Rarefaction of Skin Capillaries in Borderline Essential Hypertension Suggests an Early Structural Abnormality

Tarek F.T. Antonios, Donald R.J. Singer, Nirmala D. Markandu, Peter S. Mortimer, Graham A. MacGregor

Abstract—We recently showed that rarefaction of skin capillaries in the dorsum of the fingers of patients with essential hypertension is due to the structural (anatomic) absence of capillaries rather than functional nonperfusion. It is not known whether this rarefaction is primary (ie, antedates the onset of hypertension) or secondary (ie, as a consequence of sustained and prolonged elevation of blood pressure). The aim of the present investigation was to study skin capillary density in a group of patients with mild borderline hypertension to assess whether rarefaction antedates the onset of sustained elevation of BP. The study group included 18 patients with mild borderline hypertension (mean supine BP, 136/83 mm Hg), 32 normotensive controls (mean BP, 126/77 mm Hg), and 45 patients with established essential hypertension (mean BP, 156/98 mm Hg). The skin of the dorsum of the fingers was examined by intravital capillary videomicroscopy before and after venous congestion at 60 mm Hg for 2 minutes. Patients with borderline essential hypertension had the lowest resting capillary density when compared with normotensive controls and patients with established hypertension. Maximal capillary density with venous congestion in the borderline group remained the lowest. The study confirmed that patients with borderline essential hypertension have skin capillary densities that are equally low as or even lower than patients with established hypertension.

Key Words: hypertension, essential ■ microcirculation ■ capillaries ■ blood vessels, rarefaction

Rarefaction of capillaries and arterioles is now a well-established abnormality that occurs in many tissues in patients with human essential hypertension.1-5 We recently showed that the rarefaction of capillaries in the skin of the dorsum of the fingers in patients with essential hypertension is due to the structural (anatomic) absence of capillaries rather than nonperfusion or functional rarefaction.1 It is not yet known whether this rarefaction is primary (ie, antedates the onset of hypertension) or secondary (ie, occurring as a consequence of prolonged elevation of blood pressure). Previous studies indicated that rarefaction may occur in patients with borderline essential hypertension and only intermittent elevations of blood pressure.6 The use of the term “borderline hypertension” has been most confusing. According to the 1999 World Health Organization–International Society of Hypertension (WHO-ISH) guidelines for the management of hypertension,7 which are based on the sixth report of the United States’ Joint National Committee (JNC-VI),8 the definition of borderline mild hypertension is a systolic blood pressure (SBP) between 140 and 149 mm Hg and a diastolic blood pressure (DBP) between 90 and 94 mm Hg. A more physiologically oriented definition of borderline hypertension is a state in which blood pressures have been documented within the normal range (ie, <140/90 mm Hg), but on at least 2 occasions, they have been documented as above that level.9 The aim of this study was to assess whether rarefaction of skin capillaries in patients with essential hypertension is an early abnormality that antedates the onset of the sustained elevation of blood pressure or if it is a secondary phenomenon that occurs as a consequence of the raised blood pressure.

Methods

Subjects
Subjects consisted of 18 patients with mild borderline essential hypertension (whose blood pressures have been documented within the normal range [<140/90 mm Hg] but on at least 2 occasions were above that level but <150/95 mm Hg), 45 patients with previously untreated, established essential hypertension (SBP >160 mm Hg and/or DBP >95 mm Hg), and 32 normotensive controls (SBP <140 mm Hg and DBP <85 mm Hg on repeated measure-
All patients were assessed in the Blood Pressure Unit of St George’s Hospital Medical School, and they were included in the study if no underlying cause for their high blood pressure was found. Patients with a history of connective tissue disease, diabetes mellitus, or skin diseases or who were on vasoactive drugs were excluded from the study. The protocol was approved by the local Ethics Committee of St. George’s Hospital. Written informed consent was obtained from each patient.

Intravital Capillaroscopy

All capillaroscopy studies were done in parallel. Subjects were studied in the morning between 9 and 11 AM after an overnight fast. The capillaroscopy studies were performed in a temperature-controlled laboratory (21°C to 24°C) after the study subjects had rested for at least 20 minutes in the semisupine position. Room temperature was monitored before and during the studies and, if necessary, the temperature was adjusted by the use of fan heaters or air conditioning. Patients were seated with the left forearm and hand supported at the heart level. Both the hand and the forearm rested on a splint surrounded by a vacuum pillow (a specially constructed pillow filled with polyurethane foam that can be molded to any desired shape by creating a vacuum) to restrict movement. Video-coupled device camera (Hitachi; model, CCD HV-725K) and trans-mercury vapor lamp light source, a PL 6.3/0.2 objective (Wild-Leitz) was used. Microscopic images were recorded with a charge-coupled device camera (Hitachi; model, CCD HV-725K) and transferred with a videocamcorder (VS-1000) and videoediting (For-A VTG 33) for storage onto a video recorder (Panasonic; model, AUC 7350).

The skin of the dorsum of the middle phalanx of the nondominant (usually, left) hand was examined. Four microscopic fields (0.68 mm² each) centered around an ink spot were recorded continuously for 5 minutes to detect intermittently perfused capillaries. Still-frame video prints (Sony Multiscan Video-Printer UP-930) obtained from each recorded field were analyzed offline. The number of capillaries per field was counted by hand from these prints and from live playback of the recorded tapes. Skin temperature was monitored throughout the study with a temperature probe on the dorsum of the left index finger (YSI Telethermometers). Patients with cold hands or with Raynaud’s phenomenon were excluded from the study.

Maximization of Visualized Skin Capillaries

The enhancing effect of venous congestion on the visualization of skin capillaries by videomicroscopy was previously reported. We recently showed that venous congestion maximizes the number of visible capillaries more than reactive hyperemia; it does this by increasing their red cell content. In this study, a miniature blood pressure cuff was applied to the base of the left middle finger and the cuff was then inflated and maintained at 60 mm Hg for 2 minutes; further images were recorded with the use of 1 of the 4 microscopic fields chosen at random.

Blood Pressure and Heart Rate

Blood pressure was measured with a semiautomatic ultrasound sphygmomanometer (ArterioSonde, Roche) with an appropriate cuff size. Supine and standing BP were taken as the mean of 3 readings obtained at 1- to 2-minute intervals with the patient in the corresponding position.

Blood Analysis

Venous blood was taken without stasis after the patient had been sitting upright for 10 minutes. Variables measured included serum electrolytes, urea, creatinine, uric acid, glucose, total cholesterol, triglycerides, and full blood count.

Statistical Analysis

All results are given as means±SEM. The data were processed by StatView 5.0 (SAS Institute Inc). ANOVA and Bonferroni’s post hoc tests were used to compare groups. *P<0.05 was considered statistically significant.

### Baseline Characteristics of Study Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Borderline Hypertensive Patients (n=18)</th>
<th>Established Hypertensive Patients (n=45)</th>
<th>Normotensive Controls (n=32)</th>
<th>P value by ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>45.4±3.4</td>
<td>47±0.1±1.8</td>
<td>51.5±2.1</td>
<td>0.179</td>
</tr>
<tr>
<td>Gender, men/women</td>
<td>11/7</td>
<td>29/16</td>
<td>18/14</td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>76.9±3.7</td>
<td>84.5±3.1</td>
<td>74.2±2.2</td>
<td>0.314</td>
</tr>
<tr>
<td>Height, cm</td>
<td>170.0±2.6</td>
<td>171.9±1.5</td>
<td>171.4±1.5</td>
<td>0.787</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.1±1.0</td>
<td>28.6±0.9†</td>
<td>25.2±0.6</td>
<td>0.009</td>
</tr>
<tr>
<td>Hip/waist ratio</td>
<td>119.5±3.0</td>
<td>113.6±1.8§</td>
<td>120.2±2.7</td>
<td>0.065</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>136/83±3/1†</td>
<td>156/98±2/1‡</td>
<td>126/77±2/1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Standing</td>
<td>136/88±3/2‡</td>
<td>152/102±3/2‡</td>
<td>122/80±2/1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean</td>
<td>101±1§</td>
<td>118±1§†</td>
<td>94±1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pulse, bpm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>74±3†</td>
<td>75±2‡</td>
<td>68±2</td>
<td>0.017</td>
</tr>
<tr>
<td>Standing</td>
<td>76±3†</td>
<td>81±2‡</td>
<td>73±2</td>
<td>0.006</td>
</tr>
<tr>
<td>Room temperature, °C</td>
<td>30.6</td>
<td>30.4</td>
<td>31.2</td>
<td>0.89</td>
</tr>
<tr>
<td>Skin temperature, °C</td>
<td>24.2</td>
<td>24.2</td>
<td>24.4</td>
<td>0.39</td>
</tr>
<tr>
<td>Mean capillary density, No. per field (0.68 mm²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before venous congestion</td>
<td>57±4‡</td>
<td>58±3§</td>
<td>76±3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>With venous congestion</td>
<td>63±4§</td>
<td>70±3§</td>
<td>93±3</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SEM. *P<0.05, †P<0.01, ‡P<0.005, §P<0.0001, by Bonferroni’s post hoc test vs normotensive controls.
Skin capillary density before and after venous congestion in 18 patients with borderline hypertension, 45 patients with untreated essential hypertension, and 32 normotensive controls.

### Discussion

The present study found that significant structural rarefaction of the skin capillaries occurs in the early stages of human essential hypertension, with only mild intermittent elevation of blood pressure. Therefore, capillary rarefaction may be a primary or very early structural abnormality rather than a consequence of sustained hypertension. The results of this study agree with several previous studies on structural abnormalities in patients with borderline essential hypertension. Sullivan et al. described the rarefaction of conjunctival capillaries in patients with intermittent elevation of blood pressure. They found that capillary density was inversely related to the cardiac index but not to blood pressure. Some authors consider this rarefaction a form of autoregulation, reflecting the long-term adaptation of microcirculation to the elevated blood pressure or the initial increase of blood flow.

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Our study also agreed with the results of Noon et al., who found that people with high blood pressure whose parents also had high blood pressure had fewer capillaries on the dorsum of their fingers, suggesting that defective angiogenesis may be an etiological component in the inheritance of high blood pressure. Also, Draaijer et al. found that sodium-resistant borderline hypertensives had a possible structural reduction in nailfold skin capillary density when compared with both sodium-sensitive and control subjects.

In the Tecumseh blood pressure study, Julius et al. described the rarefaction of capillaries in hypertension. Significant structural rarefaction in nailfold skin capillary density may be an early event in the development of hypertension and, as the cardiac output returns to normal levels, may have a relative enlargement of the left ventricle as compared to normotensive patients. Primary structural rarefaction of capillaries may support the theory of reduced angiogenesis and diminished microvascular growth in primary hypertension.

In conclusion, the study demonstrates significantly low skin capillary densities in patients with mild intermittent borderline essential hypertension, equivalent to the densities in patients with established hypertension. This suggests that rarefaction may be an early event in the development of hypertension and not secondary to the sustained elevation of blood pressure. The study also strongly suggests that much of the reduction in capillary density in hypertension is due to the anatomic absence of capillaries, rather than a functional reduction.

### References


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