Impaired Left Ventricular Diastolic Filling in Patients with Acromegaly: Assessment with Radionuclide Angiography

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Acromegaly is associated with increased cardiac morbidity and mortality, but it is not clear whether this is the result of a specific disease of heart muscle or of increased incidence of hypertension. **Methods:** Twenty-six patients with acromegaly (11 male and 15 female, mean age 45 ± 13 yr) and 15 and 12 age- and sex-matched normal controls underwent high temporal resolution radionuclide angiography and two-dimensional echocardiography at rest. **Results:** Normal controls and patients with acromegaly did not differ with respect to heart rate, ejection fraction, time to end systole, peak ejection rate (PER) and time to PER. In contrast, peak filling rate (PFR), normalized to end diastolic volume (EDV), or stroke volume (SV), or expressed as the ratio of PFR-to-PER was reduced ($p < 0.01$), time to PFR (TPFR) was prolonged ($p < 0.01$), and echocardiographic left ventricular mass index was higher ($p < 0.001$) in patients with acromegaly compared to normals. Patients with acromegaly were divided in normotensives (group 1, n = 17) and hypertensives (group 2, n = 9). Although left ventricular mass index was significantly ($p < 0.01$) higher in group 2 compared to group 1, PFR and time to PFR were not different between the two groups of acromegalic patients. In the entire group of patients with acromegaly significant relationships between left ventricular mass index and EDV/s ($r = -0.56$, $p < 0.01$), SV/s ($r = -0.73$, $p < 0.001$), and PFR/PER ($r = -0.61$, $p < 0.001$) were observed. **Conclusion:** Patients with acromegaly have impaired left ventricular diastolic filling at rest related to greater left ventricular mass index even in the absence of systemic hypertension.

Key Words: acromegaly; left ventricular diastolic filling; radionuclide angiography

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Cardiac involvement is a common occurrence in patients with acromegaly and plays an important role in worsening the prognosis of such patients (*1,2*). It has been previously demonstrated that acromegalic patients frequently show structural and functional left ventricular abnormalities (*3–6*). In particular, left ventricular hypertrophy associated with impaired diastolic filling at rest is a common finding in patients with acromegaly, even in the absence of decreased systolic performance (*7–9*). Systemic hypertension and coronary artery disease have been described in 13% to 60% of the patients with acromegaly (*10*), and among those affected by hypertension and coronary artery disease, cardiomegaly or congestive heart failure has been common.

Reduced rate and extent of left ventricular filling is frequently observed at rest in patients with hypertension or coronary artery disease (*11–15*) and is often evident when resting systolic function is preserved (*16*). Although acromegaly is associated with an increased cardiac morbidity and mortality (*8*), whether this is a specific disease of heart muscle or the result of increased incidence of hypertension, diabetes mellitus and coronary artery disease still has not yet been completely clarified. Therefore, the aim of this study was to assess left ventricular diastolic filling by equilibrium radionuclide angiography in patients with acromegaly without associated cardiac diseases and in a group of acromegalic patients with systemic hypertension.

MATERIALS AND METHODS

Study Population

Two subject groups were studied. The first group included 15 asymptomatic healthy adult normal volunteers (7 male and 8 female, with a mean age of 46 ± 13 yr). This represents a series of healthy subjects who volunteered for the investigational protocol after informed consent was obtained. Subjects had no evidence of underlying cardiovascular disease by medical history, physical examination and exercise electrocardiography.

The second group consisted of 26 patients with acromegaly (Table 1). There were 11 men and 15 women with a mean age of 45 ± 13 yr. Acromegaly was diagnosed by clinical features and evidence of a resting fasting serum concentration of growth hormone (GH) higher than 10 μg/l (normal range 1–5 μg/l and 1–10 μg/l for men and women) not suppressed by oral glucose load and of IGF-I above the normal range (normal range 20–50 μg/l and 26–73 μg/l for men and women). Plasma GH concentration was measured by radioimmunoassay using a commercial kit (Radim, Pomezia, Italy) and plasma IGF-I concentration was determined by immunoradiometric technique using a commercial kit (Eurogenetics, Torino, Italy). All patients had active acromegaly at the

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TABLE 1
Clinical Characteristics of the Acromegalic Patients

Patient no.	Age (yr)	Sex	Systemic hypertension	Plasma GH levels (μg/l)	Plasma IGF-1 levels (μg/l)
1	56	M	Yes	38	807
2	48	F	Yes	25	500
3	58	F	Yes	80	910
4	49	F	Yes	25	600
5	40	F	No	22	700
6	31	M	No	20	470
7	20	F	No	14	250
8	55	M	No	22	480
9	30	M	No	20	210
10	37	M	Yes	60	967
11	48	F	Yes	15	410
12	42	M	No	115	980
13	29	F	No	45	650
14	48	M	No	13	280
15	48	F	Yes	25	315
16	58	F	Yes	15	661
17	62	M	No	38	600
18	48	F	No	40	620
19	46	M	No	30	379
20	60	F	Yes	38	636
21	26	F	No	25	380
22	37	F	No	110	500
23	51	M	No	450	550
24	22	F	No	50	430
25	67	F	No	348	1000
26	54	M	No	32	355

time of the study (duration of disease 9 ± 6 yr). Sixteen patients had been unsuccessfully treated with surgery, radiotherapy and bromocriptine (singly or in combination). The remaining ten patients were newly diagnosed. The presence of diabetes mellitus, thyroid dysfunction or major cardiac disease (other than hypertension) was excluded in all patients. In order to exclude underlying coronary artery disease, all patients underwent ^{201}Tl myocardial scintigraphy. All patients gave informed consent and the study protocol was approved by the Ethical Committee of the Medical School of the University Federico II of Naples.

The acromegalic patients were classified into two subgroups according to the presence or the absence of arterial hypertension. Blood pressure values were normal in 17 patients. Nine patients had blood pressure readings above 150 mmHg systolic and 90 mmHg diastolic on at least three consecutive readings in the outpatient clinic of the internal medicine department. Antihypertensive therapy was discontinued for at least 3 wk before the study. Blood pressure was measured while the subjects sat after a 10-min rest in a darkened room with a standard mercury sphygmomanometer with a cuff of appropriate size, according to recommendations of the American Heart Association (*17*). Secondary causes of hypertension were ruled out in all patients by laboratory and x-ray studies.

Gated Blood-Pool Cardiac Scintigraphy

In vivo labeling of red blood cells was performed with 555 MBq (15 mCi) of ^{99m}Tc. Radionuclide angiography was performed at rest in the 45° left anterior projection at a 15° craniocaudal tilt with the patient in supine position. A small field of view gamma camera (Starcam 300 A/M, General Electric, Milwaukee, WI) equipped with a low energy all purpose collimator was used. Data were recorded at a frame rate of 30 frames/cardiac cycle on a dedicated computer system (General Electric, Milwaukee, WI). At least 200,000 counts/frame were acquired.

Radionuclide angiographic studies were analyzed using a standard commercial software (General Electric, Milwaukee, WI). Left ventricular regions of interest (ROIs) were automatically drawn for each frame and a background ROI was also computer delineated on the end systolic frame. After background correction, a left ventricular time-activity curve was generated. Indexes of left ventricular 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 left ventricular 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 as the maximum positive peak after end-systole on the first derivative of the left ventricular time-activity curve. Both peak ejection rate and peak filling rate were computed in left ventricular counts/sec, normalized for the number of counts at end-diastole and expressed as end-diastolic volume/sec (EDV/s). When normalized for end-diastolic volume, both peak ejection rate and peak filling rate are influenced directly by the magnitude of the ejection fraction (*15*). To minimize this effect, we also analyzed peak filling rate using two additional normalization methods: peak filling rate was expressed relative to left ventricular stroke volume (SV/s), and as ratio of peak filling rate to peak ejection rate (*18,19*). These two latter methods have additional advantage of being background independent. Time-to-peak ejection rate was measured from the R wave and time-to-

TABLE 2
Clinical Characteristics and Hemodynamic Data from Normal Control Subjects and the Acromegalic Patients

	Controls (n = 15)	Group 1 (n = 17)	Group 2 (n = 9)
Age (yr)	46 ± 13	42 ± 14	50 ± 7
Heart rate (bpm)	73 ± 13	74 ± 13	74 ± 13
Systolic blood pressure (mmHg)	120 ± 13	120 ± 16	148 ± 21*
Diastolic blood pressure (mmHg)	74 ± 9	78 ± 11	99 ± 12*

*$p < 0.001$ compared to normal controls and Group 1.
Group 1 = acromegalic patients with normal blood pressure; Group 2 = acromegalic patients with systemic hypertension

peak filling rate was measured relative to end-systole (minimal volume on the time-activity curve).

Determination of Left Ventricular Mass

Echocardiographic studies were performed on the same day of radionuclide ventriculography using an ultrasound mechanical system equipped with 2.5 and 3.5 MHz transducers (Apogee CX, Interspec Inc., Ambler, PA). Cardiac dimensions were measured by M-mode echocardiography according to the recommendations of the American Society of Echocardiography (*20*). The left ventricular mass was calculated from the end-diastolic wall thickness and cavity dimensions using the formula described by Devereux (*21*). The left ventricular mass index was calculated by dividing the mass by the body-surface area and expressed as grams per square meter. Individuals reading the echoes were blinded as to whether the study they were interpreting was that of an acromegalic patient or a normal control. Inter-observer and intra-observer reproducibility in our laboratory has been previously reported (*6,22*).

Statistical Analysis

Data was expressed as mean ± s.d. Unpaired t-test was used to compare control group with acromegalic patients. One way analysis of variance and unpaired t-test with Bonferroni's correction were used to compare the control group with the two subgroups of normotensive and hypertensive acromegalic patients. The relationships among parameters were assessed by linear regression analysis. P values less than 0.05 were considered statistically significant.

RESULTS

The normal control subjects and patients with acromegaly did not differ with respect to heart rate, ejection fraction, peak ejection rate, time-to-minimal volume and time-to-peak ejection rate. In contrast, there was evidence of impaired diastolic filling in acromegalic patients compared to normals. Particularly, the peak rate of left ventricular filling was lower in acromegalic patients than in normals, whether normalized to end-diastolic volume (2.5 ± 0.7 vs. 3.1 ± 0.3 EDV/s; $p < 0.01$), or stroke volume (4.0 ± 1.1 vs. 4.9 ± 0.4 SV/s; $p < 0.01$), or expressed as the ratio of peak filling rate to peak ejection rate (0.71 ± 0.2 vs. 0.92 ± 0.1; $p < 0.01$). Moreover, time-to-peak filling rate was significantly prolonged in acromegalic patients (195 ± 79 vs. 131 ± 51 ms; $p < 0.01$). The mean left ventricular mass index, derived from the echocardiographic dimensions, was significantly higher ($p < 0.001$) in the acromegalic patients (132 ± 32 g/m^2) compared to the control subjects (80 ± 18 g/m^2).

The acromegalic patients were subgrouped based on the presence or absence of arterial hypertension. In 17 patients (Group 1) the blood pressure values were normal. The remaining 9 patients (Group 2) were hypertensives. The clinical characteristics and the hemodynamic parameters of the normal control subjects and of the two groups of acromegalic patients are presented in Table 2. There were no significant differences in age or heart rate among normal control subjects, Group 1 and Group 2.

Indexes of left ventricular systolic function at rest were not significantly different between the two groups of acromegalic patients and between control subjects and both normotensive and hypertensive acromegalic patients (Table 3). Although all indexes of left ventricular rapid filling at rest were significantly different between normal subjects and both normotensive (Group 1) and hypertensive (Group 2) acromegalic patients (Table 3), no significant difference between Group 1 and Group 2 were observed (Table 3).

The mean left ventricular mass index derived from the echocardiographic dimensions was significantly higher in the acromegalic patients with hypertension compared to those without hypertension (Group 2: 152 ± 31 g/m^2, Group 1: 120 ± 26 g/m^2; $p < 0.01$) (Fig. 1). The entire group of acromegalic patients ($n = 26$) showed a significant linear relation between the left ventricular mass index and the resting peak filling rate, whether normalized to end-diastolic volume ($r = -0.56$, $p < 0.01$), or stroke volume ($r = -0.73$, $p < 0.001$) or expressed as the ratio of peak filling rate to peak ejection rate ($r = -0.61$, $p < 0.01$) (Fig. 2). Patient age, systolic and diastolic blood pressure did not correlate with resting peak filling rate and time-to-peak filling rate. Furthermore, with the entire group of acromegalic patients no relationships between the duration of disease, GH or IGF-1 levels and blood pressure, left ventricular mass index and indexes of left ventricular diastolic function were observed.

DISCUSSION

The natural history of acromegalic heart disease often results in a global enlargement of cardiac cavities leading to signs and symptoms of congestive heart failure (*2,3,10*). However, the high incidence of arterial hypertension, dia-

TABLE 3
Radionuclide Angiographic Data from Normal Control Subjects and the Acromegalic Patients

	Controls (n = 15)	Group 1 (n = 17)	Group 2 (n = 9)
LV Systolic Function			
Ejection fraction (%)	65 ± 5	61 ± 7	64 ± 9
Time-to-Minimal LV volume (msec)	334 ± 56	342 ± 57	348 ± 79
Peak ejection rate (EDV/s)	3.5 ± 0.5	3.5 ± 0.5	3.6 ± 0.8
Time-to-Peak ejection rate (msec)	127 ± 45	164 ± 54	134 ± 27
LV Diastolic Function			
Peak LV filling rate			
EDV/s	3.1 ± 0.3	2.6 ± 0.7*	2.3 ± 0.6†
SV/s	4.9 ± 0.4	4.4 ± 1.1*	3.6 ± 0.8†
PFR/PER	0.93 ± 0.1	0.74 ± 0.2†	0.64 ± 0.2†
Time-to-Peak filling rate (msec)	131 ± 51	184 ± 76*	216 ± 87†

* and † = $p < 0.05$ and $p < 0.01$ compared to normal controls.
Group 1 = acromegalic patients with normal blood pressure; Group 2 = acromegalic patients with systemic hypertension; EDV = end-diastolic volume; LV = left ventricular; PER = peak ejection rate; PFR = peak filling rate; SV = stroke volume.

betes mellitus and coronary artery disease in patients with acromegaly raises the question of whether the described cardiac abnormalities are secondary to the associated diseases, or are determined by a specific heart muscle disease. Postmortem studies showed an abnormal myocardium in 59% of patients with acromegaly, suggesting that cardiac dysfunction may be more common than clinical examination suggests (*23*). The results of the present study demonstrate that patients with acromegaly have impaired left ventricular diastolic filling at rest related to greater left ventricular mass index even in the absence of systemic hypertension, diabetes mellitus and coronary artery disease. These findings support the hypothesis that in patients with acromegaly there is a specific disease of heart muscle.

Left ventricular hypertrophy is a common finding in

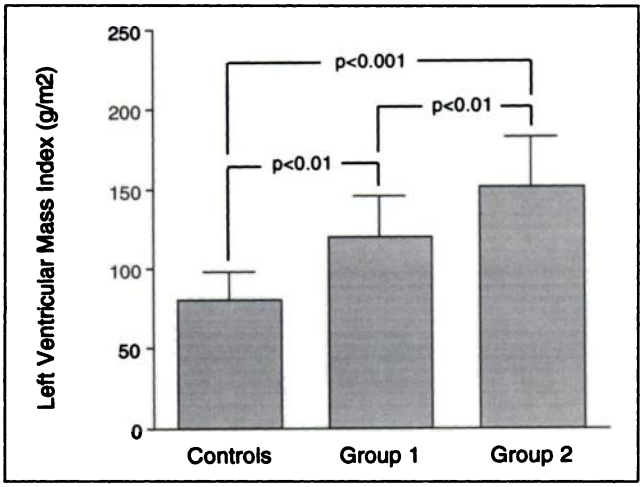

FIGURE 1. Comparison of left ventricular mass index between normotensive (Group 1) and hypertensive (Group 2) acromegalic patients and between both groups and normal subjects (Controls), respectively.

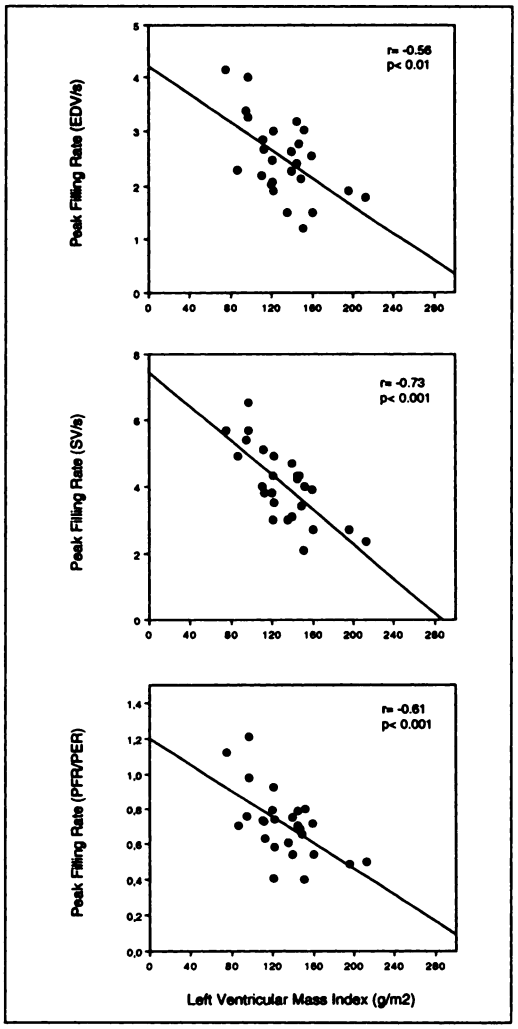

FIGURE 2. Relationship between left ventricular mass index and PFR at rest, normalized for end-diastolic volume (EDV) (upper panel), stroke volume (SV) (middle panel), and expressed as the ratio PFR to PER (lower panel).

patients with acromegaly, in the absence of decreased systolic performance (*7–9*). Although hypertrophy has the advantageous effect of preserving systolic function, it has important consequences for diastole (*24*). Increased myocardial mass and the resultant increases in interstitial connective tissue will increase left ventricular stiffness (*25–27*). In addition, left ventricular relaxation is impaired in left ventricular hypertrophy arising from chronic pressure overload (*28,29*). These passive and active processes will affect the rate and extent of left ventricular diastolic filling. Indeed, impaired left ventricular diastolic filling is common at rest in patients with acromegaly (*6–9*) and is often evident when resting systolic function is preserved.

Echocardiography has been previously used for assessing left ventricular function in patients with acromegaly (*5–7,10*). However, this technique is insensitive because of the assumptions necessary to calculate ejection fraction (*30*). It is now well established that radionuclide angiography is a more accurate method for assessing left ventricular systolic and diastolic function (*31*). Several studies have suggested that diastolic filling is more sensitive than ejection fraction for assessing early impairment in cardiac function, not only in coronary artery disease (*15*) but also in other conditions, such as hypertrophic cardiomyopathy (*32*) and systemic hypertension (*11–14,16*). However, only limited data on left ventricular diastolic function assessed by radionuclide angiography in acromegaly are currently available (*8*). In our study there was a highly significant difference in resting peak filling rate between controls and patients with acromegaly. In particular, diastolic peak filling rate was reduced and time to peak filling rate was prolonged, indicating impaired relaxation or increased chamber stiffness in patients with acromegaly. These findings are in agreement with those of previous studies (*6,8*). The impaired diastolic filling was evident even in those acromegalic patients without systemic hypertension.

Our results from patients with acromegaly support the concept that in such patients there is a specific disease of heart muscle. These findings were not related to patient age or gender. In normal subjects, there are important physiologic changes in left ventricular function that occur as part of the aging process, so that the rate and extent of left ventricular filling is reduced (*33,34*). The absence of such age-related effects in our acromegalic patients indicates that other factors contribute to the derangements in left ventricular diastolic function and override the effects of aging alone. Our data indicate that the severity of left ventricular hypertrophy is one such factor contributing importantly to impaired left ventricular diastolic filling in patients with acromegaly. Left ventricular mass index, as estimated by echocardiography, correlated significantly with indexes of diastolic filling at rest. The presence of arterial hypertension may have contributed to some extent to the development of left ventricular hypertrophy and of abnormal left ventricular filling in the hypertensive acromegalic subgroup. However, it must be stressed that acromegalic patients with normal blood pressure were also found to have increased left ventricular mass index and reduced peak filling rate compared to control subjects. Another possible mechanism of impaired left ventricular diastolic filling might include associated myocardial ischemia (*19*). In the present study, underlying coronary artery disease was excluded in all patients by exercise ^{201}Tl myocardial scintigraphy. These observations suggest that acromegalic cardiomyopathy is not simply secondary to systemic hypertension or coronary artery disease and support the hypothesis that there is a specific disease of heart muscle in acromegaly.

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