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Twenty-four hour profile of blood pressure in patients with acromegaly. Correlation with demographic, clinical and hormonal features

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ABSTRACT. Cardiovascular events are frequently reported in patients with acromegaly and they are usually related to arterial hypertension. Aim of the present study was to assess the 24-hour profile of blood pressure (BP) and heart rate (HR) in patients with active acromegaly and to correlate them with clinical and hormonal data. Sixteen patients and 16 healthy, age and sex matched subjects underwent ambulatory blood pressure monitoring by means of a portable automatic device (SpaceLabs monitor 90207, Kontron) with measurements every 20 minutes for 24 hours. The presence of the nocturnal fall was assessed by the calculation of the night-day systolic and diastolic ratio. The mean 24-hour diastolic BP was significantly higher in acromegalic patients than in controls (79.1±11.5 mmHg *vs* 70.8±5.3 mmHg, $p<0.05$) and the circadian diastolic profile was flatten. In fact, 10/16 patients were defined as nondippers while this figure was 2/16 in the control group (62% *vs* 12%, $p<0.01$). Also the mean 24-hour systolic BP was higher in acromegalic patients than in controls (124.8±17.2 mmHg *vs* 114.1±8.6 mmHg, $p<0.05$). The circadian systolic profile paralleled that of diastolic and was flatten, without a significant nocturnal fall. Ten out of 16 patients were nondippers compared to 2/16 controls (62 *vs* 12%, $p<0.01$). No significant correlation was found between mean 24-hour BP, either diastolic or systolic, and demographic or hormonal characteristics of the patients. HR patterns did not differ between patients and controls and were characterized by a prominent nocturnal fall.

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INTRODUCTION

Cardiovascular problems are frequently encountered in patients with acromegaly. Arterial hypertension is observed in about 30% of patients, mostly women (1, 2). The hypertension is usually mild-moderate but serious target organ damage, such as congestive heart failure, can occur (3).

A number of studies have indeed shown that patients with acromegaly have a reduced life expectancy (4-7). Excess mortality has been most commonly attributed to cardiovascular events. Accordingly, Wright et al. reported that blood pressure (BP) was significantly higher in the patients who died (4).

The pathogenesis of hypertension in acromegaly is still unclear but some experimental works suggest the presence of a growth hormone (GH)-induced hypervolemia (8). Several researches have found low plasma renin activity as a consequence of extracellular volume expansion, yet data on the mineralocorticoid secretion are controversial (9-10). Furthermore, it has been suggested that the sympathetic nervous system or other factors controlling renal sodium handling (atrial natriuretic factor, digitalis-like factors) may be involved (11, 12).

Circadian variations in BP and heart rate (HR) are well established. The rhythmic pattern of BP was found to be altered in some endocrine-related hypertensions, such as Cushing's syndrome (13, 14), pheochromocytoma (15, 16), hypermineralocorticism (17, 18) but there is scanty information on acromegaly (19). This issue may be of clinical relevance since it is argued that target organ damage could be related to the BP time course (20, 21). In different series of hypertensive patients a close in-

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verse relationship was found between severity of organ damage and entity of the nocturnal BP fall (22-24).
Aim of the present study was to assess the 24-hour profile of BP in patients with acromegaly and to correlate BP data with demographic, clinical and hormonal features.

SUBJECTS AND METHODS

Sixteen patients with active acromegaly (6 males and 10 females aged 29-67 years, mean age±SD, 50.6±11.7) were enrolled in the study. The diagnosis of active acromegaly was established clinically and confirmed by high serum GH concentrations (>5 µg/l that were not suppressed below 2 µg/l after an oral glucose load (75 mg), by elevated plasma insulin-like growth factor I (IGF-I) levels (>400 ng/ml) and by demonstration of a pituitary tumor on computed tomographic scan. At least 4 blood samples were drawn over 24 hours for GH measurement and the mean was used for statistical analysis while IGF-I was determined on a single morning sample. An intravenous catheter was placed in a forearm vein and kept patent with saline one hour before sampling. All samples were run in duplicate in the same assay session using commercially available kits (SORIN BIOMEDICA, Saluggia, Italy, for GH and Nichols Institute Diagnostics, San Juan Capistrano, US, for IGF-I); intra- and inter assay coefficients of variation for the above-mentioned variables were less than 4.8% and 6% for GH and 4.2% and 6.3% for IGF-I, respectively.
None of the patients has been previously treated surgically or medically for acromegalic disease and had clinical or biochemical evidence of overt pituitary deficiency. Five patients were overweight (BMI between 25 and 30) and two were obese (BMI>30). Three patients had mild diabetes mellitus treated with oral hypoglycemic agents without any sign of autonomic neuropathy.
Five out of 16 patients had mild-moderate systo-diastolic hypertension, 2 patients had isolated systolic hypertension and 1 had isolated diastolic hypertension on office measurements according to WHO criteria. All patients were studied off antihypertensive therapy, which was withdrawn at least 30 days before the study. No other cardiovascular diseases or major illnesses, in particular no clinically relevant impairment of renal or hepatic function, were present. Pertinent clinical information is given in Table 1.
Each patient underwent accurate medical interview, clinical examination, routine laboratory tests and standard cardiologic diagnostic procedures. The presumptive duration of acromegaly was assessed by comparison of photographs taken during a one- to two-decade span and by patient interview to date the onset of acral enlargement. The interval between the clinical onset of acromegaly and the time when the study was performed was calculated and recorded as the duration of disease. An accurate medical history was taken to identify cardiovascular symptoms. All information was collected by experienced medical staff by means of specifically tailored data collection forms. Sixteen healthy, normotensive subjects evenly matched for sex and age (31-68 years, mean age 50.5±11.2 years) served for case-control analysis. All patients and controls underwent 24-hour ambulatory blood pressure monitoring by means of a portable, automatic, oscillometric device (SpaceLabs monitor 90207, Kontron) staying at home (25). Systolic, diastolic BP and HR were measured every 20 minutes for 24 hours. An appropriate cuff was used for obese patients. Subjects were instructed to remain motionless during BP measurement and to record their activity on a diary sheet. All patients and controls followed the same life schedule: they were active during daytime, had breakfast at 8:00 a.m., lunch at 12:30 a.m., dinner at 7:30 p.m. and bed rest from

Table 1 - *Clinical and hormonal data of the acromegalic patients.*

Patients	Age (yr)	Body Mass Index (kg/m^2)	Duration of disease (yr)	GH (µg/l)	IGF-I (ng/ml)
1/M	35	27.6	15	28.9	1127
2/F	56	21.3	6	42.0	1066
3/F	38	27.1	11	13.6	700
4/F	42	34.6	4	7.0	1244
5/F	54	25.7	11	9.4	533
6/M	29	32.2	10	66.0	630
7/M	56	24.3	11	32.7	442
8/F	65	25	19	21.0	577
9/M	53	27.7	15	50.0	945
10/F	54	22.6	3	35.8	720
11/F	48	23	15	13.0	855
12/M	48	23.2	5	69.3	1091
13/F	67	25	10	17.0	585
14/F	37	23.2	8	8.6	423
15/F	64	19.8	10	32.5	629
16/M	64	30	10	5.0	659

Normal values: Growth Hormone (GH) <5 µg/l (mean of at least four samples over 24 hours).
Insulin-like growth factor-I (IGF-I)<400 ng/ml

Table 2 - *Comparison of blood pressure and heart rate between the acromegalics and controls.*

		Acromegalics	Controls
Diastolic			
24-hour	(mmHg)	79.1±11.5*	70.8±5.3
nighttime	(mmHg)	74.7±12.7**	62.3±5.9
daytime	(mmHg)	81.9±11.4**	75.1±5.4
night/day ratio		0.90±0.09*	0.83±0.04
Systolic			
24-hour	(mmHg)	124.8±17.2*	114.1±8.6
nighttime	(mmHg)	122.9±22.5*	106.4±8.8
daytime	(mmHg)	128.3±16.9*	118.1±8.4
night/day ratio		0.94±0.08	0.90±0.04
Heart rate			
24-hour	(bpm)	75±11.7	75±12.7
nighttime	(bpm)	66±7.3	66±6.9
davtime	(bpm)	79±7.4	80±7.5

Data are given as M±SD

Acromegalics *vs* controls: *$p<0.05$ **$p<0.01$

Nighttime *vs* daytime diastolic $p<0.01$ for controls, p=NS for acromegalics

Nighttime *vs* daytime systolic $p<0.01$ for controls, p=NS for acromegalics

Nighttime *vs* daytime heart rate $p<0.01$ for controls, $p<0.001$ for acromegalics

11 p.m. to 7 a.m. The recorder automatically discarded artifactural readings due to arm motion or sound interference during recording. Additional readings were discarded by computer processing if the differential pressure was less than 20 mmHg, the diastolic less than 40 mmHg or the systolic more than 260 mmHg. The overall rate of valid readings over 24 hours was 95%. Systolic and diastolic data are given as mean 24-hour BP, mean daytime BP and mean nighttime BP. The nighttime period was defined as the time interval between 11:00 p.m. and 7:00 a.m., while the daytime one between 7:00 a.m. and 11:00 p.m. A comparable number of patients and controls (about 20%) complained of some minor sleep disturbances during BP monitoring, but none of them showed remarkable time-related alterations in BP recording. The higher levels of normality were set at 81 mmHg for mean 24-hour diastolic BP and at 132 mmHg for mean 24-hour systolic. These thresholds are 2 SDs above the mean values recorded in healthy subjects and fit well with those previously reported (26). The presence of the nocturnal fall was assessed by comparing mean nighttime BP with mean daytime BP, and by evaluating the night-day ratio. A night-day BP ratio below 0.86 for diastolic and 0.92 for systolic was considered as normal. These thresholds are 2 SEs above the mean values of controls and are well comparable with the ratios employed in previous studies (27). Minor differences could be accounted for by variable definitions of the day- and nighttime period.

Statistical analysis was performed using non parametric tests (two-tailed Wilcoxon's rank sum test and Kruskal-Wallis one-way analysis of variance) not to assuming a gaussian distribution. For categorical variables, Fisher's exact test was used. Spearman's correlation analysis was performed as appropriate. Multiple regression analysis of mean 24-hour BP by patient age, disease duration and hormone data was performed. Data are expressed as mean±SD. Levels of statistical significance were set at $p<0.05$.

RESULTS

The mean 24-hour diastolic BP was significantly higher in acromegalic patients than in controls (Table 2). In 7 out of 16 patients (6/10 females) it was above the reference range (Table 3). The difference was more pronounced during the nighttime period than the daytime one (Fig. 1, Table 1). This is the result of a more prominent nocturnal fall of diastolic BP in the control group than in acrome-

Table 3 - *Blood pressure data of the acromegalic patients.*

Patients	Office BP (mmHg)	24 h diastolic (mmHg)	24 h systolic (mmHg)	night/day diastolic ratio	night/day systolic ratio
1/M	130/95	69	110	0.73	0.85
2/F	165/100	103	132	0.92	0.97
3/F	130/90	64	105	0.91	0.91
4/F	130/90	75	121	0.97	0.93
5/F	150/90	82	125	0.72	0.77
6/M	130/85	68	121	0.90	0.93
7/M	130/80	70	110	0.82	0.89
8/F	120/70	74	115	0.93	0.95
9/M	170/110	85	141	1.13	1.12
10/F	170/100	104	165	0.96	1.05
11/F	140/90	82	124	0.86	0.93
12/M	145/100	77	120	0.89	0.97
13/F	170/85	84	159	0.95	0.93
14/F	130/80	72	117	0.84	0.87
15/F	130/90	85	124	0.85	0.92
16/M	150/95	72	108	0.95	0.96

Office BP is the mean of at least three measurements in a week

Normal values: 24-h diastolic <81mmHg

24-h systolic <132 mmHg

night/day diastolic ratio <0.86

night/day systolic ratio <0.92

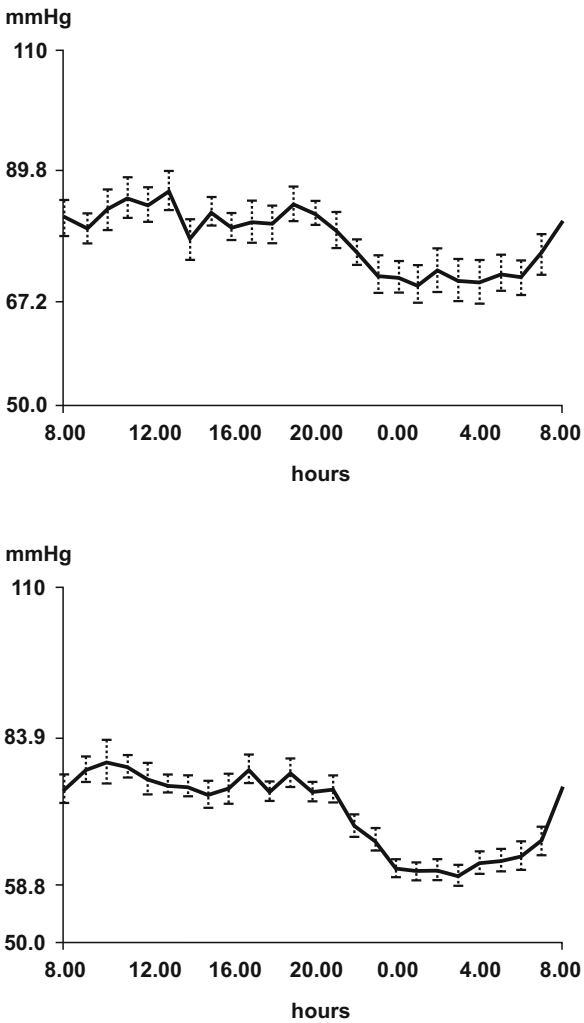

Fig. 1 - *Circadian profile of diastolic blood pressure in 16 acromegalic patients (upper panel) and 16 healthy, age-matched subjects (lower panel).*

galic patients. Subjects were divided into two groups by the presence (dipper) or absence (non dipper) of a significant nocturnal BP fall. Ten out of 16 acromegalic patients were non dippers for diastolici this figure was 2 out of 16 in the control group (62% *vs* 12%, $p<0.01$). Four out of 7 patients displaying diastolic hypertension had an altered night-day ratio for the diastolic pressure.

Also mean 24-hour systolic BP was significantly higher in acromegalic patients than in controls (Table 2). In 3 out of 16 acromegalics it was above the reference range. The systolic profile paralleled that of diastolic and the nocturnal fall was blunted in acromegalics in comparison with controls (Table 2, Fig. 2). Mean nocturnal and diurnal systolic were higher in patients than in controls (Table 2). Ten out of 16 patients and 2 out of 16 controls were non dippers for systolic (62% *vs* 12%, $p<0.01$). All the patients with systolic hypertension showed an alteration of night-day systolic ratio.

The profile of HR was characterized by a prominent night-time fall in both patients and controls and did not differ between the 2 groups in any time period (Table 2, Fig. 3). Multiple regression analysis did not disclose any significant correlation between mean 24-hour BP, either diastolic or systolic, and the demographic (age, disease duration) or hormonal (GH, IGF-I levels) characteristics of the patients.

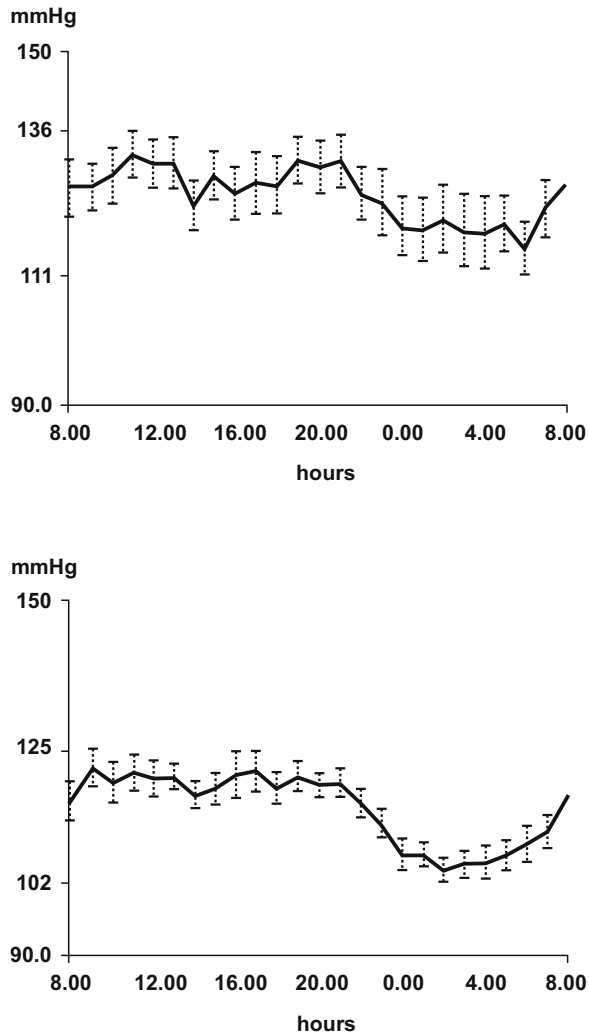

Fig. 2 - *Circadian profile of systolic blood pressure in 16 acromegalic patients (upper panel) and 16 healthy, age-matched subjects (lower panel).*

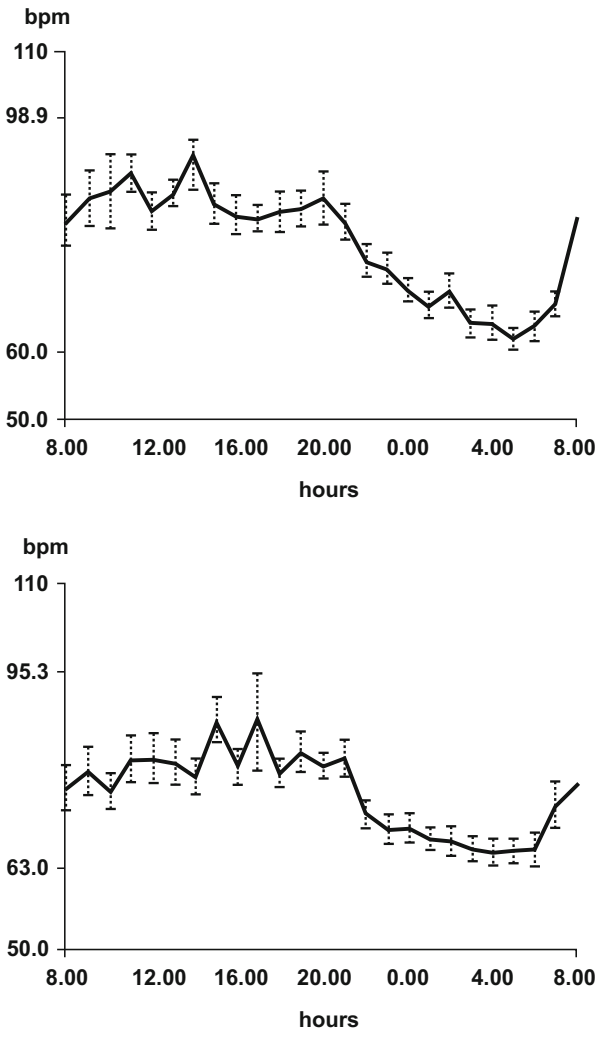

Fig. 3 - *Circadian profile of heart rate in 16 acromegalic patients (upper panel) and 16 healthy, age-matched subjects (lower panel).*

DISCUSSION

Acromegaly is a rare condition with an expectation of approximately 4 new cases per year per million population (28). The prevalence of hypertension in acromegaly ranged from 13 to 50% among different series; however, all studies have only employed office measurements (4, 29-31).

At the best of our knowledge, the present study provides the first detailed evaluation of the 24-hour pattern of BP in patients with acromegaly by ambulatory BP monitoring. Diastolic BP was found to be increased in 44% of patients, while the figure for systolic BP was 19%. Since diastolic increment was more frequent than systolic one it could be speculated that GH and IGF-I excess leads to a preferential alteration of resistance vessels, possibly inducing smooth muscle cell growth (32, 33). In fact, acute GH infusion is able to induce overexpression of the IGF-I gene and also of the PDGF2β gene that could promote hypertrophy and fibrosis of smooth muscle cells in the myocardial tissue and, possibly, in peripheral arterioles (34, 35).

The largest difference between BP levels of acromegalic patients and controls was recorded during the nighttime period. A nocturnal decrease from daytime levels was observed in most healthy subjects while a flattened 24-hour profile was typical of the acromegalics. Since the number of subjects with disturbed sleep during ambulatory BP monitoring was similar between the 2 groups, and HR patterns recorded during the night were highly comparable, the quality and quantity of sleep are not likely to explain these findings. However, in the absence of EEG recording during the sleep it is not possible to exclude unequivocally that minor sleep alterations could have influenced BP patterns. The alteration of BP profile was not associated with the entity of BP increase.

The dissociation between BP and HR profiles confirms that the control mechanisms of these variables are separate (36). It is therefore possible to argue that the fall in BP at night is blunted in acromegaly as in other secondary hypertensions. The causes for this particular BP pattern are presently unknown but they do not likely imply a disturbance of the autonomic system. Conversely, only a minority of essential hypertensives display a blunted night-day BP pattern (37).

The lack of significant correlations between 24-hour BP, either diastolic or systolic, and the GH or IGF-I levels does not reject the hypothesis that increased BP levels could ensue after prolonged and exaggerated exposure to these hormones. It has to be considered that hormone measurement at a given moment of a long-lasting disease such as acromegaly may not provide a reliable picture of the degree of hypersecretion during the previous years.

It is matter of debate if the nondipping pattern (sustained BP elevation over 24 hours with blunted nocturnal fall) could promote the development of forthcoming complications, such as left ventricular hypertrophy (20, 38), or merely reflects the severity of hypertension (39). In the present series, BP was slightly increased and no target organ damage was evident except myocardial hypertrophy that could well be a direct consequence of GH excess (40-42). This strengthens the view that the alteration of BP rhythm is a consequence of acromegaly. It is pertinent to observe that about half of nondipping acromegalic patients were normotensive.

To conclude, a blunted nocturnal fall in BP could

represent a specific cardiovascular feature of active acromegaly. Further studies are warranted to elucidate its clinical relevance, its progression over time and its eventual change after successful treatment of acromegaly.

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