The aim of the study was to investigate the effect of octreotide, a somatostatin analog drug potentially able to inhibit growth hormone (GH), on the circadian blood pressure profile in a group of patients with acromegaly. Ten patients with GH-secreting pituitary adenoma were studied before and 6 months after treatment with subcutaneous octreotide 0.2 to 0.6 mg/day. Twenty-four hour blood pressure and heart rate were measured every 15 min at daytime (07:00 to 22:59) and every 30 min at nighttime (23:00 to 06:59) using a TM-2420 recorder. No correlation was found between GH levels and 24-h blood pressure in baseline conditions. Untreated patients had a significant nocturnal decrease of both systolic and diastolic blood pressure ($P < .01$), and all showed a circadian systolic or diastolic blood pressure rhythm. During octreotide treatment, 24 h as well as nighttime systolic and diastolic blood pressures significantly increased ($P < .05$), whereas daytime systolic and diastolic blood pressures did not change. Treated patients did not have a nocturnal decline in both systolic and diastolic blood pressures ($P = \text{NS}$), and eight lost their systolic or diastolic blood pressure rhythm. In conclusion, blood pressure circadian rhythm seems to be maintained in acromegaly. Octreotide treatment is associated with an increase of 24-h and nighttime blood pressure, and with loss of circadian blood pressure rhythm. Splanchnic vasoconstriction by this drug, shifting blood to peripheral vessels, may explain this phenomenon. Am J Hypertens 1998; 11:591–596 © 1998 American Journal of Hypertension, Ltd.

**KEY WORDS:** Octreotide, acromegaly, 24-h blood pressure, growth hormone.

**A**romegaly is associated with an excess morbidity and mortality, mainly due to cardiovascular disease.¹² Growth hormone (GH) has a direct or indirect vasoactive effect, and increased prevalence of hypertension has been reported as a risk factor for the development of atherosclerosis in this condition.³⁴ Scanty data are available on the relation of disease activity to blood pressure levels and on the influence of abnormal hypersecretion of GH on the circadian blood pressure profile. In this study, we examined day/night blood pressure changes in a group of acromegalic patients before and after treatment with the somatostatin analog octreotide, a drug potentially able to inhibit GH secretion.

**PATIENTS AND METHODS**

Ten patients with acromegaly (6 men and 4 women; aged $46.4 \pm 12$ yr; body mass index $27.5 \pm 5.9$ kg/m²), admitted to our institution during the past 2 years, were studied. Before starting GH inhibitory treatment by octreotide, blood pressure measurements were taken three times at intervals of at least 1 week, in the absence of any antihypertensive therapy for at least 3
weeks. Clinic blood pressure was taken in the morning on three measurements in the supine position after 5 min of rest, using a mercury sphygmomanometer with a cuff of the appropriate size. According to the Joint National Committee criteria, 4 of 10 patients had mild to moderate hypertension. The diagnosis of active acromegaly was based on clinical features, GH levels on multiple samples >5 μg/L, insulin-like growth factor-I (IGF-I) elevated for age, failure of GH levels to suppress below 2 μg/L during a 75-g oral glucose tolerance test, and demonstration of a pituitary mass by computed tomography or magnetic resonance imaging. Four patients had newly diagnosed GH-secreting adenoma and were awaiting surgery. After octreotide treatment, they underwent successful removal of a GH-secreting pituitary adenoma, and were subsequently reevaluated. Six had residual or recurrent pituitary mass with GH hypersecretion after previous pituitary surgery.

**Protocol of the Study** All patients received the somatostatin analog octreotide subcutaneously 0.2 to 0.6 mg/day over a 6-month period. None was receiving antihypertensive or cardiovascular medications for at least 2 weeks before starting and during the study. Three patients had diabetes mellitus controlled by oral hypoglycemic agents. No neurologic, hepatic, renal disease, or sleep apnea were present. Sodium and potassium intake was ad libitum during the study. All patients were advised to follow a balanced normocaloric diet throughout the study. At echocardiography, 9 of 10 patients had left ventricular hypertrophy (defined as a left ventricular mass, indexed by body surface area, >134 g/m² in men and >110 g/m² in women). Two evaluations after admission to the hospital were performed in each patient: the first in baseline conditions, and the second after 6 months of treatment. Patients showing good control of disease, defined as GH <2 μg/L and normal IGF-I concentration for age, with octreotide 0.2 mg/day continued with this lowest dosage (0.1 mg twice a day subcutaneously at 07:00 and 19:00). In patients who failed to suppress GH with this schedule the daily dose was increased up to 0.6 mg/day (0.2 mg three times a day subcutaneously at 07:00, 15:00, and 22:00). For the follow-up, serum GH and IGF-I measurements at 09:00 were carried out monthly in all patients, titrating therapy on the results. Body weight was recorded before and after treatment. Serum GH was measured by immunoradiometric assay (IRMA) provided by Sorin Biomedica, Saluggia, Italy (HGH-CTK IRMA). The normal range is 0 to 5 μg/L. Intra- and interassay coefficients of variation (CVs) are 8.4% and 10.1%, respectively. Serum IGF-I was determined by IRMA using a kit from Diagnostic Systems Laboratories, Inc., Webster, TX. Normal range for age are 20 to 29 yr, 110 to 628 μg/L, 30 to 39 yr, 100 to 494 μg/L; 40 to 49 yr, 101 to 303 μg/L; and 50 years or older, 78 to 258 μg/L. Intra- and interassay CVs are 5.2% and 9.4%, respectively.

The day before octreotide treatment and the last day of treatment, each patient underwent 24-h noninvasive blood pressure and heart rate monitoring. All recordings were made 4 to 8 days after admittance to the hospital. Recordings were also made 3 months after surgery in the four patients who underwent successful pituitary adenomectomy at the end of octreotide treatment. The 24-h blood pressure recordings were obtained using a Takeda TM-2420 monitor (Osaka, Japan), which was calibrated against a mercury sphygmomanometer. The accuracy of both systolic and diastolic blood pressure measurements with this equipment has been well documented and compared with sphygmomanometric and direct methods.

Subjects were fitted with the recorder on the day of the recording, starting between 08:30 and 09:00. The instrument was set to take readings every 15 min from 07:00 to 22:59, and every 30 min from 23:00 to 06:59. Readings were automatically rejected with systolic blood pressure >220 or <70 mm Hg and with diastolic blood pressure >140 or <40 mm Hg. Whenever a reading could not be completed, the measurement was automatically repeated after 2 min. All subjects included in the study had complete readings (ie, >85% of data), over the 24-h period. During the monitoring, a written diary of physical and mental activities was kept. In this regard, no major differences were found between the subjects when examined before and after octreotide treatment. The sleep-span in darkness, lasting from 23:00 to 07:00, was recorded in patients’ diaries and controlled by nursing personnel. Blood pressure readings in the course of sleep disturbances were discarded. In our laboratory, all mean changes of 24-h blood pressure from baseline to repeat recording, are ≤2 mm Hg; these data are based on two 24-h blood pressure monitoring studies at least 3 months apart in 20 normotensive and 20 hypertensive subjects.

**Statistical Analysis** As previously described,6 the data from 24-h blood pressure and heart rate profiles were analyzed with a computerized procedure that we developed on a Macintosh IIcx using an application of 4th Dimension 4.1.1 (ACIUS), a relational and programmable database. Unequal readings caused by the programming of the recorder and failed measurements were equalized by the computer to 30-min classes. The presence of a circadian blood pressure rhythm was first tested against the hypothesis of a pure random variation using the Siegel’s runs-test with one-sided probability level of 1%. Subjects
showing a significant runs test for their systolic or diastolic blood pressure, or for both, were classified as having a circadian blood pressure rhythm. To describe blood pressure profile, Fourier series with four harmonics with periods of 6 h were fitted to 24-h readings of each subject by a weighted least-squares regression procedure.\textsuperscript{10,11} The overall amplitude and acrophase were computed. The amplitude is half of the difference between the maximum and minimum blood pressure level predicted by the model. The acrophase is the time lag between midnight and the maximum of the Fourier curve. Daytime and nighttime systolic and diastolic blood pressure and heart rate were also calculated. We considered daytime hours as being from 07:00 to 22:59 and nighttime hours from 23:00 to 06:59. Nighttime recordings included only supine measurements. Because of the variable time at which subjects fell asleep and woke up during the recording, truncated periods of waking and sleep were also used for the analysis of the results. This approach also avoids interferences due to periods of transition.\textsuperscript{12,13} One considered period of sleep, from 24:00 to 05:00, was considered.

The statistical significance of differences between groups was assessed by the Wilcoxon ranked-sign test or \( \chi^2 \) test corrected for the continuity, as appropriate. Correlations between variables were investigated by calculating the Spearman’s rank correlation coefficient. A \( P < .05 \) was considered statistically significant. Results are expressed as means ± SD.

**RESULTS**

There was no significant correlation between baseline GH (mean, 34.2 ± 10.1 µg/L; range, 8.6 to 52.8 µg/L) as well as IGF-I (mean, 764 ± 294 µg/L; range, 380 to 1248 µg/L) levels and either clinic or 24-h systolic and diastolic blood pressure values. At the end of octreotide treatment, six patients had GH levels <2 µg/L and normal IGF-I, and four patients had GH levels still >5 µg/L and IGF-1 above normal using a subcutaneous dose of octreotide 0.6 mg/day. No significant change in body weight was observed after treatment.

Clinic and circadian blood pressure and heart rate parameters are summarized in Table 1. Clinic blood pressure was not different before and during octreotide, whereas average 24-h systolic blood pressure values were significantly increased after therapy in our patients. In particular, clinic hypertension persisted after octreotide in two of four patients who had high blood pressure in baseline conditions. Systolic and diastolic blood pressure significantly increased after octreotide only at nighttime, whereas both systolic and diastolic daytime blood pressure did not change. Twenty-four-hour as well as daytime and nighttime heart rate did not change. Octreotide did modify the diurnal blood pressure and heart rate changes associated with the sleep–wake cycle; before treatment there was a significant blood pressure and heart rate reduction from daytime to nighttime, which was lost after treatment. Average systolic and diastolic blood pressure amplitude was decreased after octreotide, whereas acrophase was not different before and after therapy. Analysis of truncated time periods for systolic and diastolic blood pressure and heart rate (not shown) provided results similar to those obtained with fixed daytime and nighttime periods.

According to the runs-test, individual rhythm analysis showed that all 10 patients with active acromegaly had a significant circadian rhythm for systolic or diastolic blood pressure. Eight, including the four patients with inadequate control of GH and IGF-I, lost their systolic or diastolic blood pressure rhythm during octreotide treatment (\( \chi^2 \) untreated versus octreotide treated patients = 24.5, \( P < .0001 \)). Figure 1 shows a 24-h systolic and diastolic blood pressure profile of a patient in whom the circadian rhythm was lost after octreotide treatment.

The four patients who at the end of octreotide treatment underwent pituitary surgery had GH and IGF-I normalized by operation, and no longer needed octreotide treatment. One, who was hypertensive in baseline conditions, had clinic and 24-h systolic and diastolic blood pressure normalized by surgical ther-

| TABLE 1. PARAMETERS OF BLOOD PRESSURE CIRCADIAN PROFILE IN ACROMEGALIC PATIENTS BEFORE AND AFTER OCTREOTIDE |
|---------------------------------------------------------------|-----------------|-----------------|
| **Before Octreotide** | **After Octreotide** |
| Clinic SBP (mm Hg) | 137 ± 14 | 139 ± 12 |
| Clinic DBP (mm Hg) | 85 ± 11 | 88 ± 9 |
| Clinic HR (beats/min) | 74 ± 7 | 70 ± 5 |
| 24-h SBP | 127 ± 11 | 136 ± 10* |
| 24-h DBP | 76 ± 6 | 84 ± 7* |
| 24-h HR | 73 ± 7 | 70 ± 6 |
| Daytime SBP | 135 ± 12† | 138 ± 14 |
| Daytime DBP | 83 ± 9† | 86 ± 13 |
| Daytime HR | 84 ± 6† | 81 ± 5 |
| Nighttime SBP | 119 ± 10 | 130 ± 12* |
| Nighttime DBP | 71 ± 7 | 80 ± 9* |
| Nighttime HR | 68 ± 6 | 66 ± 4 |
| Amplitude SBP (mm Hg) | 20 ± 8 | 10 ± 4* |
| Amplitude DBP (mm Hg) | 11 ± 4 | 6 ± 3* |
| Acrophase SBP (hh:mm) | 12:17 ± 4:36 | 13:39 ± 7:11 |
| Acrophase DBP (hh:mm) | 13:17 ± 4:48 | 15:46 ± 8:21 |

Values are expressed as means ± SD. SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; daytime, 07:00 to 22:59; nighttime, 23:00 to 06:59.

* \( P < .05 \) after octreotide v before octreotide.
† \( P < .01 \) daytime v nighttime.
apy. After surgery and with octreotide withdrawal, all four patients showed reestablishment of circadian blood pressure rhythm. Day/night systolic and diastolic blood pressure changes were also restored.

**DISCUSSION**

The presence of a circadian blood pressure rhythm has long been recognized in humans, and can be lost in case of excess or deficient secretion of vasoactive hormones, such as in pheochromocytoma, renovascular hypertension, Cushing’s syndrome, Addison’s disease, and hypopituitarism.8,14–17 Recent interest in the study of blood pressure variability has been raised by the fact that deviations from the usual diurnal rhythm may have pathologic relevance in hypertension, leading to higher cardiovascular morbidity and mortality.18,19 Although GH is primarily involved in the regulation of somatic growth, there is solid evidence that it has a role in the regulation of cardiovascular structure and function, through direct as well as indirect mechanisms.20 A number of clinical studies have shown that GH hypersecretion is associated with signs of systemic arteriosclerosis, cardiac hypertrophy, and hypertension.3,4 Our data on patients with active acromegaly confirm a prevalence of clinic hypertension similar to that reported by others in much larger series,3 and show lack of correlation between baseline GH levels and 24-h systolic or diastolic blood pressure values. Furthermore, circadian rhythmic blood pressure profile was present in our patients with active acromegaly, indicating that GH does not play a major role in driving day/night variations of blood pressure. Octreotide is an eight-amino-acid cyclic peptide analog of somatostatin able to inhibit GH release.21,22 Somatostatin analogs have been shown to be an effective therapy for those acromegalics who still have active disease after surgery as well as for newly diagnosed patients awaiting surgery.23,24 No relationship between GH normalization and blood pressure changes after octreotide or surgery was observed in our hypertensive patients with acromegaly. Taken together, our findings do not indicate a direct pathogenic role of GH in blood pressure regulation.

Analysis of 24-h blood pressure profile parameters may explain why our results apparently contrast with other findings25–27 of decreased or unchanged clinic blood pressure after octreotide in acromegaly. Indeed, occasional blood pressure recordings do not seem to be accurate enough to detect hemodynamic variations and predict the response to antihypertensive therapy.28,29 In 8 of our 10 acromegalic patients the circadian systolic or diastolic blood pressure rhythm was lost, irrespective to the presence of adequate GH control. In addition to GH inhibition, the effects of octreotide are multiple and include somatostatin-like selective reduction of splanchnic blood flow.22 This local vasoconstrictive action leads to shifting of blood to periph-

![Figure 1](image_url)
eral vessels. This is considered the most likely explanation for the beneficial effect of the drug in reducing postural and postprandial hypotension of patients with autonomic failure.30–32 The effect is achieved in these patients at octreotide single doses 3- to 20-fold lower than those used in our study. Thus, a prolonged (6-month therapy) and continuous (two to three times/day drug administration) activation of this mechanism in our patients could have led to persistent retention of fluid into the peripheral vascular compartment with consequent increase of blood pressure. The increment of systolic and diastolic blood pressure was greater at nighttime compared with daytime. At night, octreotide might indeed counteract the fluid shift from the periphery to the central location normally occurring because of supine position. Moreover, 24-h and nighttime blood pressure increases were not associated with an increase in 24-h heart rate, not supporting sympathetic activation as a relevant mechanism for pressure variations. Other effects of octreotide, such as activation of vasoactive agents or increase in vascular sensitivity to pressor factors, cannot be excluded. Our findings suggest that during octreotide treatment in acromegalic patients, antihypertensive medication should be administered in the evening rather than in the morning, when needed.

In conclusion, 24-h blood pressure rhythm seems to be maintained in acromegaly. Octreotide treatment, either with complete or incomplete control of GH hypersecretion, is associated with loss of circadian blood pressure rhythm. Splanchnic vasoconstriction by this drug, shifting blood to peripheral vessels, may explain this phenomenon. Further studies are needed to know whether this effect may have pathologic implications.

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