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Research Article

Impaired metabolic profile is a predictor of capillary rarefaction in a population of hypertensive and normotensive individuals

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Abstract

Capillary rarefaction is typically encountered in essential hypertension, yet identification of factors interfering with this phenomenon remains substantially underinvestigated. We examined whether components of metabolic profile (dyslipidemia, insulin resistance), inflammatory (high-sensitivity C-reactive protein, high-sensitivity C-reactive protein), and angiogenic (vascular endothelial growth factor) factors are implicated in this phenomenon in a population of newly diagnosed, never-treated hypertensive patients and normotensive controls. Nailfold capillary density was estimated with nailfold capillaroscopy using specifically designed software. A total of 159 individuals, 93 hypertensives, and 66 normotensives were included. Nailfold capillary density was lower among hypertensives compared to normotensives (146.4 ± 31.0 vs. 155.4 ± 26.9, respectively; $P = .047$). In the total population, capillary density significantly correlated with high-density lipoprotein (HDL) ($r = 0.232$; $P = .003$), HDL/low-density lipoprotein ratio ($r = 0.175$; $P = .025$), age ($r = 0.236$; $P = .003$), but neither with vascular endothelial growth factor or high-sensitivity C-reactive protein. An inverse association was found with body mass index ($r = -0.174$; $P = .029$), insulin levels ($r = -0.200$; $P = .018$), and homeostasis model assessment-insulin resistance ($r = -0.223$; $P = .009$). In the separate analysis for the hypertensive population, sex ($P = .014$) and homeostasis model assessment-insulin resistance ($P = .011$) were identified as significant predictors of capillary rarefaction after adjustment for other factors. On the contrary, only HDL levels ($P = .036$) predicted capillary density in the multiple regression model for the normotensive population. Different aspects of impaired metabolic profile, that is, insulin resistance and low HDL levels, but not angiogenic or inflammatory markers, appear to be independently associated with capillary rarefaction in hypertensive and normotensive individuals. J Am Soc Hypertens 2016;10(8):640–646.

Keywords: Capillary rarefaction; hypertension; insulin resistance; metabolic profile.

Introduction

Cardiovascular diseases are thriving, and the need for identification of early, easily applicable indices of subclinical microvascular organ damage, before the progression to overt cardiovascular disease, is urgent. The microvasculature is subject to a series of functional and morphological changes in cardiovascular diseases, with capillary rarefaction representing a typical and consistent finding.[1–3] Dermal capillaries represent an ''open'' and representative window for the in vivo study of human microcirculation that can be directly, repetitively, and easily visualized by noninvasive techniques such as nailfold capillaroscopy.[4] Nailfold capillaroscopy has been used as an estimate of the microvascular status in patients with cardiovascular diseases and particularly in the field of hypertension. Of all the morphologic alterations that have been described in hypertensive patients by use of nailfold capillaroscopy, capillary

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rarefaction (ie, decreased capillary density per visual field) has been recognized as an early characteristic feature of the disease, even in ''naïve'' hypertensive patients (newly diagnosed, never-treated, free from any other comorbidities).[5,6]

Traditionally, capillary rarefaction in both experimental and clinical studies of hypertension is perceived as a consequence or even a cause of altered hemodynamics.[4] However, other pathophysiological pathways in the cause–effect links between hypertension and capillary rarefaction may be implicated. A postulated mechanism of hypertension-related capillary rarefaction involves the low-grade inflammatory response, which may contribute to the structural changes of the arterial wall and subsequent capillary loss.[7] In addition, impaired angiogenesis may characterize arterial hypertension, indicated by an imbalance of proangiogenic, including vascular endothelial growth factor (VEGF) versus antiangiogenic factors.[8] Microvascular rarefaction is a hallmark in patients treated with anti-VEGF molecules, implying a crucial role of VEGF in maintaining normal structural and functional microvasculature in humans.[9]

Although the clinical significance of hypertension-related capillary rarefaction is currently undergoing thorough investigation, the field appears uncharted when it comes to the potential impact of lipid metabolism on skin capillary density of hypertensive patients. Dyslipidemia is a major and well-established cardiovascular risk factors[10] and a very frequent comorbidity in hypertensive patients.[11] Whether and to which extent it exerts similar to high blood pressure (BP) effects on capillary density remains unknown. In addition, while evidence suggests that insulin resistance is associated with microvascular abnormalities detected with nailfold capillaroscopy in patients with metabolic syndrome,[12,13] data are scarce when it comes to healthy individuals and newly diagnosed hypertensive patients.

Therefore, the aim of the present study was to identify predictors of capillary rarefaction in a population of newly diagnosed, never-treated, otherwise healthy hypertensive patients and healthy individuals, focusing on metabolic disturbances (dyslipidemia, insulin resistance). In addition, we investigated whether angiogenic (VEGF levels) and inflammatory (high-sensitivity C-reactive protein [hsCRP]) factors might contribute to decreased capillary density in our population.

Materials and Methods

Study Population

Consecutive newly diagnosed, never-treated, otherwise healthy patients with hypertension and/or dyslipidemia attending the hypertension outpatient clinic of our department were included in the study. Healthy individuals attending their regular check-up appointments and healthy volunteers from the local community comprised the control group. A thorough medical history recording, physical examination, BP measurement, routine laboratory testing, and nailfold capillaroscopy were performed to all participants. Exclusion criteria were (1) secondary causes of hypertension, (2) known chronic or familial diseases (including previously diagnosed hypertension), and (3) regular medication use for any reason. All participants gave their written informed consent before participation. The study was conducted in accordance with the principles of Helsinki declaration and was approved by our hospital's ethics committee.

BP Measurement

Office BP was measured in both arms using a validated oscillometric device (Microlife Exact BP, Microlife AG, Widnau, Switzerland) after 10 minutes rest. Office BP was recorded as the mean of the second and third value of three consecutive measurements with a 2-minute interval in the arm with the higher BP.

Blood Samples and Analyses

Blood was obtained between 9 AM and 12 PM by venipuncture in resting conditions after overnight fasting. Total cholesterol, triglycerides (TGs), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol were measured by conventional enzymatic method (Olympus AU560, Hamburg, Germany). Dyslipidemia was defined as total cholesterol $\geq$ 240 mg/dL and/or LDL $\geq$ 160 mg/dL, HDL $<$ 40 mg/dL, and TG $\geq$ 200 mg/dL.[14]

Insulin levels were estimated with immunoradiometric assay. Insulin resistance was evaluated with the homeostasis model assessment-insulin resistance (HOMA-IR) index, based on the equation HOMA-IR = fasting glucose (mmol/L) $\times$ fasting insulin (μU/mL)/22.5.[15]

VEGF and hsCRP were used as markers of angiogenesis[16] and vascular inflammation,[17] respectively. Both were measured in patient's serum by the use of immunoenzymatic ELISA method (Quantikine Human VEGF Immunoassay kit, DVE00, R&D systems, Inc, Minneapolis, USA, and high sensitive CRP ELISA kit, IBL, Hamburg, Germany).

Nailfold Capillaroscopy

Nailfold capillary density was estimated with nailfold capillaroscopy (DS Medica, Milan Italy, $\times$200 magnification). Images of the distant phalanx were taken after mineral oil placement to improve image quality, where the capillaries could be seen in transverse section. The subjects were seated with the hand supported. All procedures were conducted in the same temperature-controlled room. To determine the capillary number/visual field, a