Impact of disease activity on left ventricular performance in patients with acromegaly

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Background In patients with acromegaly, abnormalities of systolic and diastolic left ventricular (LV) performance, mostly associated with hypertension or LV hypertrophy, have been reported. We used 2-dimensional/Doppler echocardiographic methods and tissue Doppler imaging (TDI) to elucidate the impact of disease activity on LV function in patients with acromegaly.

Methods In a prospective study design, 15 patients with active acromegaly (AA group; mean age–adjusted serum insuline-like growth factor–I [IGF-I] level, 420 ± 170 ng/mL, mean growth hormone nadir during 75-g oral glucose load, 12.3 ± 30.1 μg/L), 18 patients with cured (n = 14, mean IGF-I level 205 ± 115 ng/mL, mean growth hormone nadir during glucose load 0.72 ± 0.34 μg/L) or well-controlled (n = 4, normal age-adjusted ranges of IGF-I levels with medication with somatostatin analogues 354 ± 88 ng/mL) acromegaly (CA group), and 24 control subjects (control group) underwent 2-dimensional/Doppler echocardiographic measurements, including assessment of the Tei index (isovolumic contraction time and isovolumic relaxation time divided by ejection time). Systolic and diastolic mitral annular velocities (peak systolic velocity, peak early diastolic velocity [E'], peak late diastolic velocity [A'], E'/A' ratio) were derived from pulsed TDI.

Results No significant differences between study groups were observed with respect to muscle mass and systolic parameters, such as ejection fraction, fractional shortening, and peak systolic velocity. In patients with AA, E' and the E'/A' ratio were lower than in control and CA subjects (AA 6.8 ± 1.7 cm/s, control 10.0 ± 1.7 cm/s, CA 9.1± 3.0 cm/s, $P < .01$ AA vs control, $P < .05$ AA versus CA, AA 0.68 ± 0.22, control 0.98 ± 0.16, CA 0.89 ± 0.37, $P < .01$ AA vs control and CA, respectively). In comparison with control subjects and patients with CA, patients with AA had a reduced mitral peak velocity of early/late filling ratio (AA 0.78 ± 0.22 m/s, control 1.12 ± 0.33 m/s, CA 1.11 ± 0.36 m/s, $P < .05$ AA vs control and CA) and a prolonged deceleration time (AA 223 ± 41 ms, control 188 ± 26 ms, CA 185 ± 25 ms, $P < .05$ AA vs control and CA). The Tei index was significantly elevated in patients with AA in comparison with control subjects and patients with CA (AA 0.54 ± 0.13, control 0.40 ± 0.09, CA 0.44 ± 0.10, $P < .05$ AA vs control and CA). No significant differences were observed between control subjects and patients with CA with respect to mitral flow–derived variables, TDI parameters, and the Tei index.

Conclusion Disease activity has a significant impact on LV performance in patients with acromegaly. In subjects with active disease, diastolic dysfunction and beginning impairment of overall LV performance are present. In patients with cured/well-controlled disease, systolic and diastolic function appear normal. (Am Heart J 2002;144:538-43.)

In patients with acromegaly, cardiovascular abnormalities, such as systemic hypertension and coronary artery disease, have been found to represent the major cause of increased morbidity and mortality rates.[1,2] In such patients, congestive heart failure frequently develops even in the absence of predisposing factors, such as hypertension, diabetes mellitus, or cardiac arrhythmias,[3] so that a specific acromegalic cardiomyopathy has been postulated.[4-6] Features of this cardiomyopathy include left ventricular (LV) hypertrophy and impaired cardiac function leading to reduced exercise capacity.[7] These cardiac abnormalities seem to be related to the duration of exposure to elevated growth hormone (GH) and insulin-like growth factor–I (IGF-I).[8,9] However, little is known about the impact of disease activity on systolic and diastolic performance in patients with acromegaly.

Echocardiographic studies in patients with acromegaly have mainly focused on structural abnormalities,[10-12] whereas functional data, particularly on diastolic function, are rather scant. Tissue Doppler

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imaging (TDI) is a new echocardiographic method that has been shown to complement established parameters in evaluation of systolic and diastolic LV performance.[13-15] The peak early diastolic velocity of the mitral annulus (E′) has been found to behave as a preload-independent index of LV relaxation.[13,15] As a measure of overall LV performance, a Doppler scan-derived index was introduced by Tei.[16] The Tei index, which is defined as the summation of the isovolumic contraction time and the isovolumic relaxation time (IRT) divided by the ejection time (isovolumic contraction time + IRT/ejection time), provides useful information about disease severity in patients with cardiac amyloidosis[17] and dilated cardiomyopathy[16] and in subjects with mild to moderate congestive heart failure of various origins.[18] The aims of this investigation were to study LV systolic and diastolic function in patients with active acromegaly (AA) and cured/well-controlled acromegaly (CA) with conventional 2-dimensional/Doppler echocardiography and to assess the diagnostic role of TDI and the Tei index in this setting.

Methods

Study population

In a prospective study design, 33 patients with acromegaly (15 female/18 male) were included in the study. The diagnosis of acromegaly was made on the basis of the presence of the classical clinical features, elevated age-adjusted serum IGF-I concentration, and lack of suppressibility of serum GH concentration below 1 μg/L during a 75-gram glucose oral load. For study inclusion, significant coronary artery stenosis (>70% luminal narrowing of an epicardial coronary vessel) was excluded either with cardiac catheterization (n = 5) or with a negative clinical history and a negative bicycle exercise stress test (n = 24) or radionuclide perfusion exercise stress test (n = 4). Patients with acromegaly with a history of systemic hypertension or diabetes mellitus according to established definitions[19,20] were excluded.

Patients were divided into those with AA or CA according to the consensus statement of criteria for cure of acromegaly.[21] Cure was defined as IGF-I levels within the age-adjusted normal range and a nadir GH value after a 75-gram oral glucose load (OGTT) of <1 μg/L. Patients treated with somatostatin analogues were defined as having well-controlled conditions with an age-adjusted normal range of IGF-I levels (25-39 years 114 to 492 μg/L, 40-54 years 90 to 360 μg/L, ≥55 years 71-290 μg/L). With these criteria, 14 patients were found to have cured acromegaly (mean IGF-I level, 205 ± 115 ng/mL, mean GH nadir during OGTT 0.72 ± 0.34 μg/L) and 4 patients were found to have well-controlled acromegaly (mean IGF-I level 354 ± 88 ng/mL). Patients with acromegaly with cured or well-controlled disease constituted the CA group (n = 18, 9 female/9 male, aged 53 ± 15 years). Fifteen patients were found to have AA (6 female/9 male, aged 54 ± 15 years, mean age-adjusted serum IGF-I level 420 ± 170 ng/mL, mean GH nadir during OGTT 12.3 ± 30.1 μg/L). In the CA group, 4 patients were treated with somatostatin analogues (2 lanreotide [Ipsen, Paris, France] 30 mg every 2 weeks intramuscularly, 2 octreotide acetate 30 mg Sandostatin LAR [Novartis Pharma, Nürenberg, Germany] every 4 weeks intramuscularly), whereas 4 patients in the AA group received medication (1 lanreotide 30 mg every 2 weeks intramuscularly, 3 octreotide acetate 30 mg Sandostatin LAR every 4 weeks intramuscularly). All patients with acromegaly with anterior pituitary insufficiency, which met the criteria for study inclusion, were receiving adequate substitution therapy at the time of the study. Twenty-four asymptomatic age-matched subjects without history of systemic hypertension, diabetes mellitus, or coronary artery disease and with no evidence of heart disease served as a control group (14 female/10 male, aged 59 ± 9 years).

Hormone assays

Serum GH levels were determined with a chemiluminescence immunometric assay (Nichols Institute Diagnostics GmbH, Bad Nauheim, Germany). The assay was calibrated against the World Health Organization first international standard (80/505) for human GH. Normal range was ≤5 μg/L. Intraassay and interassay coefficients of variation for a low point of the standard curve were 5.4% and 7.9%, respectively. Plasma IGF-I concentrations were measured with an immunoradiometric assay (Nichols Institute Diagnostics GmbH). The assay was calibrated against the World Health Organization first international reference reagent 87/518. Intraassay and interassay coefficients of variation for low IGF-I concentrations were 2.4% and 5.2%, respectively. All other parameters were determined with routine methods.

Echocardiographic examination

Images were taken with a 3.75-MHz sector probe with a Toshiba SSA 380 A Power Vision machine (Nasu Works, Ottawara, Japan). The echocardiographic examination was done according to the guidelines of the American Society of Echocardiography.[22] From Doppler scan recordings of the mitral inflow and the aortic outflow, the following variables were derived: peak velocity of early (E) and late (A) filling, deceleration time, and IRT.[23] The index isovolumic contraction time plus IRT divided by ejection time (Tei index) was calculated as described by Tei.[16] Pulsed wave TDI was performed with activation of the TDI function on the same machine. From the apical 4-chamber view, a 5-mm sample volume was located at the septal side of the mitral annulus.[15] From TDI recordings, the following measurements were performed: peak systolic velocity (S′), E′, A′, and the E′/A′ ratio.

Reproducibility

Intraobserver variability was assessed in 10 patients by repeating the measurements on 2 occasions (1-12 days apart) with the same basal conditions. To test the interobserver variability, the measurements were performed offline from video recordings by a second observer who was unaware of the results of the first examination. Variability was calculated as the mean percent error, derived as the difference between the 2 sets of measurements, divided by the mean of the observations.

Statistical analysis

Data are expressed as the mean ± SD. Variables derived from echocardiographic measurements were compared

Table I. Clinical data

	Control (n = 24)	AA (n = 15)	CA (n = 18)
Age (y)	59 ± 9	54 ± 15	53 ± 15
Sex (m/f)	10/14	9/6	9/9
BSA (m^2)	1.9 ± 0.2†	2.0 ± 0.2	2.1 ± 0.3
Disease duration (y)	–	8 ± 8	6 ± 5
SBP (mm Hg)	127 ± 18	124 ± 17	125 ± 19
DBP (mm Hg)	84 ± 14	83 ± 11	82 ± 16
Heart rate (beats/min)	73 ± 8	76 ± 10	74 ± 10
LVMMI (g/m^2)	110 ± 27	123 ± 31	124 ± 35
LVDDI (cm/m^2)	2.7 ± 0.2†	2.6 ± 0.2	2.4 ± 0.3
LVSDI (cm/m^2)	1.7 ± 0.2	1.6 ± 0.2	1.6 ± 0.2
LVDVI (ml/m^2)	46 ± 14*	66 ± 25	55 ± 16
LVSVI (ml/m^2)	17 ± 6*	25 ± 9	23 ± 8
SVI (ml/m^2)	30 ± 9*	40 ± 16	33 ± 12

SBP, Systolic blood pressure; *DBP*, diastolic blood pressure; *BSA*, body surface area; *LVMMI*, left ventricular muscle mass index; *LVDDI*, left ventricular end-diastolic diameter index; *LVSDI*, left ventricular end-systolic diameter index; *LVDVI*, left ventricular end-diastolic volume index; *LVSVI*, left ventricular end-systolic volume index; *SVI*, stroke volume index.
*$P < .05$ control versus AA group.
†$P < .05$ control versus IA group

Table II. Two-dimensional echocardiographic and Doppler derived variables

	Control (n = 24)	AA (n = 15)	CA (n = 18)
EF (%)	60 ± 9	58 ± 9	59 ± 9
FS (%)	33 ± 6	35 ± 9	35 ± 5
E (m/s)	0.74 ± 0.19	0.56 ± 0.21*	0.70 ± 0.13
A (m/s)	0.67 ± 0.11	0.71 ± 0.22	0.68 ± 0.22
E/A ratio	1.12 ± 0.33	0.78 ± 0.22*	1.11 ± 0.36
DT (ms)	188 ± 26	223 ± 41*	185 ± 25
ICT (ms)	49 ± 15	69 ± 27*	52 ± 25
ET (ms)	316 ± 45	286 ± 43†	302 ± 36
IRT (ms)	77 ± 19	85 ± 32	80 ± 30
ICT + IRT (ms)	126 ± 28	154 ± 28*	132 ± 35
ICT + IRT/ET "Tei-Index"	0.40 ± 0.09	0.54 ± 0.13*	0.44 ± 0.10
E/E′	8 ± 3	10 ± 4	9 ± 4

EF, Ejection fraction; *FS*, fractional shortening; *DT*, deceleration time; *ICT*, isovolumic contraction time; *ET*, ejection time.
*$P < .05$ compared with other groups.
†$P < .05$ AA versus control group.

among the distinct groups with 1-way analysis of variance and post hoc Bonferroni analysis. For variables with a nonnormal distribution, a 1-way analysis of variance on ranks was used. Receiver operating characteristic (ROC) curve analysis was generated to test the predictive discrimination of patients with AA and CA. To analyze the predictive discrimination of mitral flow and TDI-derived variables and the Tei index, the areas under the curve were generated and tested for significant differences.[24] A difference was considered significant at a P value of $<.05$.

Results

Clinical data

The 3 study groups did not differ significantly with respect to age, heart rate, muscle mass index, systolic and diastolic blood pressure, and LV systolic diameters. In the CA group, the body surface area was increased and LV diastolic diameters were reduced in comparison with control subjects. No significant difference was found in disease duration between the AA and CA group. In the AA group, LV end-diastolic and end-systolic volumes were elevated and the stroke volume was increased as compared with control subjects (Table I) .

Two-dimensional and Doppler echocardiographic measurements

The 3 study groups did not differ significantly with respect to ejection fraction, fractional shortening, peak mitral A velocity, IRT, and the E/E' ratio. In the AA group, peak mitral E velocity and the E/A ratio were reduced, and the deceleration time was prolonged in comparison with the control and CA groups. The Tei index was significantly elevated in the AA group compared with the control and CA groups. No significant difference was seen between control subjects and patients with CA with respect to mitral A velocity, E/A ratio, deceleration time, or Tei index (Table II).

With ROC curve analysis, the E/A ratio and the deceleration time yielded an area under the curve of 0.69 ± 0.08 (± standard error of the mean [SEM]) and 0.65 ± 0.10, respectively, for separation of patients with AA and patients with CA. With E/A ratio <0.95 cm/s and deceleration time >205 seconds as cut-off values, sensitivity and specificity for identification of patients with AA were 76% and 68% for the E/A ratio and 71% and 68% for the deceleration time. The Tei index yielded an area under the curve of 0.68 ± 0.09 for separation of patients with AA and patients with CA. With a Tei index of ≥0.48 as a cutoff value, patients with AA were separated from patients with CA with a sensitivity of 76% and a specificity of 68%.

TDI analysis of mitral annulus velocity

TDI analysis of mitral annulus velocity was readily obtained in all study subjects (Table III). No significant differences between the study groups were observed with respect to S′ and A′. In the AA group, the E′ and the E′/A′ ratio were significantly reduced in comparison with the control and CA groups. Representative examples of a control subject and a patient with AA are shown in Figures 1 and 2.

With ROC curve analysis, E′ and the E′/A′ ratio yielded an area under the curve of 0.74 ± 0.07 (± SEM) and 0.73 ± 0.08 (± SEM) for separation of patients with AA versus CA. With E′ <7.9 cm/s and E′/A′ ratio <0.83 as cutoff values, sensitivity and specificity

Table III. TDI-derived variables

	Control (n = 24)	AA (n = 15)	CA (n = 18)
S′ (cm/s)	8.3 ± 1.3	7.8 ± 1.7	8.2 ± 1.5
E′ (cm/s)	10.0 ± 1.7*	6.8 ± 1.7	9.1 ± 3.0†
A′ (cm/s)	10.0 ± 1.7	10.3 ± 1.8	11.1 ± 2.7
E′/A′ ratio	0.98 ± 0.16	0.68 ± 0.22‡	0.90 ± 0.32

*$P < .01$ control versus AA group.
†$P < .05$ CA versus AA group.
‡$P < .01$ compared with other groups.

for identification of patients with AA were 74% and 80% for E′ and 82% and 70% for E′/A′. The predictive discrimination of TDI-derived variables (E′, E′/A′ ratio) yielded no statistically significant differences as compared with mitral flow–derived variables (E/A ratio, deceleration time) or Tei index.

Reproducibility

Intraobserver and interobserver variability for measurements derived from TDI analysis of mitral annulus velocity (S′, E′, A′, E′/A′) and Doppler scan–derived parameters (E, A, E/A ratio, deceleration time, IRT, Tei index) ranged from 2% to 11%.

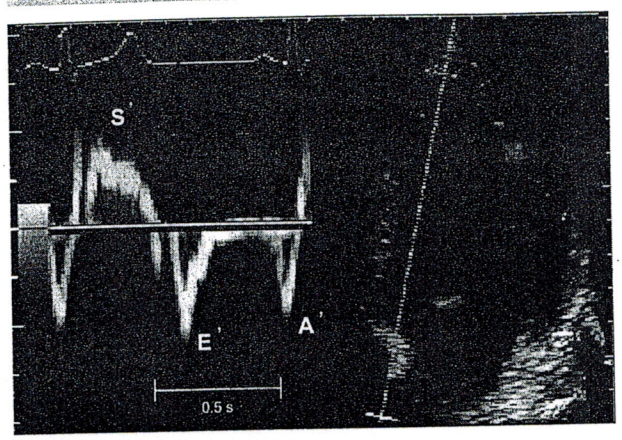
Discussion

The results of our study show that disease activity strongly impacts LV performance in patients with acromegaly. In subjects with active disease, diastolic dysfunction and beginning impairment of overall LV performance are present, as shown with conventional mitral flow–derived variables, TDI analysis of mitral annulus velocity, and assessment of the Tei index (Tables II and III, Figures 1 and 2). In this study, patients with acromegaly with concomitant coronary artery disease, systemic hypertension, diabetes mellitus, or pituitary insufficiency were excluded. Thus, known factors with potential influence on LV function were eliminated. Our findings indicate that functional changes may precede morphologic changes, mandating a careful echocardiographic work-up in patients with acromegaly.

Features of acromegalic cardiomyopathy

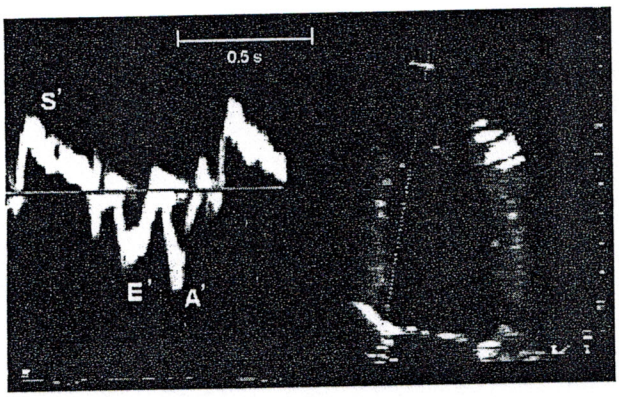
In acromegaly, cardiovascular complications reduce life expectancy and double the death rate as compared with the healthy population, especially after the age of 45 years.[9] In these patients, heart failure symptoms may develop even in the absence of systemic hypertension, diabetes mellitus, coronary artery disease, or other predisposing factors.[3] In this context, clinical and experimental studies suggest that chronic GH and IGF-I excess lead to the development of an acromegalic cardiomyopathy.[4,12] This cardiomyopathy is characterized by interstitial fibrosis, lymphomononuclear infiltration, and areas of monocyte necrosis. With conventional 2-dimensional and M-mode echocardiography, structural abnormalities, such as concentric LV hypertrophy and increased muscle mass, have been identified in patients with acromegaly.[10-12,25] However, echocardiographic studies that provide functional data, particularly with impact of disease activity, are scarce.[5,26] With inclusion of patients with active or cured/well-controlled disease and an age-matched control, our study was designed to focus on the impact of disease activity on LV performance in these patients.

Figure 1



TDI tracings of mitral annulus in control subject. *Right side*, 2-dimensional echocardiogram shows sample volume of pulsed wave TDI located at septal side of mitral annulus. *Left side*, measurement of S′, E′, and A′. Note magnitude of E′.

Figure 2



TDI tracings of mitral annulus in patient with AA. Note reduction of E′ with resulting inversion of E′/A′ ratio.

Previous echocardiographic studies in patients with acromegaly

With conventional Doppler scan analysis of the mitral inflow, LV filling abnormalities have been reported by different investigators in patients with acromegaly.[5,9,11,25] Colao et al[6] studied 20 asymptomatic patients with acromegaly estimated to have had the disease for no longer than 5 years. In these subjects, an increased LV muscle mass and a prolonged IRT were observed, suggesting beginning impairment of relaxation.[9] In these patients, a 6-month treatment with octreotide lead to a significant decrease of cardiac mass and interventricular septum thickness,[11] whereas functional parameters remained nearly unchanged. However, in these studies, patients with acromegaly with concomitant systemic hypertension, diabetes mellitus, or coronary artery disease were not separately evaluated. In addition, the analysis of mitral flow–derived parameters was limited to the measurement of the isovolumic relaxation period, and TDI-derived parameters or the Tei index were not considered.

Lopez-Velasco et al[5] studied the relation of LV function to the presence and duration of GH hypersecretion and to the presence or absence of systemic hypertension. Independent from a history of hypertension, patients with AA were found to have a higher LV muscle mass and a prolonged IRT in comparison with healthy control subjects.[5] However, in patients with active disease, the mitral E/A ratio did not differ from that of control subjects. This may be attributed to the younger age of the patients with active disease or to the small sample size of the study population (control subjects n = 17, patients with active nonhypertensive acromegaly n = 6).

In conclusion, these previous studies suggest but do not provide direct evidence for diastolic dysfunction and beginning impairment of overall cardiac performance in patients with AA. In our study, cardiac performance was assessed with conventional 2-dimensional/Doppler scan measurements but also with TDI analysis of mitral annulus velocity. In patients with AA, the mitral E/A ratio was reduced and the deceleration time was prolonged in comparison with subjects with cured/well-controlled disease and healthy control subjects (Table II). Most importantly, the results of conventional mitral flow–derived parameters were confirmed with TDI analysis of mitral annulus velocity (Table III, Figures 1 and 2). In contrast to mitral flow–derived variables, TDI-derived measurements have been shown to be less preload dependent.[13-15]

Mercuro et al[27] previously used pulsed wave TDI in 18 patients with AA and 13 healthy control subjects. In patients with acromegaly, the regional E′/A′ ratio was reduced and the regional IRT derived from TDI was prolonged in comparison with control subjects.[27] However, in this study, no attempt was made to differentiate between subjects with active or cured/well-controlled disease (ie, the impact of disease activity on LV performance was not systematically evaluated). However, the results of this study and our findings support evidence for the adjunctive role of TDI in the work-up and management of patients with acromegaly.

In our study, the Tei index was significantly elevated in patients with AA (Table II). This finding was attributable to a significant prolongation of isovolumic contraction time and shortening of ejection time (Table II), strongly suggesting also beginning impairment of systolic function in patients with AA.[16] However, other systolic parameters, such as ejection fraction or fractional shortening, did not allow for a separation between subjects with active or cured/well-controlled disease. Further studies have to show the potential clinical impact of this promising new index.

Limitations

Because of exclusion of patients with acromegaly with coronary artery disease, systemic hypertension, diabetes mellitus, or pituitary insufficiency, the final study population was small. Thus, the results should be confirmed in larger trials.

Conclusion

The results of our study indicate that diastolic dysfunction and beginning impairment of overall cardiac performance are present in subjects with AA most likely because of a causal relationship between GH hypersecretion and cardiac function. In patients with cured/well-controlled disease, systolic and diastolic function appear normal. TDI analysis of mitral annulus velocity and assessment of the Tei index complement the evaluation of LV performance and might be a useful addition in the diagnostic work-up of patients with acromegaly.

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