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Effect of clustering of metabolic syndrome factors on capillary and cerebrovascular impairment

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ABSTRACT

Background: Hypertension and metabolic disorders, attended by impaired microcirculation, represent major risk factors for cerebrovascular impairment, as well as being individual components of the metabolic syndrome (MetS). Aim of the study was to establish whether mild hypertensives, aged ≤65 years, may be affected by progressive microvascular damage impairing cerebrovascular perfusion, related to a progressive clustering of MetS components.

Methods: Twenty-two normotensives with no MetS component (NTN-0), 29 hypertensives with no (HTN-0), 30 with one (HTN-1), 29 with two (HTN-2), 27 with three (HTN-3), 25 with all four (HTN-4) MetS components, were recruited. The study required office and twenty-four hour ambulatory blood pressure monitoring and video capillaroscopy. Functional (fCD), anatomical (aCD) and recruited (RECR) phalangeal skin capillarity were assessed. Cerebral vasodilatory reserve was measured by the breath-holding index (BHI), using transcranial Doppler, in HTN-1 and HTN-2 with MetS.

Results: The fCD and aCD were reduced in hypertensives and progressively reduced in those with MetS, while RECR was also impaired. BHI was lower in HTN-2 than in HTN-1 ($p<0.001$). BHI was correlated with fCD in HTN-1 (.396, p: .046), HNT-2 (.497, p: .011), and with aCD in HTN-2 (.494, p: .012), by partial Pearson test.

Discussion: The findings show that hypertensives exhibit an increasing microvascular rarefaction with MetS progression and that an impaired cerebral perfusion occurs when the MetS is established. The data underline the importance of preventing MetS in mild hypertensives, as it causes microvascular damage and impairs cerebral arterial perfusion.

1. Introduction

Stroke is the most invalidating consequence of hypertension (HTN). Cerebral ischemic disorders may be caused by underlying atheromas or thickening of the hyaline deposits in small perforating terminal arterioles [1]. Moreover, impaired cerebral macro- and/or micro-vascular perfusion [2] hampers the cerebral vasodilatation reserve [3], as shown by the reduced response to vasodilating stimuli. The association of high blood pressure with a cluster of metabolic disorders gives rise to the metabolic syndrome (MetS) that significantly enhances the risk for cardiovascular events [4]. The syndrome has reached epidemic proportions in western society [5] and it has been associated with a two-to-fourfold rise in the risk of brain infarction [6,7], even in patients without diabetes [8]. In particular, the MetS, by facilitating macro- and micro-vascular lesions, may induce vascular-mediated dementia in elderly patients [9].

The structure and function of the microcirculation are altered in HTN because of the combined effects of reduced vasodilator responses, structural alterations and reduction in the number of arterioles and capillaries [10]. Moreover, normotensives with a genetic risk for developing HTN and mild hypertensives show capillary rarefaction prior to manifesting macro-vascular damage [11]. Thus, microcirculatory dysfunction should be recognized early as it may herald the development of target organ damage [12,13]. Aim of the present pilot study is to establish whether adults with mild hypertension, aged ≤65 years, with a similar estimated history and state of hypertension, may be differently affected by peripheral microvascular damage in proportion to the number of MetS components they exhibit, and whether they show an impaired cerebral functional vasodilatation at the onset of the MetS.

2. Methods

Patients were recruited between June 2006 and October 2010 at the Department of Neurology, Unit of Cerebrovascular Prevention

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and Hypertension. The procedures were approved by the Institutional Ethical Review Board, and patients gave informed consent to take part.

During the run-in phase, office systolic (SBP) and diastolic blood pressure (DBP) and heart rate (HR) measurements were taken initially and repeated, after 10 min of rest, 10–14 days after the first medical examination, to confirm their hypertensive state. No patient was taking antidiabetic medication. Patients with potential sources of limited cerebral blood flow, such as carotid artery stenosis, were excluded. Any drug interfering with BP and blood lipids was suspended for four weeks prior to recruitment. The patients remained under strict medical supervision by open access to our outpatients clinic and telephone interviews. A total of 162 subjects (M/F: 92/70) were recruited. Patients' visits were scheduled at the clinic between 8:00 and 9:00 a.m., after a twelve-hour fasting period, for a general physical examination, twelve-lead electrocardiogram, chest X-rays and routine blood chemistry to exclude any significant complication. Those patients who presented fasting plasma glucose >120 mg/dl had a repeat blood test and, if necessary, the standard oral glucose tolerance test.

Body mass index (BMI) and abdominal circumference (AC) were calculated. After 10 min of rest in recumbent position, HR and SBP/DBP were measured at both arms, in triplicate, in a temperature-controlled room (23–25 °C). The values obtained were averaged.

Although any metabolic component of MetS may represent an independent risk factor for cardiovascular events, following the diagnostic criteria for the MetS (NCEP ATP-III), we considered clusters of subjects characterized by increasing numbers of these determinants [14]. Thus, following the ESC-ESH 2007 guidelines, we included in the study 22 normotensives with no MetS component (NTN-0), who served as control group, and 140 patients with normal-high blood pressure or grade-1 hypertension who were subdivided into 29 hypertensives with no further MetS determinant (HTN-0), 30 hypertensives with one (HTN-1), 29 hypertensives with two (HTN-2), 27 hypertensives with three (HTN-3) and, finally, 25 hypertensives with all four additional factors constituting the MetS (HTN-4).

A decreased microvascular density and an impaired capillary recruitment are the basic expression of a microcirculatory dysfunction, which impairs the capillary perfusion and the pattern of blood flow [15].

Therefore, within three days, in the same environment, skin capillary density was assessed by video capillaroscopy [16,17]. Although the method we previously used allowed us to identify microvascular damage in mild hypertensives with sleep apnoea [18], we reproduced, for the present study, the method [19] recently used by others to study patients with MetS. Briefly, capillaroscopy was executed at the non-dominant hand, resting on a splint, surrounded by a vacuum pillow, at the middle third of the middle phalanx of the second and the fourth fingers, using an epi-illuminated microscope containing a 100 W mercury vapor lamp light source, a PL 6.3/0.2 lens (Videocap 300, Scalar Co, DS Medica, Milano, I) and a final magnification of 200×. Four microscopic fields (1 mm^2 each), centered on an ink spot, were considered.

Baseline (functional) capillary density (fCD) was determined by counting the perfused capillaries (n/mm^2) by hand from still-frame video prints and live playback (5 min.). To enhance the visualization of functionally excluded capillaries [17–19] a blood pressure cuff was applied around the wrist and the cuff was inflated at 50 mmHg for 2 min. Then, four further images were taken at the same areas. Results were averaged to obtain the structural (anatomical) capillarity, as the number of capillaries counted during venous congestion (aCD). The difference between aCD and fCD represented the measure (recruitment) of functionally excluded capillarity (RECR). The measurements were performed by two independent operators. The results obtained were averaged.

Continuous ambulatory blood pressure monitoring (ABPM) was performed afterwards to evaluate SBP and DBP and HR circadian changes (AND TM 2430, A&D Instruments Ltd., Oxford, UK) [20,21]. Measurements were taken every 20 min throughout the day and night. Awake and sleeping times were determined from diary card entries [22].

The effect of MetS was evaluated also in a different vascular district. HTN-1 and HTN-2, being the borderline groups, diagnosed immediately before and after the onset of the MetS, underwent cerebral arterial dilating reserve evaluation [23]. The evaluation of cerebral blood flow changes during the breath-holding test [24] was carried out under the same conditions, with patients in a recumbent position. Bilateral middle cerebral artery (MCA) blood flow was obtained by transcranial Doppler (Aplio XV, Toshiba, Tokyo, Japan). Two dual 2.0 MHz pulse wave probes, fitted on a headband and placed on the ultrasound temporal bone window, were used to obtain bilateral continuous measurement of the mean blood flow velocity (MFV) in both the MCAs. After the optimization of the signal, baseline velocity was recorded during the last 3 min of an initial 10 min of resting trial. Then, we induced hypercapnia by 25 to 30 s of breath holding [25] and we evaluated the cerebral vasodilatation reserve on the basis of the breath-holding index (BHI). BHI was obtained by dividing the rise in MFV occurring during the breath holding maneuver by the length of time [(MFV at the end of breath holding − rest MFV)/rest MFV]×(100/s of breath holding). Three sets of measurements were performed, after 5 min of rest and the values obtained were averaged [24,25].

Six patients underwent a repeat ABPM because of an insufficient number of measurements (<80%). Transcranial Doppler could not be executed in four patients because of a scarce ultrasound temporal bone window [25]. They were replaced by new subjects.

The values obtained are expressed as mean ± S.D. Data were analyzed by ANOVA followed by Bonferroni post hoc test, setting significance at $p<0.05$. Partial Pearson test was performed to highlight the association between BHI and capillarity indices.

3. Results

Age and smoking habit did not differ among patients. Family histories of hypertension and diabetes and the estimated history of HTN were similar among mild hypertensives (Table 1).

Hypertensives showed similar office SBP and DBP. HR was similar in all subjects. Awake and nocturnal ABPM confirmed the diagnosis of HTN with no difference among hypertensives. Patients with MetS showed a lower nocturnal blood pressure fall (Table 1).

BMI was higher in HTN. Those with an increasing number of MetS determinants showed a progressive increase of BMI and AC (Table 2).

Total-cholesterol was higher in hypertensives with the MetS. LDL-cholesterol was higher only in those with the highest clustering of components. HDL-cholesterol became progressively lower in hypertensives with MetS parallel to the progressive clustering of components. Triglycerides and blood glucose also progressively rose in these patients. A retrospective analysis, based on ADA guidelines, showed that 1 HTN-2 presented impaired fasting glucose and that 5 HTN-3 and 4 HTN-4 were affected by type-2 diabetes (Table 2).

Video capillaroscopy showed that fCD was reduced in hypertensives and, in particular, lower in those with an increasing number of MetS determinants. Similarly, aCD was lower in HTN but this was more serious when the MetS was superimposed on hypertension. The microvascular structural damage was confirmed by RECR which was reduced to a similar extent in all the hypertensives with MetS (Table 3). Then, the incidence of type-2 diabetes did not affect the capillary rarefaction which was similarly displayed in HTN-2, who were affected by MetS but not by diabetes.

The cerebral arterial vasodilatation response was significantly reduced in the patients with MetS (HTN-1 = 1.45 ± 0.24 vs HTN-2 = 1.01 ± 0.25, $p<0.001$), suggesting that MetS may reduce arterial compliance and functional blood flow (Fig. 1) in the cerebral vascular district of mild hypertensives.