Cardiovascular Aspects in Acromegaly: Effects of Treatment

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Patients with acromegaly have significant morbidity and mortality, associated with cardiovascular disease. Acromegaly is often complicated by other diseases such as diabetes mellitus, hypertension, and coronary artery disease, so the existence of acromegalic cardiomyopathy remains uncertain. Cardiac performance was investigated in patients with uncomplicated acromegaly. A subgroup of hypertensive acromegalics was also studied. In addition, the effects of chronic octreotide therapy or surgery on cardiac structure and function in acromegaly were studied. Twenty-six patients and 15 healthy controls underwent gated blood-pool cardiac scintigraphy and echocardiography at rest and during exercise. Echocardiography was repeated after 6 months of octreotide therapy (n = 11). Cardiac scintigraphy was repeated after 12 and 24 months of octreotide therapy (n = 10) or 12 to 24 months after surgery (n = 8). ECG, blood pressure, and heart rate were monitored during cardiac scintigraphy. Left ventricular mass (LVM) was calculated from the findings of the echocardiography. Serum growth hormone (GH) levels and plasma insulin-like growth factor-1 (IGF-1) levels were monitored. LVM index was significantly higher ($P < .003$) in acromegalics than controls and in hypertensive acromegalics than normotensives, but all other indices of cardiac function were similar. Chronic octreotide decreased GH and IGF-1 levels and improved the structural abnormalities as measured by echocardiography. Chronic octreotide or surgery did not alter cardiac function parameters. Thus, important changes in cardiac structure and function occur in uncomplicated acromegaly, and improvements can be demonstrated after chronic octreotide therapy. Heart disease in acromegaly appears to be secondary to high circulating GH levels.

ACROMEGALY is a condition associated with significant morbidity and reduction in life expectancy.[1-3] In particular, mortality from cardiovascular and cerebrovascular causes is increased in acromegalic patients. Cardiovascular disease is due to both lipid metabolism abnormalities and congestive heart failure, which is a potential late complication of acromegaly.[4-6] Specifically, it has been shown that marked hypertrophy of both right and left ventricles is almost invariably present in acromegalic patients.[7,8] At rest, cardiac hypertrophy is associated with a depressed diastolic filling rate, whereas systolic function is normal, even when investigated using radionuclide angiography.[9-11] However, heart systolic function during physical exercise has been poorly investigated. Moreover, acromegaly is often complicated by other diseases, such as diabetes mellitus, hypertension, and coronary artery disease, which may affect heart function. Thus, the existence of acromegalic cardiomyopathy is still debated.

To further investigate the pathophysiology of cardiac performance in acromegaly, we assessed right and left ventricular systolic function at rest and during physical exercise, as well as filling dynamics, in rigorously selected patients who had active acromegaly but were free of other concomitant diseases. Moreover, due to the frequent association of acromegaly with arterial hypertension, a subgroup of hypertensive acromegalics was studied to investigate the potentially additive effects of hypertension on acromegalic heart dysfunction.

Growth hormone (GH) suppression during medical therapy or after surgery may cause a decrease of cardiac mass[12] and may modify cardiac function. Therefore, the effects of chronic octreotide therapy or surgery on cardiac structural and functional abnormalities were evaluated by Doppler echocardiography and radionuclide angiography.

PATIENTS AND METHODS

Patients

The patient population consisted of 47 acromegalics. Twenty-one were subsequently excluded from the study (due to diabetes mellitus in six, thyroid dysfunction in four, mitral valve regurgitation in one, atrial fibrillation in one, myocardial perfusion defects in two, and poor-quality echocardiographic tracing in seven). Clinical features of the remaining 26 patients who underwent gated blood-pool cardiac scintigraphy and echocardiography are shown in Table 1. Fifteen healthy subjects, sex- and age-matched with the patients, served as a control group. Echocardiography was repeated after 6 months of octreotide therapy at a dose of 150 to 600 μg/d in 11 patients. Gated blood-pool cardiac scintigraphy was repeated after 12 and 24 months of octreotide therapy at a dose of 150 to 600 μg/d in 10 patients and 12 to 24 months after surgery in eight patients.

Gated Blood-Pool Cardiac Scintigraphy

All patients and control subjects underwent supine exercise testing using a bicycle ergometer. ECG (aVF and V_5) was continuously monitored, as well as blood pressure and heart rate. Exercise load was raised by 25 W every 2 minutes up to 100 W. Equilibrium radionuclide angiography was performed at rest and during exercise in vivo using red blood cells labeled with 15 to 20 mCi technetium 99m–pyrophosphate, with a small field of view γ-cam-

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Table 1. Clinical Features of Acromegalic Patients

	Patients (sex/age)	ECG	Duration of Disease (yr)	Serum GH (μg/L)	Plasma IGF-1 (μg/L)
a) Normotensive					
1	f/20	N	7	14	250
2	f/22	N	1	50	430
3	f/26	N	1	25	380
4	f/29	N	8	45	650
5	m/30	N	3	20	210
6	m/31	N	6	20	470
7	f/37	N	3	110	500
8	f/40	N	10	22	700
9	m/42	N	10	115	980
10	m/46	N	15	30	379
11	f/48	LVH	19	40	620
12	m/48	N	1	13	280
13	m/51	N	1	450	550
14	m/54	N	20	32	355
15	m/55	N	1	22	480
16	m/62	N	20	38	600
17	f/67	LVH	7	348	1,000
Mean ± SD			7.8 ± 1.7	82 ± 30.1	519 ± 54.7
b) Hypertensive					
1	m/37	N	3	20	210
2	f/48	N	15	25	500
3	f/48	N	15	15	410
4	f/48	N	9	25	315
5	f/49	N	16	25	600
6	m/56	LAFB	11	38	807
7	f/58	LVH	10	80	910
8	f/58	N	15	15	661
9	f/60	LVH	10	38	636
Mean ± SD			11.6 ± 1.4	31.2 ± 6.7	561 ± 75.4

Abbreviations: f, female; m, male; LAFB, left anterior fascicular block; N, normal; LVH, left ventricular hypertrophy.

era equipped with a low-energy, all-purpose collimator. Details of the procedure used to quantify the ejection fraction (EF) and diastolic filling have been previously reported.[13]

Echocardiography

One- and two-dimensional echocardiography was performed using an ultrasound mechanical system equipped with 2.5- and 3.5-mHz transducers, according to the method previously reported,[7] to obtain left ventricular mass (LVM). LVM was calculated using the Penn convention and was indexed by body surface area.[14]

Assays

Serum GH was assayed by radioimmunoassay (Radim kits, Pomezia, Italy). Plasma insulin-like growth factor-1 (IGF-1) was assayed by immunoradiometric assay (IRMA) (Diagnostic System Laboratories, Webster, TX).

Statistical Analysis

Data are reported as the mean ± SD. Paired or unpaired Student's *t* tests and linear regression were used where appropriate.

RESULTS

Table 2 summarizes the hemodynamic data of the patients and the controls. When acromegalics were divided, taking into account the presence of hypertension, the LMV index was considerably higher in hypertensive compared with normotensive acromegalics (152 ± 31 *v* 115 ± 25 g/m^2, $P < .003$). Conversely, all other indices of systolic and diastolic function either at rest or during exercise were similar in hypertensive and normotensive patients. A significant correlation between LVM index and peak filling rate was observed ($r = -.54, P < .01$).

During chronic treatment with octreotide, decreases in GH (from 34 ± 6.5 to 4.6 ± 0.9 μg/L) and IGF-1 (from 767.4 ± 72.3 to 235 ± 10.3 μg/L) levels were found, and the thickness of the interventricular septum and left posterior wall, the LVM and LVM indexed by body surface area were reduced (Fig 1). Conversely, no significant changes in cardiac function parameters were found after either octreotide therapy (Fig 2) or surgery (Fig 3). However, after successful surgery, an increase in the EF was found (Fig 3).

CONCLUSIONS

These data demonstrate that in uncomplicated acromegaly, besides cardiac hypertrophy, there are also important alterations in systolic and diastolic function of both ventricles, leading to a significant impairment of cardiac performance. Moreover, an improvement of cardiac structural and functional abnormalities was observed by echocardiography after 6 months of octreotide therapy. Conversely, no significant improvement was observed by gated blood-pool cardiac scintigraphy. However, the series of patients studied by scintigraphy was too small to draw definitive conclusions. Nevertheless, it seems that heart disease is secondary to high circulating GH levels.

Table 2. Cardiac Function in the 26 Acromegalics and 15 Control Subjects

	Controls		Patients	
Cardiac Function	At Rest	During Exercise	At Rest	During Exercise
Heart rate (beats/min)	73.0 ± 10	141.0 ± 10	74.0 ± 13	135.0 ± 15
Systolic blood pressure (mm Hg)	120.0 ± 13	170.0 ± 22	129.0 ± 22	187.0 ± 26*
Diastolic blood pressure (mm Hg)	74.0 ± 9	92.0 ± 14	85.0 ± 15*	106.0 ± 15*
LV EF (%)	66.0 ± 6	75.0 ± 8	62.0 ± 9	61.0 ± 11*
LV peak filling rate (EDV/s)	3.1 ± 0.3		2.5 ± 0.7*	
RV EF (%)	49.0 ± 7	58.0 ± 11	47.0 ± 8	45.0 ± 13*
RV peak filling rate (EDV/s)	2.6 ± 0.5		1.8 ± 0.7*	
LVM index (g/m^2)	80.0 ± 18		129.0 ± 33*	

Abbreviations: LV, left ventricle; RV, right ventricle.
*$P < .05$ *v* controls.

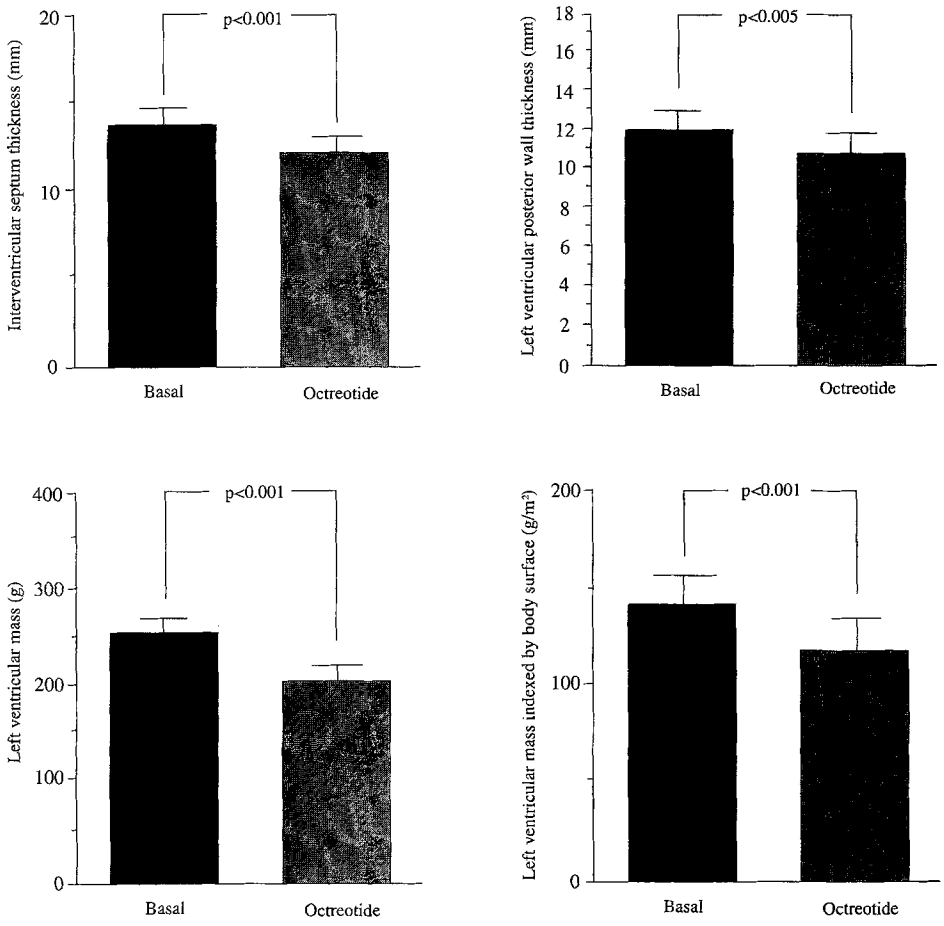

Fig 1. Effects of 6 months of treatment with octreotide on cardiac structure in 11 acromegalics.

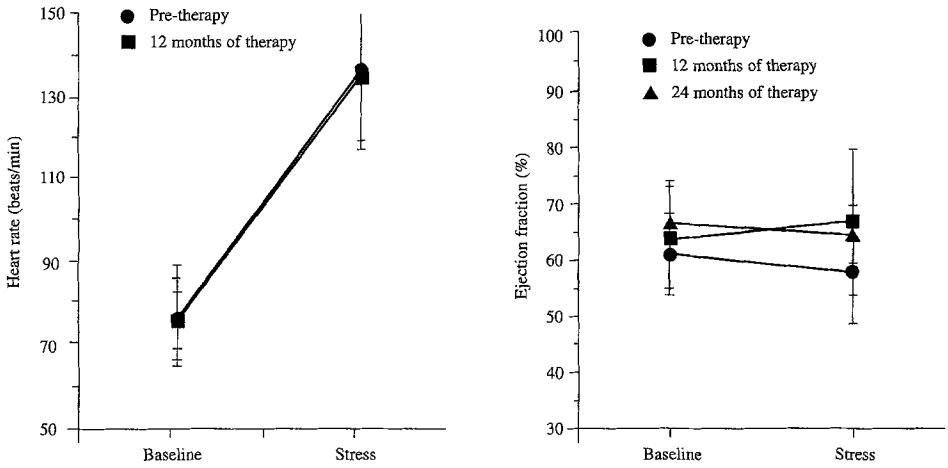

Fig 2. Effects of 12 and 24 months of treatment with octreotide on heart rate and EF at rest and during exercise in 10 acromegalics.

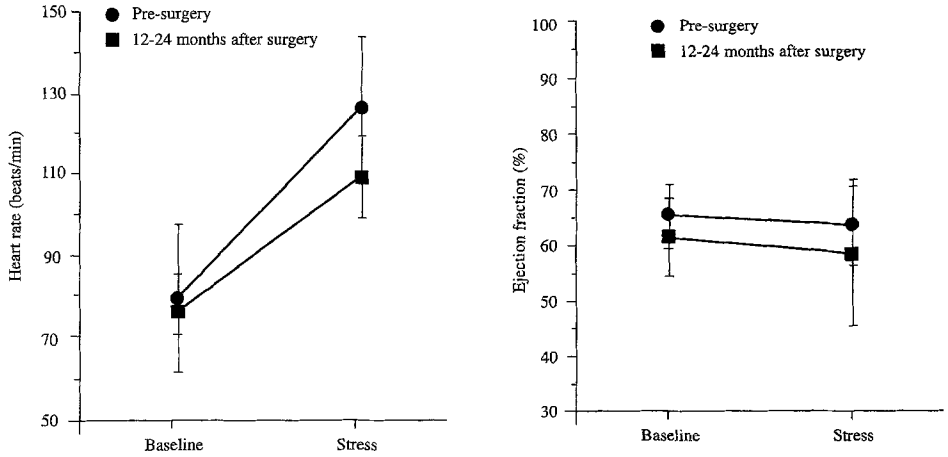

Fig 3. Heart rate and EF at rest and during exercise in 8 acromegalics 12 to 24 months after successful surgery.

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