

Office normotensives with a minimal augmentation of intima-media thickness of common carotid arteries: really normotensives?

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Abstract. – BACKGROUND AND AIM: Blood pressure is an independent predictor of target organ damage (TOD). Recent data from literature suggest that TOD can be present also in pre-hypertensive subjects, diagnosed with pressure monitoring (PM). Aim of this study is to clarify whether an augmentation of the carotid Intima-Media Thickness (cIMT) in office prehypertensives is a TOD associated to monitoring prehypertension (MP).

PATIENTS AND METHODS: We have analyzed our database of individuals office normotensives showing an increase of cIMT. The ambulatory blood pressure monitoring (ABPM) of these was compared with those of office monitoring normotensives, matched by age and gender, antropometric characteristics, negative for familial hypertension and other risk factors (true normotensives, TN).

RESULTS: We have selected 15 presumable prehypertensives (PP) and 8 TN subjects. The ABPM (ambulatory blood pressure monitoring) analysis confirmed that neither the PP nor TN showed systolic (S) and diastolic (D) BP within-day values above their day-night upper reference limits. However the statistical comparison between PP and TN revealed that the first group had a significant elevation of SBP and DBP Daily Mean Level (DML_(SBP/DBP): $121 \pm 2/81 \pm 2$ vs $112 \pm 2/70 \pm 2$ mmHg, respectively, $p = 0.007$ and $p = 0.002$), confirming the MP diagnosis.

CONCLUSIONS: These results demonstrate that cIMT increase in PP fulfill the criteria for MP diagnosis, suggesting that MP should be undertaken in all PP with altered cIMT, but larger prospective studies are needed.

Key words:

ABPM, ABPM-Diagnosable Prehypertension, Monitoring Prehypertension, Masked Prehypertension, Target Organ Damage, TOD, End Organ Damage, Cugini's syndrome.

Introduction

In 2003, the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (BP), in its Seventh Report (JNC-7) suggested a classification, still in vogue, introducing a new grade of hypertension severity, namely "prehypertension", characterized by systolic (S) and diastolic (D) sphygmomanometric values of 120-139/80-90 mmHg, respectively^a. Subsequently the JNC-7 has introduced in this classification exactly term, ranges and meaning that Robinson and Brucer, firstly used in 1939 to indicate a BP regimen, laying between office normotension and office hypertension, playing the role of a preclinical risk factor for future development of a manifest hypertension², without a required pharmacological treatment.

In 2002, Pickering et al³ provided us with a classification on four conditions of concordance/discordance between office sphygmomanometry (OS) and ambulatory blood pressure monitoring (ABPM): (1) Normotensives at both OS and ABPM, namely "true normotensives"; (2) Hypertensives at both OS and ABPM, namely "true hypertensives"; (3) Hypertensives at OS, really normotensives at ABPM, namely "white coat hypertensives"; (4) Normotensives at OS, really hypertensives at ABPM, namely "masked hypertensives".

According to these evidences it has been argued that the association between Minimal TOD (target organ damage) and MP could be regarded as a clinical syndrome, in which the prehypertensive regimen had a causative role as tensile pathogenetic noxae.

Thus we wanted to perform a retrospective study by consulting our ABPM database in order to verify whether or not there were office normotensives showing a minimal TOD, given by augmentation of

the Intima-Media Thickness of common carotid arteries (CCA-IMT), that could be associated to MP.

Materials and Methods

From our patients database, via a blind procedure, a first observer extracted office normotensives who showed a minimal increase of CCA-IMT, namely pre-hypertensives (PP); those had intradiem SBP and DBP values within the normal range, also lacking of other potential atherogenic risk factors.

A second observer was asked to extract from the ABPM database those subjects classifiable as “true normotensives”, i.e., office normotensives and monitoring normotensives, lacking atherogenic risk factors and familiarity for hypertension, matched by age and gender, with prehypertensives.

In order to perform the statistical comparisons, the true normotensives were used as the control group, namely the Group A, while the presumable prehypertensives, were regarded as the experimental Group B.

Ultrasonography

The study included ultrasound examination of the supra-aortic vessels. Particular attention was given to detect a selective slight increase of the cIMT in absence of any other TOD. Ultrasonography was performed by means of the Acuson/Siemens Sequoia 512 apparatus®, equipped with linear array probes (6 and 15 Mhz) for superficial arteries. Standard presets were used for all the subjects. Linear probes (6 and 15 MHz) were used for conventional duplex ultrasonography, according to a routine protocol used in our echographic unit, and comprising the recordings of the B mode evaluation of cIMT on the far wall 1 cm below the bifurcation, according to standardized methods⁴. The B mode, Colour and Power mode evaluation was made of the distal and proximal internal and external carotid arteries, both in longitudinal as well as in transverse axes, in order to exactly evaluate vessel patency, morphology and plaque characteristics, when present. In addition, vertebral and subclavian arteries were evaluated too, according to the international guidelines⁴.

ABPM protocol

Each ABPM of our database has been carried out by means of the device TM 2430® (A&D Company Ltd, Japan), an oscillometric equipment validated by AAMI (Association for the Advancement of Medical Instrumentation) and BHS (British Hypertension Society).

In all the monitored cases, besides the anthropometric data, we asked information about office BP, hypertension matroclinic or patroclinic familiarity, awakening-sleeping time, physical-rest activity, meal timing schedule, eating as well as drinking and smoking habits.

We adopted the following exclusion criteria for life-style:

1. Disorder in awakening-sleeping time as well as meal time;
2. Assumption of any drug;
3. Incidence of stressor factors;
4. Abuse in smoking, drinking (especially alcohol, coffee, caffeinated beverages, tea, mineral water) as well as eating (especially foods containing vanilla and salt);
5. Licorice consumption;
6. Shifting in work.

Clinical criteria of exclusion were:

1. Metabolic disorders referred to carbohydrates (hyperglycemia or hypoglycemia), lipids (hypertriglyceridemia, hypercholesterolemia), purines (hyperuricemia);
2. Positive familiarity for hypertension;
3. Any cardiovascular risk factors.

The ABPM was performed by asking the investigated subjects to follow their own lifestyle, paying, however, a particular attention in avoiding: sexual activity, excessive efforts, stressing situations, excessive eating and drinking, environmental thermal excursions.

All the monitored subjects were requested to record in a diary the times of their main daily life activities (e.g., meals, sleep) as well as unusual events. Additionally, they were requested to adhere to the following advices in order to have a less randomized ABPM:

1. Sleeping-awakening time (waking: 06:30-08:30; sleeping: 21:00-23:00);
2. Meal timing schedule (breakfast: 07:00-08:30; lunch: 12:00-14:00; dinner: 19:30-21:30).

Each ABPM was started at 09:00 h of an usual working day and stopped 24-h later. In order to avoid the effects of non-equidistant data on the biometric estimation of the SBP and DBP daily mean level, we adopted an equispaced protocol of data acquisition with measurements performed every 30 min, daily and by night.

Pressurometric estimates and statistical comparison

Each ABPM of the control cases (Group A) as well as of the PP (Group B) was biometrical-

ly estimated by means of a dedicated software provided by the monitor device manufacturer.

The most important pressurometric estimates for MP diagnosis were: (1) The 24-h within-day SBP and DBP raw values; (2) the SBP and DBP Daily Mean Level - $DML_{(SBP/DBP)}^{3-8}$. Therefore, the presumable significant difference between the group-related $DML_{(SBP/DBP)}$ was statistical evaluated via Student's *t* test for unpaired data (a *p* value ≤ 0.05 was postulated to be a probability indicative for a significant difference between the statistical contrasts).

Due to the fact that the comparison was to be made between the group-estimated means, their goodness was established via the Standard Error of the Mean (SEM).

A chi-square test (χ^2) was performed when related to nominal instances, namely the percent number of SBP and DBP intradiam values above their upper time-qualified reference limits.

Results

The two observers extracted from our database, according to the criteria explained above, 15 PP, with increased cIMT, and 8 normotensives.

Table I shows the two patients groups characteristics. Demographics of the two groups were comparable with no significant differences for all the parameters in analysis.

Figure 1 shows the SBP and DBP time-qualified mean values ($\pm$ SE) in subjects belonging to the

Group A of true normotensives (*n*=8) as well as to Group B (*n*=15) of PP.

From the group-specific 24-h profiles, it was clearly seen that the prehypertensives (PP) were showing an upper dislocation of their SBP and DBP within-day values as compared to the true normotensives (TN).

According to this result, we performed the statistical comparison of the group related SBP and DBP daily mean levels - $DML_{(SBP/DBP)}$ - as shown in Table II. From the first and second column of the table it is shown that both groups did not include subject classifiable as hypertensive. From the third and fourth column it is shown that the $DML_{(SBP/DBP)}$ values are significantly higher in Group B of presumable prehypertensives as compared to Control Group A of true normotensives.

Discussion

Data from the present study show that BP measurement is not able to detect office prehypertensive subjects with or without minimal TOD, such as increased IMT. On the other hand ABPM can be useful in office normotensives showing a initial TOD, in that a MP has to be suspected, especially those without other cardiovascular risk factors belonging to the metabolic syndrome constellation. In fact several recent reports from literature support the association between initial TOD, such as the increased common-carotid or radial artery IMT and the MP status^{5,6}.

Table I. Anthropometric and laboratory data in true normotensives (Group A) and suspected monitoring prehypertensives due to an increased Intima-Media Thickness of common carotid arteries (CCA-IMT) (Group B).

Parameters	Control Group A: True normotensives (<i>n</i> =8)	Experimental Group B: Suspected monitoring prehypertensives due to a minimal augmentation of CCA-IMT (<i>n</i> =15)	Statistical comparisons (Significance of <i>p</i> values)
Age (yrs)	44 $\pm$ 10	45 $\pm$ 12	NS*
Sex (M/F)	4/4	7/9	NS**
Weight (kg)	82 $\pm$ 1627	84 $\pm$ 18	NS*
Height (m)	1.69 $\pm$ 0.6	1.7 $\pm$ 0.5	NS*
BMI (kg/m ²)	27 $\pm$ 3	29 $\pm$ 4	NS*
Office SBP/DBP (mmHg)	112 $\pm$ 8/72 $\pm$ 8	127 $\pm$ 7/84 $\pm$ 5	NS*
Total CHO (mg/dl)	201 $\pm$ 6	223 $\pm$ 47	NS*
HDL CHO (mg/dl)	55 $\pm$ 4	49 $\pm$ 12	NS*
Triglycerides (mg/dl)	132 $\pm$ 30	150 $\pm$ 95	NS*
Glycemia (mg/dl)	97 $\pm$ 5	94 $\pm$ 7	NS*
Creatinine (mg/dl)	0.90 $\pm$ 0.11	0.91 $\pm$ 0.13	NS*
Hypertensive familiarity (Y/N)	0/8	2/6	NS**
Smoking (Y/N)	0/8	2/6	NS**

IMT: Intima-Media Thickness; CHO: Cholesterol; *: Student's *t* test; **: χ^2 test; NS: not significant.

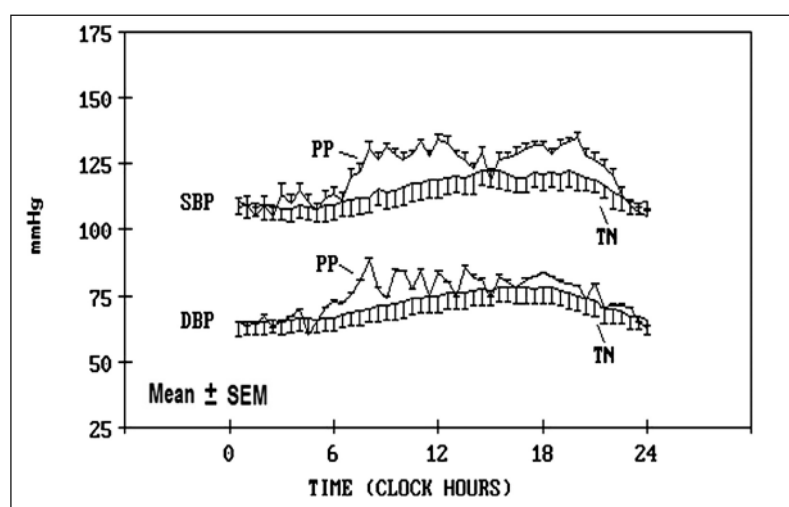


Figure 1. 24-h profiles of systolic (S) and diastolic (D) blood pressure (BP) in presumable prehypertensives (PP) with a minimal augmentation of Intima-Media Thickness of common carotid arteries (CCA-IMT), vs true normotensives (TN).

While the JNC-7 suggested that the office prehypertension has to be simply treated via non-pharmacological countermeasures devoted to reduce other facilitating risk factors in human life style, our data are in favour of the hypothesis that due to the occurrence of a prehypertensive regimen, responsible of TOD, a pharmacologic anti-hypertensive treatment could be precociously started in conjunction with the non-pharmacological countermeasures (diet, lifestyle changes etc).

Among the other studies highlighting the existence and clinical relevance of prehypertensive subgroup of patients, Cugini et al⁷ had inferred that there is a fifth group of subjects, i.e., normotensives at OS, that physicians are requested to diagnose as really monitoring prehypertensives at ABPM, namely “masked hypertensives”.

From 1997 to 2002 Cugini et al^{8,9} demonstrated that some subjects, considered to be normotensive at the casual Riva-Rocci sphygmomanometry, but unexplicably showing minimal signs of target organ damage (TOD) were showing an ABPM-diagnosable prehypertension, alias MP. Thus these subjects were classified by Cugini as “pre-hypertensive” in that the 24-h values of their blood pressure (BP), measured via ABPM, were invariably below the upper reference limits given at that time by WHO, but, notwithstanding that, their systolic (S) and diastolic (D) daily average was significantly higher than in “true normotensive” subjects. In 2007, as confirmed in 2009, such a clinical picture received the nosological eponym of “Cugini’s syndrome” (CS)¹⁰, i.e. ON subjects but unexplicably showing initial signs of hypertensive organ damage.

Table II. Report and statistical comparison of the biometric estimates regarding the systolic (S) and diastolic (D) blood pressure (BP) 24-h values measured via ABPM in true normotensives (Group A: Control group) and presumable prehypertensives (Group B: Experimental group) with augmentation of the Intima-Media Thickness of common carotid arteries (CCA-IMT).

Investigated groups	Number of time-qualified 24-h values (mmHg) above 135/85 (day-time), 125/75 (night-time)*		Daily mean level ($\pm$ SEM)** (mmHg)	
	SBP	DBP	SBP	DBP
Control Group A True normotensives	0	0	112 $\pm$ 3	70 $\pm$ 3
Experimental Group B Monitoring presumable prehypertensives with augmentation of CCA-IMT	0	0	121 $\pm$ 3	81 $\pm$ 2
Statistical comparisons	NA	NA	$p < 0.033$	$P < 0.002$

Statistical comparison via χ^2 test: Na = not applicable in that all the estimates are equal to zero. **: Statistical comparison via Student’s t test for unpaired data.

However it is important to stress that Cugini's studies have been originally conducted in office normotensives who were showing one of the following minimal TOD: (1) First stage retinopathy; (2) Interventricular septum hypertrophy; (3) Ongoing interventricular septum hypertrophy of the transplanted heart; (4) Altered gestational blood flow of uterine arteries; (5) Reduced intrauterine gestational fetal growth; (6) Endothelial dysfunction¹⁰.

So far masked monitoring prehypertension may be seen as a silent preclinical condition of potential cardiovascular risk. According to the above cited evidences from literature^{5,6} the monitoring prehypertensive regimen may be seen as associated to several minimal TODs, including the augmentation of the CCA-IMT, resulting, in an actual pathogenetic noxae of tensile cardiovascular damage. In fact office prehypertension is regarded also by the JNC-7 as a risk factor for the future development of a high BP regimen^{1,11,12}.

This study being a retrospective work, limits its prognostic and statistical significance.

Conclusions

This retrospective study has shown, that prehypertensive subjects may have an increased cIMT, considered as TOD. These subsets of patients may benefit from both lifestyle and, if larger prospective interventional multicenter studies will confirm these findings, pharmacological treatment in order to prevent hypertensive evolution until irreversible TOD.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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