Ambulatory blood pressure measurement, smoking and abnormalities of glucose and lipid metabolism in essential hypertension

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Objective: Casual (mercury sphygmomanometer) and ambulatory blood pressure measurements were determined in 61 subjects with sustained essential hypertension.

Design: Patients were classified into three subgroups: smokers or non-smokers; patients with or without hyperglycemia; and patients with or without plasma lipoprotein abnormality. Mean casual blood pressures were shown to be identical in these three subgroups.

Results: When ambulatory blood pressure was analyzed, smokers exhibited a significant increase in pulse pressure exclusively during the activity period, whereas diastolic blood pressure and mean arterial pressure (MAP) were not modified in comparison with controls. Patients with abnormal plasma glucose showed a significant increase in systolic and pulse pressure during both activity and non-activity periods, with a slight increase in MAP during the activity period. Patients with and without plasma lipid abnormality displayed similar ambulatory blood pressure.

Conclusion: The study provides evidence that, in spite of similar casual blood pressure levels among smokers and non-smokers, as well as among those with elevated fasting glucose levels, smokers and patients with hyperglycemia have a higher systolic and pulse pressure during 24-h monitoring, pointing to the possible role of cyclic stress in the deterioration in the structure of the hypertensive arterial wall.

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Introduction

It is generally accepted that antihypertensive treatment is effective in preventing cardiovascular complications in moderate and severe hypertension [1]. However, several limitations have been demonstrated. First, results of various therapeutic trials are contradictory with respect to the protection afforded to hypertensive patients with a diastolic blood pressure (DBP) of 90–94 mmHg. Second, although there is a consistent reduction in the incidence of stroke, even in mild hypertension, the rate of improvement resulting from primary prevention does not exceed 50% in any therapeutic trials. Third, one of the most important issues in patients with mild hypertension is the effectiveness of treatment in preventing ischemic cardiac disease. Whether treatment with antihypertensive drugs is effective in preventing myocardial infarction remains in doubt.

There are several possible explanations for the heterogeneity of the results of therapeutic trials on hypertension. First, from the various controlled, randomized clinical studies [1], it is difficult to determine which type of antihypertensive treatment achieves better control of blood pressure. Second, it is possible that the epidemiologically expected reduction for stroke is much more rapid than coronary heart disease in therapeutic trials [2]. Third, the improvement resulting from drug therapy mainly involves complications directly related to the mechanical effects of elevated blood pressure, such as cerebral hemorrhage, congestive heart failure and abdominal aneurysms. In contrast, the incidence of ischemic vascular accidents, as

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observed in coronary and carotid–cerebral circulation, remains high despite adequate treatment. The latter observation suggests that alterations of larger arteries are important to evaluate in the cardiovascular morbidity and mortality of patients treated for hypertension. In this regard, it is important to recognize that other risk factors such as smoking and abnormalities of glucose and lipid metabolism are even stronger cardiovascular risk factors for the general population than elevated blood pressure itself [3–6].

There is considerable evidence that smoking and abnormalities of glucose and lipid metabolism occur very frequently in untreated patients with hypertension [7–9]. For the metabolic abnormalities, it has recently been proposed that hyperinsulinism may be the common link associating elevated blood pressure and increased plasma levels of glucose and lipids [10–12]. This observation suggests that smoking and defects in glucose and lipid metabolism may play a particular role in both the etiology and the clinical course of hypertension. In this article, an attempt is made to develop this latter hypothesis, taking into account the fact that casual blood pressure may be an insufficient approach to evaluate the complex relationship between blood pressure, smoking and abnormalities of glucose and lipid metabolism in patients with hypertension.

Several studies have shown that ambulatory blood pressure is more reproducible than casual measurement [13–17]. It correlates more strongly than clinical or casual blood pressure with echocardiographic indices of left ventricular hypertrophy [18,19], non-invasive indices of arterial rigidity [20], or with indices of target organ damage in the heart, optic fundi and the kidney [21–23]. The purpose of the present study of 61 patients with essential hypertension was to evaluate the relationship of ambulatory blood pressure with three well known cardiovascular risk factors: smoking and abnormalities in plasma glucose and lipid metabolism.

Materials and methods

Patients

The study was carried out in 61 subjects (43 males and 18 females) aged 24–74 years. Mean age was 45 ± 12 years ($\pm$s.d.), mean weight, 74 ± 12 kg and mean height, 171 ± 9 cm. In all subjects, treatment was discontinued at least 4 weeks before the study. During the untreated period, hypertensive patients were defined as those in whom a supine DBP >95 mmHg was recorded using a mercury sphygmomanometer (see below). Subjects with evidence of secondary cause of hypertension were excluded on the basis of thorough clinical and biological investigations, as previously described [20]. None of the 61 subjects had clinical evidence of congestive heart failure, coronary insufficiency or any other occlusive artery disease, vascular heart disease or neurological impairment. Patients with glucose or lipid metabolic abnormalities requiring pharmacological treatment were excluded from the study.

After informed consent had been obtained, based on a detailed description of the procedure, patients were investigated at 0800 h for day hospitalization. After overnight fasting, blood samples were taken for plasma glucose and lipid determination according to standard techniques [24,25]. Blood pressure was then measured after 45 min rest in the supine position using a mercury sphygmomanometer. An average of three measurements were taken for each patient. Korotkoff phase I was used for the determination of systolic blood pressure (SBP). Phase V was used for the evaluation of DBP. Mean blood pressure was calculated as the sum of DBP plus one-third of the pulse pressure.

Non-invasive 24-h blood pressure monitoring

Automated blood pressure monitoring was carried out in each patient using a Novacor apparatus (model DIASYSF 200-R, Rueil, Malmaison, France) to measure and record blood pressure and heart rate over a full 24-h period. The reliability of this method has been published in detail elsewhere [26–29]. Recordings were performed every 15 min during the 24 h. Ambulatory monitoring was undertaken for a full active day; the patient worked as usual during the day and then went home as usual in the evening. Recordings that showed an inconsistent increase or decrease in SBP or DBP without changes in heart rate, or readings with a calculated pulse pressure <10 mmHg, were deleted before further data analysis [20].

Each full day recording was divided into an activity (diurnal) period (0700 to 2200 h), and a non-activity (nocturnal) period (2200 to 0700 h), based upon the patient diary. Mean values were used for statistical analysis.

Patient classification

The 61 patients were successively classified into three independent subgroups: smokers or non-smokers; those with or without hyperglycemia; and those with or without lipid abnormalities. Limits for normal values of glucose and lipid metabolism are indicated in Table 1. Abnormalities were taken as these beyond the upper limit of indicated normal values. It should be noted that, for plasma glucose, the upper limit was lower than the generally accepted level e.g. according to the World Health Organization (<6.7 mmol/l), thus making it easy to exclude subjects on antidiabetic drugs. For lipoproteins, classification was achieved using total plasma cholesterol or high-density lipoprotein cholesterol (HDLC; Table 1), or a combination of the two. Clinical characteristics of each subgroup are presented in Table 2.

Table 1. Metabolic abnormalities: the limits of normal values in this study.

	Normal values
Plasma glucose (mmol/l)	3.8–5.3
Total plasma cholesterol (mmol/l)	4.00–6.50
Plasma HDLC (mmol/l)	1.05–1.80
Total plasma cholesterol : HDLC ratio	<5

HDLC, high-density lipoprotein cholesterol.

Statistical analysis

Statistical analyses were performed independently in each group (smoker, glycemia and lipid abnormality) using the same study plan [30]. For each classification parameter, the homogeneity of the distribution of the other risk factors (i.e. lipid and glycemia abnormality) was analyzed using the χ^2 test for the qualitative parameters and the unpaired t-test to compare means. Bonferroni's correction for multiple test analysis was used; $P<0.05$ after correction was considered statistically significant. For the cumulative score comparison, analysis of variance was performed to test between group differences.

Results

Table 2 shows the clinical characteristics of each subgroup. No significant difference in age, weight, height or reclassification according to sex was observed between groups, for either smokers, lipid or glucid classification.

Table 3 shows the values of mercury sphygmomanometer measurements in each subgroup. Smokers, non-smokers and patients with metabolic abnormalities all had the same blood pressure levels. Analysis of variance indicated that smokers and non-smokers had the same plasma glucose and lipoprotein levels; subjects with or without hyperglycemia had the same results after reclassification for tobacco excess and lipoprotein abnormalities; patients with and without lipoprotein abnormality had the same results as those reclassified for tobacco excess and increased plasma glucose.

Tables 4, 5 and 6 indicate values of ambulatory blood pressure in each of these subgroups. Smokers had significantly increased pulse pressure with normal mean

Table 2. Clinical characteristics of the three subgroups.

	Male	Female	Age (years)	Weight (kg)	Height (cm)
Abnormal plasma glucose:					
Absence	21	10	43 ± 14	74 ± 12	171 ± 9
Presence	22	8	46 ± 8	74 ± 11	171 ± 9
Smoking:					
Absence	27	15	45 ± 12	73 ± 12	170 ± 9
Presence	17	2	43 ± 10	75 ± 10	174 ± 8
Lipid abnormality:					
Absence	17	6	42 ± 12	74 ± 11	171 ± 9
Presence	27	11	46 ± 11	74 ± 11	171 ± 9

Values are expressed as means ± s.d.

Table 3. Mercury sphygmomanometer measurements.

	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	Pulse pressure (mmHg)	Heart rate (beats/min)
Abnormal plasma glucose:					
Absence	159 ± 17	102 ± 10	121 ± 11	58 ± 12	73 ± 14
Presence	161 ± 13	105 ± 6	124 ± 8	56 ± 10	74 ± 14
Smoking:					
Absence	161 ± 15	104 ± 8	123 ± 9	57 ± 11	75 ± 15
Presence	157 ± 15	102 ± 9	120 ± 10	55 ± 10	71 ± 8
Lipid abnormality:					
Absence	157 ± 16	103 ± 9	121 ± 11	54 ± 11	72 ± 13
Presence	161 ± 14	103 ± 8	123 ± 9	58 ± 11	75 ± 14

Values are expressed as means ± s.d. SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure.

arterial pressure (MAP) during the activity period, but this disappeared during the non-activity periods. Subjects with hyperglycemia had significantly higher values of SBP and pulse blood pressure than controls, but there was no difference in DBP. MAP was augmented only during the activity period. Ambulatory blood pressure was similar in patients with and without lipoprotein abnormalities (Table 6).

Figure 1 shows the classification of the entire study population when SBP and pulse ambulatory blood pressure were measured in the presence or absence of either or both of the two criteria, smoking and plasma glucose abnormality. In patients displaying both criteria, there was no significantly higher value for SBP or pulse pressure.

Table 4. Ambulatory blood pressure in smokers and non-smokers.

	Non-smokers (n = 42)	Smokers (n = 19)	Between-group difference 95% confidence limits	P
Twenty-four hours:				
SBP (mmHg)	137 ± 14	142 ± 12	−12, +3	–
DBP (mmHg)	99 ± 11	97 ± 13	−5, +8	–
MAP (mmHg)	112 ± 11	112 ± 11	−7, +6	–
Pulse pressure (mmHg)	39 ± 10	44 ± 11	−11, +0.05	0.05
Heart rate (beats/min)	75 ± 9	79 ± 9	−9, +0.9	–
Activity period (0700–2200 h):				
SBP (mmHg)	145 ± 15	152 ± 14	−15, +1	–
DBP (mmHg)	105 ± 11	105 ± 14	−6, +7	–
MAP (mmHg)	118 ± 12	120 ± 13	−9, +5	–
Pulse pressure (mmHg)	40 ± 11	47 ± 11	−14, −2	0.01
Heart rate (beats/min)	80 ± 11	85 ± 12	−11, +2	–
Non-activity period (2200–0700 h):				
SBP (mmHg)	129 ± 15	130 ± 13	−9, +7	–
DBP (mmHg)	92 ± 12	90 ± 14	−4, +10	–
MAP (mmHg)	104 ± 12	103 ± 13	−5, +8	–
Pulse pressure (mmHg)	37 ± 10	41 ± 10	−9, +2	–
Heart rate (beats/min)	69 ± 8	73 ± 7	−8, +0.7	–

Values are expressed as means ± s.d. SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure.

Table 5. Ambulatory blood pressure in subjects with or without abnormal plasma glucose.

	Normal glycemia	Abnormal glycemia	Between-group difference 95% confidence limits	P
Twenty-four hours:				
SBP (mmHg)	134 ± 13	143 ± 13	−16, −3	0.006
DBP (mmHg)	96 ± 11	99 ± 11	−9, +3	–
MAP (mmHg)	109 ± 11	114 ± 10	−10, +0.6	–
Pulse pressure (mmHg)	37 ± 11	44 ± 10	−12, −1	0.01
Heart rate (beats/min)	76 ± 10	76 ± 7	−5, +5	–
Activity period (0700–2200 h):				
SBP (mmHg)	141 ± 14	152 ± 15	−19, −4	0.003
DBP (mmHg)	102 ± 12	107 ± 11	−10, +2	–
MAP (mmHg)	115 ± 11	122 ± 12	−13, −0.8	0.03
Pulse pressure (mmHg)	39 ± 12	46 ± 10	−13, −1	0.01
Heart rate (beats/min)	81 ± 12	82 ± 10	−7, +5	–
Non-activity period (2200–0700 h):				
SBP (mmHg)	125 ± 14	133 ± 13	−15, −1	0.02
DBP (mmHg)	89 ± 13	91 ± 12	−8, +5	–
MAP (mmHg)	101 ± 12	105 ± 11	−10, +2	–
Pulse pressure (mmHg)	35 ± 9	42 ± 10	−12, −2	0.01
Heart rate (beats/min)	70 ± 9	71 ± 6	−4, +4	–

Values are expressed as means ± s.d. SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure.

Table 6. Ambulatory blood pressure in subjects with or without plasma lipid abnormality.

	No lipid abnormality	Lipid abnormality	Between-group difference 95% confidence limits
Twenty-four hours:			
SBP (mmHg)	137 ± 15	139 ± 12	−10, +5
DBP (mmHg)	98 ± 11	98 ± 11	−5, +6
MAP (mmHg)	111 ± 12	112 ± 10	−6, +5
Pulse pressure (mmHg)	39 ± 10	42 ± 11	−9, +3
Heart rate (beats/min)	78 ± 8	76 ± 9	−3, +7
Activity period (0700 h–2200 h):			
SBP (mmHg)	145 ± 16	148 ± 14	−12, +4
DBP (mmHg)	105 ± 12	104 ± 12	−6, +7
MAP (mmHg)	118 ± 13	119 ± 12	−7, +5
Pulse pressure (mmHg)	40 ± 11	44 ± 12	−10, +2
Heart rate (beats/min)	83 ± 11	81 ± 11	−4, +8
Non-activity period (2200 h–0700 h):			
SBP (mmHg)	129 ± 15	129 ± 13	−8, +7
DBP (mmHg)	91 ± 12	90 ± 13	−5, +8
MAP (mmHg)	104 ± 13	103 ± 12	−6, +7
Pulse pressure (mmHg)	37 ± 10	39 ± 10	−7, +3
Heart rate (beats/min)	72 ± 7	70 ± 8	−2, +6

Values are expressed as means ± s.d. SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure.

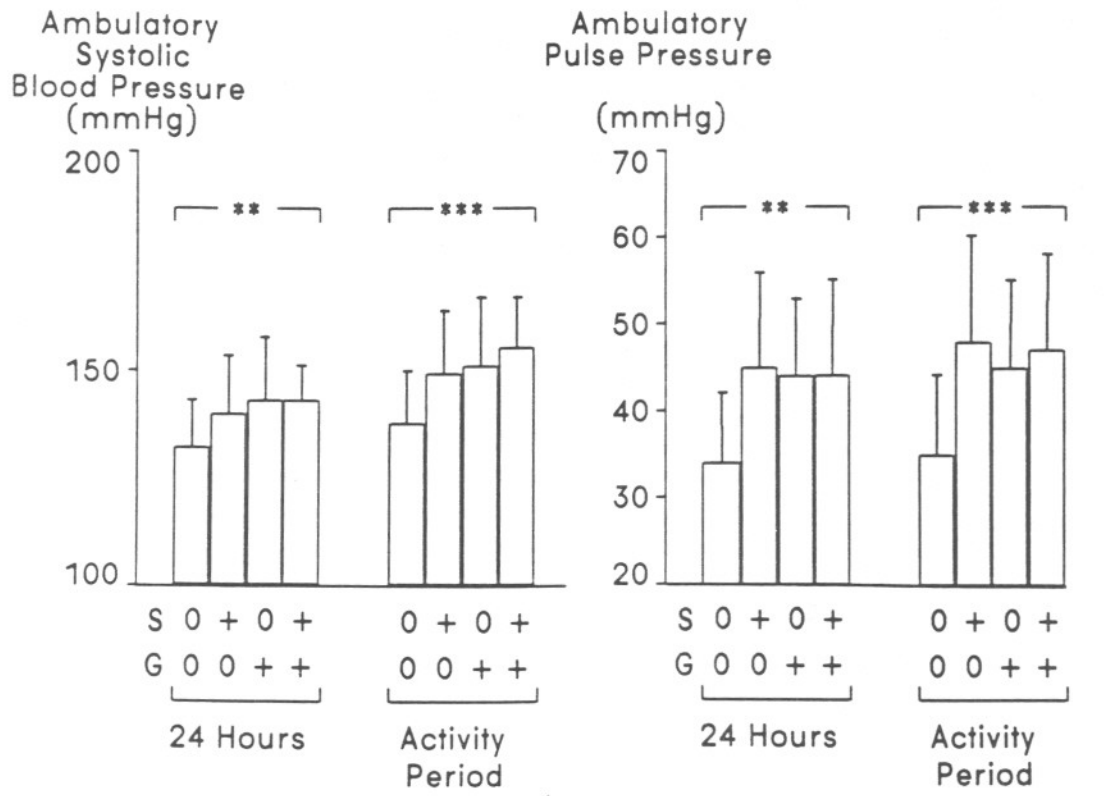

Fig. 1. Values of systolic and pulse ambulatory blood pressure in patients classified into smokers or non-smokers (S) and with or without plasma glucose abnormality (G). 0, absence of classification characteristic; +, presence of classification characteristic. $^{**}P < 0.01$, $^{***}P < 0.001$.

Discussion

The patients in the present study were selected because they were all hypertensive. Thus, the results cannot be generalized for the population as a whole. However, hypertensive subjects who smoked or had hyperglycemia exhibited the same blood pressure values as controls when sphygmomanometer measure-

ments were used. In contrast, increased values were observed when ambulatory blood pressure recordings were performed. One possibility is that the use of repeated blood pressure measurements increased their reliability and therefore favoured the finding of increased blood pressure values. An alternative view is that the methodology enabled better evaluation of the complex relationships between blood pressure, smoking and metabolic abnormalities.

Patients with increased plasma glucose exhibited higher values of SBP and pulse pressure. In a previous study, we showed that ambulatory blood pressure recordings were strongly and positively correlated with increased carotid–femoral pulse wave velocity, an index of aortic distensibility [20]. On the other hand, it has been well established that patients with diabetes are often characterized by an increase in pulse wave velocity, a parameter which is altered even at an early phase of the disease [31–33]. Since increased pulse wave velocity contributes to produce a disproportionate increase in SBP in hypertensives [34], it seems likely that patients with hypertension and mild hyperglycemia may have a predominant increase in SBP compared with DBP.

It has been known for many years that cross-sectional population studies including both normotensives and hypertensives show that smokers tend to have a somewhat lower blood pressure at screening examination [6,9]. It is usually thought to be because smokers are in an abstinence phase when blood pressure is measured. Hemodynamic studies [35] have shown that acute smoking produces an increase in blood pressure in association with increased sympathetic activity and tachycardia. The present finding of a significant increase in pulse pressure and SBP during active periods may well be a reflection of the increased blood pressure caused by acute smoking. The use of ambulatory blood pressure measurements and the lack of increase in pulse pressure during the non-activity period confirms this important aspect of the relationship between smoking and blood pressure. However, our relatively small number of patients does not permit stronger correlations to be made.

Although smokers and subjects with mild hyperglycemia exhibited substantial blood pressure abnormalities, no comparable finding was observed in subjects with modifications in lipid metabolism. This negative result should be analyzed with caution. First, the criteria of lipid abnormalities were those chosen for a limited population within a given Parisian hospital and cannot be extended to other populations. Second, the investigation was limited to patients with mild plasma lipoprotein abnormalities which did not require the indication of pharmacological agents. Third, the chosen criteria of judgement were essentially qualitative (normal versus abnormal value). It is possible that such a classification was not sufficiently sensitive for plasma lipids, despite sufficing for plasma glucose and tobacco abnormalities.

The principal finding of the present study was that blood pressure modification affected SBP and pulse pressure, whereas MAP was very mildly affected. Studies of pulsatile arterial hemodynamics [34,36] have repeatedly shown that the blood pressure curve may be divided into two components; a steady component (MAP), which is influenced by cardiac output and total vascular resistance, and a pulsatile component (pulse pressure), which is influenced by other independent hemodynamic variables such as ventricular ejection and distensibility of large arteries. For a long time, studies have shown that cyclic stress (as generated by pulse pressure) damages the arterial wall much more than continuous stress (as generated by MAP) [36]. Recent clinical and epidemiological studies have confirmed the important contribution of pulse pressure and cyclic stress to the morbidity and mortality of patients with heart and arterial diseases [37–39]. In this respect, it is remarkable to notice that smokers and patients with abnormalities of glucose metabolism are particularly prone to ischemic accidents of the heart and large vessels [2–9].

In conclusion, the present study has shown that, by using ambulatory blood pressure recordings, hypertensives who smoke or have elevated plasma glucose are characterized by a disproportionate increase in SBP and pulse pressure, with resulting changes in the pulsatile stress of the arterial wall. Whether this finding may be observed in larger populations remains to be investigated.

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