FSH/LH insufficiency, 5 had TSH insufficiency, and 6 had ACTH insufficiency. Hypothyroidism and hypoadrenocorticism were treated with L-T_4 (50–100 μg, orally, daily) and cortisone acetate (25–37.5 mg/day). All males with hypogonadism were treated with testosterone depot (250 mg, im, monthly). Adequacy of hormone replacement therapy was periodically assessed by serum free thyroid hormones, testosterone, urinary free cortisol, and serum and urinary Na^+ and K^+ measurements. At study entry, these hormonal parameters were in the normal range for age in all patients. None of the patients had ever received GH treatment. Magnetic resonance imaging of the hypothalamus-pituitary region documented empty sella in 5 and residual tumor in 6. To avoid overestimation, the duration of the disease was calculated from the time of diagnosis, and the retrospective evaluation of symptoms presumably related to the pituitary disease was not considered.

Study protocol

At study entry, all subjects underwent a careful clinical evaluation, including electrocardiogram, blood pressure and heart rate measurements, routine blood and urine analysis, including total cholesterol and triglycerides levels, plasma IGF-I and IGF-binding protein-3 (IGFBP-3) assays, complete M-mode and two-dimensional echocardiographic evaluation, and equilibrium radionuclide angiography. All subjects were tested with the combined arginine (ARG) plus GHRH test (ARG+GHRH). ARG (arginine hydrochloride, Damor, Naples, Italy) was administered at a dose of 0.5 g/kg up to a maximal dose of 30 g slowly infused from 0–30 min; GHRH-(1–44), (Serono, Rome, Italy) was given at a dose of 1 μg/kg as an iv bolus at 0 min. Blood samples were taken every 15 min from −15 up to 90 min. According to recent studies (22–25), a GH response to ARG+GHRH below 9 μg/L was considered diagnostic of GHD.

Assays

Serum GH levels were measured by immunoradiometric assay using commercially available kits. The sensitivity of the assay was 0.2 μg/L. The intra- and interassay coefficients of variation (CVs) were 4.5% and 7.9%, respectively. Plasma IGF-I was measured by immunoradiometric assay after ethanol extraction. The normal range in over 60-yr-old subjects was 78–258 μg/L. The sensitivity of the assay was 0.8 μg/L. The intraassay CVs were 3.4%, 3.0%, and 1.5% for low, medium, and high points of the standard curve, respectively. The interassay CVs were 8.2%, 1.5%, and 3.7% for low, medium, and high points of the standard curve. Plasma IGFBP-3 was measured by RIA after ethanol extraction. The normal range in over 60-yr-old subjects was 2–4 mg/L. The sensitivity of the assay was 0.5 μg/L. The intraassay CVs were 3.9%, 3.2%, and 1.8% for low, medium, and high points of the standard curve, respectively. The interassay CVs were 0.6%, 0.5%, and 1.6% for low, medium, and high points of the standard curve.

Gated blood pool cardiac scintigraphy

In vivo labeling of red blood cells was performed with 555 megabecquerels (15 mCi) of ^{99m}Tc. Radionuclide angiography was performed at rest and during dynamic physical exercise in the 45° left anterior projection with a 15° craniocaudal tilt with the patient in supine position. A small field of view γ-camera (Starcam 300 A/M, General Electric, Milwaukee, WI) equipped with a low energy all purpose collimator was used. Data were recorded at a rate of 30 frames/cardiac cycle for the resting study and 16 frames/cardiac cycle for the exercise study on a dedicated computer system (General Electric). At least 200,000 counts/frame were acquired. Exercise studies were performed using a bicycle ergometer with a restraining harness to minimize patient motion under

TABLE 1. Patients' profile at study entry

Patients (sex/age)	Final diagnosis	Pituitary hormone deficiencies	Present treatment	GH peak at ARG+GHRH (μg/L)	Plasma IGF-I (μg/L)
1. m/60	Nonfunctioning adenoma	ACTH,FSH,LH,TSH	C,T,L-T	0.7	54
2. f/60	Craniopharyngioma	FSH,LH		0.4	45
3. f/62	Nonfunctioning adenoma	FSH,LH		0.2	8
4. m/63	Nonfunctioning adenoma			2.3	98
5. m/65	Nonfunctioning adenoma			4.9	85
6. m/65	Nonfunctioning adenoma	ACTH,FSH,LH,TSH	C,L-T	0.5	75
7. f/66	Nonfunctioning adenoma	ACTH,FSH,LH,TSH	C,L-T	4.0	30
8. m/67	Nonfunctioning adenoma	ACTH,FSH,LH,TSH	C,T,L-T	1.2	40
9. f/67	Nonfunctioning adenoma	ACTH,FSH,LH	C	7.9	24
10. m/68	Meningioma			1.8	60
11. m/72	Nonfunctioning adenoma	ACTH,FSH,LH,TSH	C,T,L-T	0.1	22

C, Cortisone acetate; T, testosterone depot; L-T, T_4.

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the camera. Exercise loads were increased by 25 watts every 2 min until angina, limiting dyspnea, or fatigue developed. No patient developed high grade ventricular arrhythmias necessitating termination of exercise. Heart rate and blood pressure (by cuff sphygmomanometer) were monitored during exercise at each stage.

Radionuclide angiography studies were analyzed using a standard commercial software system (General Electric). LV regions of interest were automatically drawn for each frame, and a background region of interest was also computer delineated on the end-systolic frame. After background correction, a LV time-activity curve was generated. Indexes of LV function were derived by computer analysis of the background-corrected time-activity curve. Ejection fraction was computed on the basis of relative end-diastolic and end-systolic counts. Peak LV ejection and filling rates were also calculated after a Fourier expansion with four harmonics. Peak ejection rate was computed as the minimum negative peak before end-systole, and peak filling rate was the maximum positive peak after end-systole on the first derivative of the LV time-activity curve. Both peak ejection rate and peak filling rate were computed in the LV counts/s, normalized for the number of counts at end-diastole, and expressed as end-diastolic volume (EDV) per s. When normalized for EDV, both peak ejection rate and peak filling rate are influenced directly by the magnitude of the ejection fraction (26). To minimize this effect, we also analyzed peak filling rate using two additional normalization methods; the peak filling rate was expressed relative to LV stroke volume (SV) per s and as the ratio of peak filling rate to peak ejection rate (27, 28). These two latter methods have the additional advantage of being background independent. The time to peak ejection rate was measured from the R wave, and the time to peak filling rate was measured relative to end-systole (minimal volume on the time-activity curve).

Echocardiography evaluation

Complete M-mode and two-dimensional analyses were performed using an ultrasound mechanical system equipped with a 3.5-mHz transducer (Apogee CX, Interspec, Ambler, CA). M-Mode and two-dimensional recordings were made with subjects in a lateral recumbent position according to the standardization of the American Society of Echocardiography (29). Interventricular septum and LV posterior wall thickness and LV end-diastolic and end-systolic cavity dimensions were measured by averaging the values for four consecutive cycles. Individuals reading the studies were blind as to whether the exam they were interpreting was that of an adult GHD patient or a normal control subject. Calculation of the LVM was performed using the Penn convention with the following regression-corrected cube formula: Echo LVM = $1.04[(ISV + LVID + PWT)^3 - (LVID)^3] - 14$ g (30). LV hypertrophy was considered when LVM values, corrected for body surface area (LVMi), were greater than or equal to 135 g/m^2 in males and greater than or equal to 110 g/m^2 in females.

Statistical analysis

Data are reported as the mean ± SEM. The statistical analysis was performed by means of the SPSS, Inc. (Cary, NC), package using ANOVA. Linear correlation analysis was carried out, calculating the Pearson's coefficient, to assess the relationship among different parameters. Stepwise multiple linear regression was performed to evaluate the relative importance of disease duration and GH and IGF-I levels on structural (IST, LVPWT, and LVMi) and functional (PFR, PER, and resting and exercising EF) parameters. $P < 0.05$ was considered statistically significant.

Results

Circulating IGFBP-3 (2.4 ± 0.3 *vs.* 2.5 ± 0.3 mg/L), glucose (97.1 ± 7.3 *vs.* 92.2 ± 1.6 mg/dL), and high density lipoprotein cholesterol levels (44.0 ± 5.7 *vs.* 47.1 ± 3.2 mg/dL), were similar in patients and controls. Plasma IGF-I were lower in patients than in controls (Table 2), although the difference was not statistically significant, and they were below the normal range in eight patients and three controls. Similarly,

TABLE 2. Cardiac parameters assessed by equilibrium radionuclide angiography and echocardiography in GH-deficient elderly patients and control subjects

	Controls (n = 11)	Patients (n = 11)	*P* value
Mean age (yr)	63.5 ± 0.9	64.7 ± 1.0	0.4
BMI (kg/m^2)	24.9 ± 1.2	26.1 ± 0.6	0.4
Peak GH levels after ARG+GHRH test (μg/L)	23.2 ± 2.3	2.2 ± 0.7	0.000
Plasma IGF-I (μg/L)	71.8 ± 7.5	49.2 ± 8.5	0.06
Disease duration (yr)		10.5 ± 1.0	
Echocardiography study			
Left ventricular mass index (g/m^2)	99.9 ± 1.5	97.6 ± 1.8	0.3
Interventricular septum thickness (mm)	9.1 ± 0.2	9.1 ± 0.2	1
Left ventricular posterior wall thickness (mm)	9.0 ± 0.2	9.1 ± 0.2	0.7
Equilibrium radionuclide angiography study			
Systolic blood pressure (mm Hg)			
At rest	125.4 ± 1.2	127.3 ± 7.1	0.8
Exercise	150.4 ± 2.1	176.4 ± 9.3	0.01
Diastolic blood pressure (mm Hg)			
At rest	80.9 ± 1.5	80.9 ± 4.1	1.0
Exercise	100.4 ± 4.4	101.8 ± 3.9	0.8
Heart rate (beats/min)			
At rest	72.0 ± 3.9	66.7 ± 2.3	0.3
Exercise	130.0 ± 6.2	127.8 ± 7.2	0.8
Left ventricular ejection fraction (%)			
At rest	63.2 ± 2.5	57.1 ± 2.1	0.07
Exercise	73.3 ± 3.0	51.0 ± 2.5	0.000
Exercise-induced changes (%)	15.8 ± 3.5	−10.2 ± 4.0	0.000
Left ventricular peak ejection rate (EDV/s)	3.7 ± 0.4	3.3 ± 0.2	0.4
Peak rate of left ventricular filling			
Peak filling rate (EDV/s)	2.6 ± 0.2	2.5 ± 0.2	0.7
Peak filling rate (SV/s)	4.0 ± 0.3	4.3 ± 0.3	0.5
Peak filling rate/peak ejection rate	0.7 ± 0.006	0.74 ± 0.004	0.000
Exercise duration (min)	9.1 ± 0.2	7.2 ± 0.1	0.000
Exercise capacity (watts)	97.7 ± 5.3	76.3 ± 4.0	0.004

Data are shown as the mean ± SEM.

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total blood cholesterol levels were significantly higher in patients than controls (231.7 ± 8.9 *vs.* 184.3 ± 6 mg/dL; $P < 0.001$). Serum triglycerides (182.2 ± 20.1 *vs.* 161.2 ± 9.5 mg/dL) and low density lipoprotein cholesterol (150.5 ± 21.6 *vs.* 117.2 ± 9.7 mg/dL) levels were also slightly higher in GHD patients than in controls, but the difference was not statistically significant.

Morphological study

Interventricular septum thickness, LV posterior wall thickness, and LVMi were similar in elderly GHD patients and controls (Table 2).

Functional study

At rest, no significant difference was found in systolic blood pressure between patients and controls, whereas systolic blood pressure at peak exercise was significantly higher in patients than in age-matched controls ($P < 0.05$). No significant difference was found in diastolic blood pressure or heart rate either at rest or at peak exercise between patients and controls (Table 2). The LV ejection fraction at rest was similar in patients and controls. In particular, the LV ejection fraction was normal (≥50%) in all controls and in 10 of 11 patients. By contrast, at peak exercise it was markedly depressed in elderly GHD patients compared to age-matched controls ($P < 0.001$). A normal increase (≥5% of basal value) in the LV ejection fraction at peak exercise was found in eight controls (72.7%) and two elderly GHD patients (18.2%; Fig. 1). The peak rate of LV filling, normalized to EDV or SV, was not different between patients and controls. On the other hand, the ratio of LV peak filling rate to peak ejection rate was significantly higher in GHD patients compared to controls ($P < 0.01$). Finally, the exercise duration was significantly shorter in elderly GHD patients than in age-matched controls ($P < 0.01$).

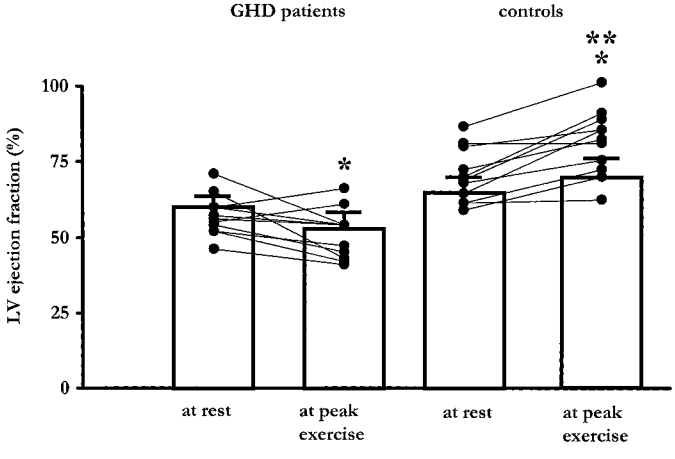

FIG. 1. LV ejection fraction at rest and at peak exercise in GHD patients and controls measured by radionuclide angiography. The *bars* represent the mean ± SEM. *, $P < 0.05$ compared to LV ejection fraction at rest; **, $P < 0.001$ to LV ejection fraction in GHD patients.

Correlation study

In the patient group, a significant relationship was observed between GH peak after the ARG+GHRH test and LV ejection fraction at rest (r = 0.822; $P < 0.01$). IGF-I was significantly correlated with the peak rate of LV filling, whether the peak filling rate was normalized to EDV (r = −0.863; $P < 0.001$) or SV (r = −0.616; $P < 0.05$) or expressed as the ratio of peak filling rate to peak ejection fraction rate (r = −0.736; $P < 0.01$). Disease duration was significantly correlated with heart rate at peak exercise (r = 0.614; $P < 0.05$) and with systolic and diastolic blood pressure both at rest (r = 0.745; $P < 0.01$ and r = 0.650; $P < 0.05$, respectively) and at peak exercise (r = 0.684; $P < 0.05$ and r = 0.617; $P < 0.05$, respectively).

The multiple regression analysis (Table 3) showed that IGF-I levels were the strongest predictor of diastolic filling, whether the peak filling rate was normalized to EDV or SV or expressed as the ratio of peak filling rate to peak ejection fraction rate. The peak GH level after the ARG+GHRH test was the strongest predictor of LV ejection fraction at rest, and consequently, it was the second strongest predictor of the peak filling rate normalized to SV.

Discussion

GHD is associated with changes in bone turnover and body composition, impairment in the serum lipid profile, reduction in exercise capacity, and abnormalities in cardiac function (1, 2). A reduction of LVM and an impairment of LV ejection fraction have been described in childhood and adult GHD patients (1, 2, 7, 31). Diastolic function was also impaired in GHD patients (31). Young adults with childhood-onset GHD had both reduced LVM and impaired systolic function (7), whereas patients with adulthood-onset GHD receiving conventional replacement therapy with T_4, cortisone, and sex steroids, but not GH were reported to have either a normal (10) or abnormal LVM and systolic function (7–9). In addition, no difference was reported in LV systolic and diastolic functions between childhood-onset and adulthood-onset patients with GHD and age below 40 yr (32). This finding indicated that when GHD occurred in young age, a detrimental effect on heart function could be observed in the great majority of patients. Cardiac abnormalities were partially reversed by GH replacement therapy, supporting a

TABLE 3. Results of multistep correlation analysis

Independent variable	Dependent variable	β	P
Peak filling rate (EDV/s)	IGF-I	−0.946	0.001
Peak filling rate (SV/s)	IGF-I	−0.882	0.005
	Peak GH after ARG+GHRH	−0.620	0.02
Peak filling rate/peak ejection rate	IGF-I	−0.804	0.00
Left ventricular ejection fraction at rest	Peak GH after ARG+GHRH	0.797	0.0000
	Disease duration	−0.497	0.02

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cause/effect relationship of GHD on cardiac performance (1, 2, 13, 31, 33). However, the impairment in cardiac function was only investigated in young/adult GHD patients, whereas no data are available in elderly ones.

The investigation of clinical symptoms in elderly patients with GHD is more difficult than in adults, as normal aging and GH deficiency share several clinical signs and symptoms, such as decreased muscle strength, increased osteoporosis and fracture risk, thinned skin, diminished psychosocial health, and sense of well-being. Because of these similarities, the relative GH insufficiency in the elderly has been postulated as one important factor contributing to their frailty (34). Aging is a process associated with a decline in the somatotroph axis function (35). Many of the catabolic sequelae found in normal aging have been attributed to decrease in circulating GH and IGF-I levels (36). At the age of 65 yr, spontaneous daily secretion of GH is reduced by 50–70%, and IGF-I levels decline progressively from the age of 40 yr. This hormonal pattern is distinct from the pathological decrease in GH and/or IGF-I levels associated with hypo-pituitarism. In the present study, the GH response to ARG+GHRH, a very potent GH stimulation test, was markedly decreased compared to that in healthy age-matched controls, in line with previous studies (14, 18). In addition, the median area under the curve of the GH profile, the median stimulated peak GH response to arginine, and the median serum IGF-I concentration, were reported to be lower in GHD elderly than in controls (35). However, in contrast with the clear-cut association between deficient/insufficient GH secretion and clinical symptoms reported in adult GHD patients, whether GHD could be responsible for clinical abnormalities in elderly patients is less clear. In a previous study we demonstrated that body composition was altered, and bone mass and turnover were impaired in elderly GHD patients compared to those in sex-, age-, and BMI-matched controls (18), in partial disagreement with the findings of Toogood *et al.* (16, 17). In the present study impaired cardiac performance was demonstrated at peak exercise, whereas both cardiac mass and diastolic function were normal. In the great majority of hypopituitary elderly (81.8%), at peak exercise the LV ejection fraction did not adequately increase, whereas systolic blood pressure increased significantly. Although aging is associated with a decrease in exercise capacity, hypopituitary patients had a significantly shortened exercise duration than age-matched healthy controls. Therefore, the results of cardiac function in elderly GHD patients cannot be interpreted as a physiological response of the heart less able to adapt to hemodynamic challenge in advancing age. In aging, a progressive loss of myocytes is observed, although myocyte volume per nucleus increases in both ventricles (37); additionally, although the overall size of the heart does not increase, LV wall thickness may increase slightly (37). Cardiac output tends to decrease with advancing age, both at rest and during exercise (38). These changes only partly reflect decreased demand and reduced skeletal mass. Heart rate, loading conditions, intrinsic muscle performance, and neurohormonal regulation are among the determinants of cardiac output that may be influenced by age, and with physical exercise, the maximal increase in the ejection fraction tends to be smaller in elderly than in younger people as an adaptive response. Despite the physiological decline in heart function in aging, the results of the present study demonstrated that elderly patients with GHD have a significantly reduced LV ejection fraction at peak exercise, suggesting that in these patients the heart is less able to adapt to hemodynamic challenge. The finding that IGF-I levels were the strongest predictor of diastolic filling and peak GH levels after the ARG+GHRH test was the strongest predictor of LV ejection fraction at rest confirmed the role played by the insufficient secretion of GH and IGF-I in determining the impaired cardiac performance in these patients. Thus, GH replacement therapy may be able to correct some abnormalities of cardiac function. Whether such correction results in a clinically significant improvement in well-being remains to be determined.

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