CLINICAL STUDY

Baseline and stimulated catecholamine secretion in normotensive patients with active acromegaly: acute effects of continuous octreotide infusion

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Abstract

Objective: Alterations in catecholamine plasma levels may contribute to the cardiovascular complications of acromegaly. Since few data are available on the catecholamine secretory dynamics in active acromegaly and no evidence exists on catecholamine variations during GH decrease, we studied acromegalic patients before and during octreotide administration.

Methods: We evaluated the catecholamine responses to upright posture and a cold press test (CPT) in 11 acromegalic (A) patients before and during continuous administration of octreotide (500 μg/24 h by s.c. pump) compared with 11 normal (N) subjects.

Results: All the acromegalic patients showed left ventricular cardiac hypertrophy. The cardiovascular responses to upright posture were similar between normal subjects and acromegalics both before and during octreotide treatment. The basal levels of norepinephrine (NE) were significantly higher in A patients compared with N subjects (423 ± 45 vs 264 ± 32 pg/ml, P < 0.05) and decreased during therapy (291 ± 32 pg/ml; P < 0.01). The increase in plasma NE during upright posture was significantly lower in A than in N subjects (P < 0.01), but was restored to normal during octreotide treatment. CPT increased systolic and diastolic blood pressure, pulse rate and NE plasma levels in N (P < 0.05) but not in A subjects both before and during octreotide treatment.

Conclusions: Our data demonstrate the presence of increased basal NE levels in acromegalic patients with a defective sympathetic response to stimuli. Short-term octreotide infusion is able to induce a reduction in the basal levels of NE and a normalization of the catecholamine response to posture.

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Introduction

Acromegaly, in addition to causing cosmetic disfigurement, is accompanied by arthropathy, peripheral neuropathy and heart disease (1). Cardiovascular complications of acromegaly, including hypertension, premature coronary artery disease, congestive heart failure and cardiac arrhythmia are a major cause of morbidity and mortality in affected patients (2). Baseline Doppler studies performed in acromegalic patients showed that changes in ventricular size consisted of increased wall thickness and reduced chamber volume, with consequent abnormalities in left ventricular diastolic filling (3, 4) and unaltered systolic function.

Echocardiographic assessments of acromegalic patients show the heart to be affected early in the disease (1, 4–7). A cause-effect relationship between growth hormone (GH) hypersecretion and cardiovascular complications of acromegaly has been suggested (1, 8, 9), and normalization of growth hormone secretion, obtained by octreotide administration, is associated with a significant improvement in cardiac activity (1, 3). The reduction of left ventricular mass seems correlated with the decrease in GH and insulin-like growth factor (IGF)-I levels (1).

Few data are available on baseline and stimulated catecholamine plasma levels in acromegalic patients. Increased urinary excretion of catecholamines (10) or norepinephrine (11) has been reported. However, Cryer (12) found normal plasma catecholamine concentrations in unselected acromegals both in the supine resting state and in response to standing. Although it has been suggested that plasma catecholamines are elevated only in active acromegaly (13), other authors (14) noted abnormal plasma epinephrine and norepinephrine responses to bromocriptine and luteinizing hormone releasing hormone (LHRH) in acromegalic patients, and it has been shown that thyrotropin releasing hormone (TRH) may stimulate norepinephrine release in acromegals (13).
Recently, it has been shown that GH alters tissue sensitivity to epinephrine (15, 16); particularly, in vitro and in vivo studies in animals have shown that GH treatment increases the response of adipose tissue to the lipolytic action of epinephrine (15, 17), even if some reports appear conflicting (18).

Very few data obtained with appropriate methodologies are available on the catecholamine secretory dynamics in active acromegaly, and no data have so far been reported on the influence that the normalization of GH levels, obtained via octreotide administration, exerts on catecholamine levels in acromegalic patients.

The aim of our study was, therefore, to investigate the cardiovascular and catecholamine responses to physiological stimuli for the sympathoadrenal system in acromegalic patients before and during acute normalization of GH levels by continuous octreotide infusion.

Patients and methods

Patients

We have studied 11 newly diagnosed acromegalic normotensive (systolic blood pressure $\leq$140 mmHg, diastolic blood pressure $\leq$90 mmHg) patients during octreotide (500 $\mu$g/24 h) or placebo (isotonic saline solution) administration by subcutaneous continuous pump infusion (Microjet MC 20, 55397A, Miles Italiana, Milan, Italy). The patients entered the study in a randomized order, i.e. six patients were studied first during octreotide therapy while five patients were studied first during active acromegaly (placebo infusion). The mean age of the patients (four men and seven women) was 45 $\pm$ 3 years. The diagnosis of acromegaly was established clinically and confirmed by high GH levels, not suppressed below 2 $\mu$g/l after oral administration of 100 g glucose, by high IGF-I levels for age and sex, and by computed tomographic demonstration of a pituitary tumor. No alteration in pituitary function was observed in the patients included.

The control group consisted of eleven age- (42 $\pm$ 5 years) and weight-matched subjects (eight female and three male) with normal electrocardiogram, normal arterial blood pressure, and no physical findings or history of cardiac diseases. They underwent only one session with subcutaneous infusion of saline solution.

The study was approved by the Local Ethical Committee and all the subjects gave their informed consent to the experimental procedure.

Protocol

All the subjects were studied over two 48-h hospitalization periods, separated by, at least, a 3-week interval. All the subjects were prohibited from the use of alcohol, caffeine, cacao, banana, vanilla and nicotine during the 24 h before the study. A portable pump treatment with subcutaneous infusion of octreotide (500 $\mu$g/24 h) or isotonic saline infusion was begun in each subject at the time of admission to the hospital. The decision to use constant infusion of octreotide and not the standard subcutaneous injections of the drug was based on previous studies showing a better suppression of GH levels with the constant infusion compared with a regimen of intermittent injections (19).

During the first session, patients underwent hematological examinations, a baseline pulmonary function test, and an electrocardiogram to rule out signs of cardiac and pulmonary diseases. All active acromegalic and control subjects were submitted to echocardiographic examination at basal conditions. Blood samples for IGF-I (0800 h) and GH (every 4 h, from 0800 h until 0800 h of the following day) assays were withdrawn. On the second day of hospitalization, all subjects underwent tests in the upright position and were subjected to a cold pressure test (CPT).

Test procedures

At 0700 h, after an overnight fast, a 18-gauge catheter was placed in an antecubital vein and 0.9% saline infusion was started at a slow rate. After the subjects had remained supine for at least 60 min, blood samples for the basal determination of GH, norepinephrine (NE) and epinephrine (E) were withdrawn and systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse rate (PR) were measured. Patients were asked to stand up and blood samples for GH, NE, and E determination were withdrawn at 5 and 10 min. Blood pressure and pulse rate were measured with an automated cuff device (Lifestat 200-Physiocontrol, Richmond, USA) immediately before blood sampling. Patients were then asked to sit, and blood sampling and pressure determination were performed at 25 and 35 min. Thereafter, a cold pressure test was performed by immersing the sitting subject’s right hand up to the wrist in iced water (1°C) for 2 min. At 37, 40 and 50 min blood samples were withdrawn for GH, NE, and E determination, and SBP, DBP, and PR were measured. All active acromegalic and control subjects underwent, at basal conditions, an echocardiographic examination. They were studied in the left lateral position: sector scans with color flow mapping were used to screen for wall motion or valvular abnormalities. Chamber dimensions, left ventricular thickness and functional systolic indexes were calculated from M-mode echocardiograms recorded according to the recommendations of the American Society of Echocardiography (20, 21). Left ventricular mass index was calculated with the method described by Devereux and Reichek (22), and left ventricular end-diastolic volume was calculated with the Teicholtz formula (23).

After at least a 3-week interval from the first session, a second session was performed following the same procedures as described above.
Assays
Plasma GH levels were measured by a commercial fluororimmunometric assay (Wallac, Kabi Pharmacia, Milan, Italy); the intra- and interassay coefficients of variation for GH were 3% and 5% respectively. The sensitivity of the assay was 0.5 IU/l.

Plasma catecholamines were determined by using reverse phase high performance liquid chromatography with electrochemical detection (24); the intra-assay coefficients of variation for E and NE were 4% and 3% respectively. The interassay coefficients of variation for E and NE were 8% and 7% respectively. The lowest sensitivity level of the assay was 29 pmol/l for NE and 16 pmol/l for E.

Statistics
Data are presented as means ± S.E.M. The normal distribution of data was assessed using the Kolmogorov-Smirnov test, and parametric (repeated measures analysis of variance followed by multiple comparison test for catecholamine and blood pressure) and non parametric (Wilcoxon test for GH) tests were applied when appropriate. A P value less than 0.05 was considered significant.

Results
The echocardiographic indexes are reported in Table 1; left ventricular hypertropy was present in all the acromegalic patients when compared with control subjects.

Hormone levels
Mean daily plasma GH levels in acromegalic (A) patients before octreotide infusion were 10.5 ± 3.1 ng/ml and during continuous infusion of octreotide at a dose of 500 μg/24 h they were 2.7 ± 1.9 ng/ml. A significant decrease in GH plasma levels was observed in all the patients during octreotide infusion (P < 0.001). 

Upright posture test
Basal systolic and diastolic blood pressure were not different between normal (N) subjects (SBP: 116 ± 4 mmHg; DBP: 70 ± 3 mmHg) and acromegalic patients (SBP: 123 ± 10 mmHg; DBP: 80 ± 6 mmHg) (F = 0.5 and F = 1.8 respectively; P = not significant (NS) for both). Pulse rate was similar (F = 1.1, P = NS) between the two groups studied (N = 71 ± 4 beats/min; A = 68 ± 4 beats/min). The upright test did not change systolic and diastolic blood pressure values in either N (SBP: F = 0.8, DBP: F = 0.5, P = NS for both) or in A patients (SBP: F = 0.7, DBP: F = 0.9, P = NS for both) (Fig. 1); a significant increase in PR during the upright test was observed in N (F = 5.1, P < 0.05) and in A (F = 9.1, P < 0.001) subjects. The net increase in PR during the upright test was not different between N and A patients (F = 1.0, P = NS) (Fig. 2).

Basal levels of NE were higher in acromegalic patients compared with normal subjects (423 ± 45 vs 264 ± 32 pg/ml respectively; P < 0.05) (Fig. 3). The upright test induced a significant increase in NE levels both in N (F = 8.4, P < 0.01) and in A patients (F = 7.9, P < 0.01) (Fig. 3). The net increase in NE plasma levels was also significantly lower (F = 6.7, P < 0.05) in A patients compared with N subjects when basal levels of NE were considered as covariates in the analysis, and when the data were analyzed as percentage increase from basal values (Fig. 4). Basal E levels were not different between N and A patients (31 ± 4 pg/ml vs 27 ± 6 pg/ml; the upright test did not change E levels either in N (F = 0.3, P = NS) or in A patients (F = 0.6, P = NS; Fig. 3).

Table 1 Echocardiographic parameters and functional indexes in 11 normal subjects and 11 acromegalic patients during active acromegaly. Values are means ± S.E.M.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal subjects</th>
<th>Acromegalic patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interventricular septal thickness (mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic</td>
<td>7 ± 1</td>
<td>11 ± 1*</td>
</tr>
<tr>
<td>Systolic</td>
<td>13 ± 1</td>
<td>16 ± 2*</td>
</tr>
<tr>
<td>Posterior wall thickness (mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic</td>
<td>7 ± 1</td>
<td>9 ± 1*</td>
</tr>
<tr>
<td>Systolic</td>
<td>13 ± 1</td>
<td>16 ± 1*</td>
</tr>
<tr>
<td>Left ventricular internal diameter (mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic</td>
<td>48 ± 2</td>
<td>51 ± 2.5</td>
</tr>
<tr>
<td>Systolic</td>
<td>30 ± 1</td>
<td>31 ± 2</td>
</tr>
<tr>
<td>End-diastolic volume (ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic</td>
<td>105 ± 3.5</td>
<td>130 ± 5</td>
</tr>
<tr>
<td>Systolic</td>
<td>33 ± 3</td>
<td>44 ± 1.5</td>
</tr>
<tr>
<td>Mass (g)</td>
<td>150 ± 9</td>
<td>287 ± 7*</td>
</tr>
<tr>
<td>Shortening fraction (%)</td>
<td>36 ± 2</td>
<td>35 ± 1</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>68 ± 3.5</td>
<td>67 ± 0.5</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>84 ± 3</td>
<td>77 ± 7</td>
</tr>
</tbody>
</table>

* P < 0.05 vs normal subjects.
Cold pressure test

The cardiovascular responses to the CPT are shown in Figs 1 and 2. CPT induced a significant increase in systolic blood pressure in N (F = 6.3, \( P < 0.01 \)) but not in A patients (F = 1.6, \( P = NS \)) (Fig. 1). The increase in DBP during CPT was significant in N (F = 5.1, \( P < 0.01 \)) but not in A patients (F = 0.9, \( P = NS \)) (Fig. 1). Pulse rate increased in N (F = 4.2, \( P < 0.05 \)) but not in A (F = 1.1, \( P = NS \)) (Fig. 2) during CPT. The NE levels significantly changed during CPT in N (F = 4.9, \( P < 0.05 \)) but not in A (F = 1.5, \( P = NS \)) (Fig. 3); CPT induced a significant increase in E levels in N (F = 3.6, \( P < 0.05 \)) while it did not influence E levels in A (F = 1.6, \( P = NS \); Fig. 3).

Treated compared with untreated acromegalics

Octreotide treatment did not influence the basal SBP (122 ± 10 mmHg), DBP (78 ± 6 mmHg) and PR (61 ± 4 beats/min) in A patients (\( P = NS \)); in octreotide-treated patients the increase in SBP (F = 1.4, \( P = NS \)) and DBP (F = 1.5, \( P = NS \)) during the upright test was not significant and did not differ from the before treatment value (Fig. 1). PR during upright posture significantly increased (F = 9.6, \( P < 0.01 \)) in octreotide-treated patients and the magnitude of the increase was similar to that seen before treatment (Fig. 2). Cold pressure test did not induce significant variations in SBP (F = 0.77, \( P = NS \)), DBP (F = 0.3, \( P = NS \)) or PR (F = 0.2, \( P = NS \)) in octreotide-treated patients (Figs 1 and 2).

Octreotide treatment induced a significant decrease in basal plasma NE levels (291 ± 32 pg/ml; \( P < 0.01 \) vs before treatment). The NE response to the upright test was significant during octreotide treatment (F = 19.1, \( P < 0.01 \); Fig. 4) and was higher compared with untreated patients (F = 6.7, \( P < 0.05 \); Fig. 4). Octreotide treatment did not influence the NE response to CPT in A patients (F = 1.0, \( P = NS \); Fig. 3).

Neither basal plasma E (30 ± 6 pg/ml) in A patients (\( P = NS \)) nor E response to the upright test...
Discussion

Cardiovascular abnormalities represent the main clinical problem in patients with acromegaly. Catecholamines are involved in the pathogenesis of several cardiovascular diseases such as hypertension and chronic heart failure as well as ventricular hypertrophy. Previous studies have not been able to clarify if acromegalic patients may have abnormal circulating catecholamine levels per se. In fact, a significant increase in resting plasma levels of norepinephrine in patients with active acromegaly has been shown by several authors, although other authors were not able to confirm this finding (10–14).

Possible explanations for these discrepancies may be found in the different criteria of inclusion: in one study, six out of the eight acromegals studied had hypogonadism which, by itself, can influence norepinephrine levels (25). Concomitant hypertension also represents a confounding factor in the evaluation of catecholamine secretion in acromegalic patients.

Our data clearly show that in normotensive acromegalic patients with no other endocrine alterations and elevated circulating levels of GH, basal levels of catecholamines were higher than those observed in normal subjects.

A strict relationship between NE plasma levels and muscle sympathetic nerve activity has been reported (26). We cannot exclude the possibility that the changes in the catecholamine plasma levels were induced by altered clearance rate rather than altered secretion; however, there is no data in the literature suggesting a GH or octreotide involvement in catecholamine clearance.

A stimulatory role of GH on catecholamine release has been proposed (27). However, GH administration did not result in increased catecholamine levels (28), neither GH-releasing peptides nor IGF-I stimulated catecholamine release (Ong et al., personal communication, 29), and Sverrisdottir et al. (30) suggested an increased activity of the sympathetic nervous system in GH-deficient patients. At the moment, very little data are available on baseline and stimulated catecholamine plasma levels in acromegalic patients.

A cardiac hyperkinetic syndrome, including increased heart rate and cardiac output and decreased vascular resistance, could be found in the initial stage of acromegaly and in normal subjects after 1-week exposure to GH excess (31).

It could be hypothesized that baseline norepinephrine secretion is increased as a counteregulatory mechanism in response to hemodynamic and cardiovascular modifications induced by elevated GH levels. The postulated vasodilating effects of GH (32, 33) may be sufficient to increase sympathetic activity, that in turn may induce heart rate abnormalities. Reduction in the protodiastolic left ventricular filling, increase in intraventricular septum thickness and other modifications that are related to the acromegalic cardiomyopathy, could also induce an augmented sympathetic drive. However, our patients showed no differences in basal and stimulated heart rate compared with normal subjects, although octreotide treatment tended to reduce heart rate (Fig. 2).

Among the physiological maneuvers which have been used to elucidate the function of the autonomic
nervous system in humans, the catecholamine response to cold and to upright posture still represents one of the most reliable, standardized and accurate evaluations (34).

We have found a significantly blunted postural change of NE in acromegalic patients before therapy; the percentage increase in NE during the upright test was fourfold less than in normal subjects, indicating a defective baroreceptor influence on catecholamine secretion. The finding of increased muscle sympathetic activity with concomitant impairment of baroreceptor control of heart rate and sympathetic traffic is a distinct feature of mild congestive heart failure (35), and it could be hypothesized also in acromegalic patients, although no clinical and/or echocardiographic signs of heart failure were found in our patients.

The original finding of our study was that short-term octreotide infusion was able to restore basal NE levels to the normal range; furthermore, the NE response to standing was ameliorated and similar to that of normal subjects, suggesting a rapid restoration of a normal sympathetic activity and baroreceptor activation in acromegalic patients after acute lowering of circulating GH levels. A treatment arm of octreotide infusion in normal subjects would have strengthened these data and clarified the role of octreotide per se on catecholamine levels, but this implied some ethical and practical problems in our hospital. Thus, a direct role of octreotide in modulating NE levels cannot be ruled out from our study. It has been demonstrated that somatostatin inhibited the release of NE in a concentration-dependent manner in animals (36), and a decrease in NE concentration during octreotide therapy has been reported (37). The epinephrine response to hypoglycemia is blunted in normal subjects during octreotide infusion (38). Another study, however, reported that somatostatin did not modify basal levels of NE in humans (39). The effects of somatostatin and its analogs on catecholamine secretion may be quite different depending on the subtype of somatostatin receptor activated (40). Octreotide is able to reduce insulin secretion in acromegalic patients and it is known that insulin may stimulate muscle sympathetic activity. Overall, data from the literature have not been able to clarify the role of GH and octreotide in modulating NE levels. Therefore, it is, at present, unlikely that octreotide per se would have induced the observed changes in catecholamine levels.

The alternative hypothesis is that the octreotide-mediated acute decrease in GH levels may have normalized basal and upright posture-stimulated noradrenaline levels. Previous data (3) have shown that a 24-h i.v. octreotide infusion and/or a single i.m. lanreotide injection (41) are able to normalize the cardiopulmonary performance during exercise in acromegaly. On the other hand, it has been shown that a 24-h i.v. infusion of exogenous GH is able significantly to improve hemodynamic parameters in patients with heart failure. On the basis of these data, it has been hypothesized that GH may have an acute and, therefore,
a functional effect on the cardiovascular system: these effects may well be exerted either directly by stimulating heart contractility, or indirectly via a systemic and/or pulmonary vasodilatation (33).

Importantly, the findings of the present study suggest that at least part of these cardiovascular acute GH effects may be mediated via an increase in basal catecholamine plasma levels. Interestingly, cardiovascular and catecholamine responses to cold stimuli were also found to be blunted in acromegalic patients. However, octreotide infusion was able to increase but could not normalize the norepinephrine response in acromegalic patients. This finding may indicate that the cutaneous receptor involved in the recruitment of the sympathetic response did not operate normally and that 24-h GH inhibition was not a long enough period to restore complete normality of this cutaneous response. The alterations to the skin in acromegaly are well known and our findings suggest that their reversibility is slower than that of baroreceptors. This may also suggest that the altered response to the cold pressure test is linked not only to a functional (rapidly reversible) alteration (as is the abnormal response to upright posture) but also to structural (therefore less rapidly reversible) alterations.

In conclusion, our data demonstrate the presence of increased basal norepinephrine plasma levels in acromegalic patients with defective sympathetic responses to stimuli. Short-term octreotide infusion is able to induce a reduction in the basal levels of norepinephrine and a normalization of the catecholamine response to posture. These findings suggest that different levels of sympatoadrenal activity may be involved in the functional effects of GH on the cardiovascular system.

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