Structural Skin Capillary Rarefaction in Essential Hypertension

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

Abstract—A reduction in the density of capillaries (rarefaction) is known to occur in many tissues in patients with essential hypertension. This rarefaction may play a role in increasing peripheral resistance. However, the mechanism underlying this capillary rarefaction is not understood. The aim of this study was to assess the extent of structural versus functional capillary rarefaction in the skin of dorsum of fingers in essential hypertension. The capillary microcirculation was examined with video microscopy before and after maximizing the number of perfused capillaries by venous congestion. The study group comprised 17 patients with essential hypertension (mean supine blood pressure, 155/96 mm Hg) and 17 closely matched normotensive controls (mean blood pressure, 127/77 mm Hg). We used intravital video microscopy with an epi-illuminated microscope to examine the skin of the dorsum of left middle phalanx before and after venous congestion at 60 mm Hg for 2 minutes. A significantly lower mean capillary density occurred at baseline in hypertensive subjects versus normotensive subjects. With venous occlusion, capillary density increased significantly in both groups; however, maximal capillary density remained significantly lower in the hypertensive subjects than in the normotensive subjects. The study strongly suggests that much of the reduction in capillary density in the hypertensive subjects is caused by structural (anatomic) absence of capillaries rather than functional nonperfusion. (Hypertension. 1999;33:998-1001.)

Key Words: hypertension, essential | microcirculation | capillaries | vascular resistance | rarefaction

The established phase of human essential hypertension is characterized by a normal cardiac output and an elevation in the peripheral vascular resistance.1 A considerable part of this increased vascular resistance is determined at the microvascular level: in particular, at the small arteries and precapillary arterioles. However, abnormalities (such as capillary hypertension, increased looping, increased transcapsillary filtration, and a reduction in capillary density per volume of tissue) are also known to occur in the capillary circulation in essential hypertension.2-4 Rarefaction of capillaries and arterioles has been reported in nearly all animal models of hypertension.5-6 More than 6 decades ago, Ruedemann,7 using microphotography, reported rarefaction of capillaries in the conjunctival circulation of humans. Similar findings were also reported by Lack.2 Recently, with the introduction of intravital capillary video microscopy, rarefaction of capillaries has been reported in nail-fold skin8 and by our own group in forearm skin.9 These abnormalities suggest that capillaries may also be involved in increasing peripheral resistance in essential hypertension. However, it is not clear whether this reduction in capillary density in essential hypertension is caused by a structural (anatomic) absence of capillaries or a functional rarefaction, in which capillaries are present but not perfused.

The aim of this study was to assess whether rarefaction of capillaries in hypertension is a structural or functional defect by examining capillary density in the skin of the dorsum of fingers under resting conditions and after maximizing the number of perfused capillaries.

Methods

Subjects

Seventeen patients with essential hypertension who had not received treatment for their high blood pressure (systolic blood pressure (BP) >160 mm Hg and/or diastolic BP>90 mm Hg) and 17 age- and weight-matched normotensive controls (BP<140/85 mm Hg) were studied. All patients were assessed in the Blood Pressure Unit, St George’s Hospital Medical School. 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, skin diseases, or use of 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. Subjects were studied in the morning between 9 and 11 AM after an overnight fast. All subjects were nonsmokers except for 2 hypertensive patients and 2 normotensive controls. Smokers were asked to refrain from smoking on the day of the study. The capillaroscopy studies were performed in a temperature-controlled laboratory (21°C to 24°C) after the study subjects had at least a 20-minute semisupine rest. Each subject was seated with the left forearm and hand...
supported at 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.

**Intravital Capillaroscopy**

Video microscopy with an epi-illuminated microscope containing a 100-W mercury vapor lamp light source and a PL 6.3/0.2 objective (Wild-Leitz type 307–143.004, Leica UK Ltd), final magnification of \( \times 196 \), was used. Microscopic images were recorded on a CCD camera (Hitachi, model CCD HV-725K) and transferred using a video scalar (VS-1000) and video timer (For-A VTG 33) for storage onto a video recorder (Panasonic model AUC 7350). The skin of the dorsum of middle phalanx of the nondominant (left) hand was examined. Four microscopic fields (0.68 mm\(^2\) 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 as well as 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 Tele-thermometers). Patients with cold hands were excluded from the study.

**Maximization of Skin Capillaries Visualized**

Different techniques have been used previously to maximize the number of skin capillaries visualized during dynamic capillaroscopy. In a separate study, we examined 33 subjects 21 to 68 years of age (16 men, 17 women) to compare the effects of venous congestion versus postocclusive reactive hyperemia on skin capillary density.

**Venous Congestion**

The enhancing effect of venous congestion on the visualization of skin capillaries by video microscopy has been previously reported.\(^{10-12}\) Venous congestion maximizes the number of visualized capillaries by increasing their red cell content. A miniature BP cuff was applied to the base of the left middle finger, the cuff was inflated and maintained at 60 mm Hg for 2 minutes, and further images were recorded using 1 of the 4 microscopic fields, chosen at random.

**Reactive Hyperemia**

This produces a vasodilative response mediated by myogenic and/or local chemical factors. We applied 2 different techniques. First, arterial blood flow into the forearm and hand was stopped for 3 minutes by inflating a sphygmomanometer cuff to 200 mm Hg. Second, we inflated a miniature cuff applied to the base of the middle finger and again stopped arterial blood flow in the finger for 5 minutes by inflating the cuff to 200 mm Hg. In both cases, the cuff was deflated abruptly by breaking the connection, and, subsequently, capillaroscopic images were obtained continuously for 2 minutes.

The results showed that the baseline mean skin capillary density of the dorsum of finger was 76±20/68 mm\(^2\). With venous occlusion, capillary density increased to 84±5/68 mm\(^2\), and with reactive hyperemia it dropped to 71±30/68 mm\(^2\) (\(P<0.0001\); ANOVA) (Figure 1). These results clearly show that when using intravital capillary video microscopy venous congestion maximizes the number of visualized capillaries more significantly than does postocclusion reactive hyperemia. It is well known that capillary blood-cell velocity (CBV) increases with postocclusive reactive hyperemia.\(^{13,14}\) With reactive hyperemia the number of capillaries showing active flow motion increased.\(^{15}\) Given these last 2 findings, it may not be surprising that fewer capillaries were visible during reactive hyperemia than with venous congestion.

**Blood Pressure and Heart Rate**

Blood pressure was measured with a semiautomatic ultrasound sphygmomanometer (Arteriosonde, Roche) with appropriate cuff size. Supine blood pressure was taken as the mean of 3 readings obtained at 1- to 2-minute intervals with the patient supine. Body weight was recorded in the morning after the patient voided and with each patient wearing indoor clothing and no shoes.

**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 mean±SE. The data were processed by use of StatView 4.0 software (Abacus Concepts, Inc). ANOVA for repeated measurements was used to compare groups. \(P<0.05\) was considered statistically significant.

**Results**

The Table shows baseline characteristics and capillaroscopic data before and after 2 minutes of venous occlusion at 60 mm Hg in 17 hypertensive patients and 17 age- and weight-matched normotensive controls.

Mean capillary density at baseline (before venous congestion) was significantly lower (17\%) in the hypertensive subjects than in the normotensive controls (62±2.4 versus 73±5 capillaries per 0.68 mm\(^2\) respectively) (\(P=0.049\); ANOVA) (Figure 2). With venous occlusion, capillary density increased significantly in both groups; however, maximal capillary density was significantly lower (19\%) in the hypertensive subjects (73±5 capillaries per field in the hypertensives) compared with 87±4 capillaries per field in the normotensives (\(P=0.0325\); ANOVA) (Figure 2).

**Discussion**

The study demonstrates that in patients with essential hypertension who have never received any treatment for their high blood pressure, maximal skin capillary density with venous occlusion is significantly lower compared with normotensive controls. This suggests that much of the reduction in capillary...
Baseline Characteristics of 17 Patients With Untreated Essential Hypertension and 17 Normotensive Controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypertensive Patients</th>
<th>Normotensive Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>53.5±2.4</td>
<td>53.9±2.1</td>
</tr>
<tr>
<td>Gender, n (men/women)</td>
<td>9/8</td>
<td>11/6</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>74.3±3.5</td>
<td>73.3±3.1</td>
</tr>
<tr>
<td>Height, cm</td>
<td>170±2</td>
<td>173±2</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.7±0.9</td>
<td>24.4±0.7</td>
</tr>
<tr>
<td>Skin temperature, °C</td>
<td>30.4±0.6</td>
<td>31.1±0.5</td>
</tr>
<tr>
<td>Smokers, n</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Supine blood pressure, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>155±3†</td>
<td>127±2</td>
</tr>
<tr>
<td>Diastolic</td>
<td>96±1†</td>
<td>77±2</td>
</tr>
<tr>
<td>Mean blood pressure, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before venous congestion</td>
<td>62±4*</td>
<td>73±3</td>
</tr>
<tr>
<td>After 2 minutes venous occlusion</td>
<td>73±5*</td>
<td>87±4</td>
</tr>
<tr>
<td>Absolute increase in density</td>
<td>11±3 (19±4)</td>
<td>15±29 (20±3)</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SE. *P<0.05; †P<0.0001, vs normotensive controls.

density in hypertension is due to anatomic absence of capillaries rather than functional reduction.
Venous occlusion (congestion) during capillaroscopy enhances the visualization of red cell–filled capillaries and allows the trapping of red cells in plasma-only perfused capillaries as well as intermittently perfused capillaries. The enhancing effect of venous congestion on the visualization of capillaries has been used in many previous studies. The venous backpressure reduces the pressure gradient driving flow, which by temporarily reducing flow and washout of vasodilators causes vasodilation. Prolonged venous occlusion on the other hand, could increase precapillary resistance through the vеноarteriolar response. However, this response is noted in the dependent parts of the body and is known to be reduced in patients with essential hypertension compared with healthy volunteers. Furthermore, in our study, we examined the capillaries with the hand held at heart level, which abolishes the effects of this reflex.

Are Capillaries Resistance Vessels?
The resistance increase in hypertension is believed to be localized primarily in the small arteries and in the microcirculation (arterioles, venules, and capillaries). The relative contribution of these 2 segments of the vascular system to the resistance increase may vary from tissue to tissue. Small differences in vessel number, length, diameter and branching characteristics may be sufficient to shift pressure and flow distribution in particular tissues. In fact, the pressure drops gradually from the level of the small arteries to the capillaries without a specific, single site of resistance control along this segment of the vascular tree. Despite their thin walls, capillaries are relatively nondistensible and their endothelial cell nuclei encroach on the lumen to reduce luminal cross-sectional area by ≥50%. These deformations are accompanied by a slowing or diversion of the blood stream to other vessels. Capillary endothelial cells in mammals also have been shown to contain actin filaments and heavy meromyosin, which may indicate some form of contractility. The capillary network thus can contribute to the resistance control by virtue of their narrow caliber, by the reduction in their number (rarefaction), or possibly through their deformations.

**Capillary Rarefaction**
Capillary rarefaction has been described in various tissues from patients with essential hypertension not only in the established phase but also in early phases of hypertension, with only intermittent elevations of blood pressure. Recently, with the introduction of intravital video microscopy, a 15% to 20% reduction in the capillary density of the nail-fold skin capillaries was found. Recently, our own group using intravital fluorescein angiography, found a similar 20% reduction in capillary density in the forearm skin of hypertensive subjects compared with normotensive subjects. Furthermore, in that study, there was a significant negative correlation between capillary density and systolic blood pressure in patients with essential hypertension. In this present study, there is a significant negative correlation between systolic blood pressure and capillary density for the whole group, but this correlation did not reach statistical significance in the hypertensive group, probably as a result of the narrow range of blood pressures in the hypertensive subjects compared with the previous study.

Much evidence now indicates that microvascular rarefaction could be an important mechanism in the pathogenesis of human essential hypertension, as first suggested by Hutchins and Darnell. Recently, Greene et al used a mathematical model of the hamster cheek-pouch intraluminal microcirculation to perform separate simulations of rarefaction and constriction of small arterioles. Their results showed that
vessel rarefaction up to 42% (within the range observed in hypertensive humans or animals) can increase tissue resistance by 21%, an amount comparable to vessel constriction. They postulated that functional rarefaction is caused by microvascular constriction to the point of nonperfusion of the vessel, whereas structural rarefaction represents a true anatomical absence of the vessels. However, their theory cannot explain structural rarefaction observed in very early stages of hypertension. It is yet not clear whether the reduction in capillary density is primary or secondary to the hypertension. Recently, Noon et al. studied subjects from a novel, 4-corner epidemiological model, in which subjects were identified as having either high or low blood pressure in early adulthood and were further classified on the basis of their parents’ blood pressures. They found that offspring with high blood pressure whose parents also had high blood pressure had fewer capillaries on the dorsum of fingers, suggesting that defective angiogenesis may be a causal component in the inheritance of high blood pressure. Structural rarefaction of capillaries, on the other hand, may support the theory of reduced angiogenesis and diminished microvascular growth in primary hypertension. Depressed angiogenesis can be caused by genetic influences or by autoregulatory mechanisms. The potential genetic mechanisms are still unknown, although recently the spontaneously hypertensive rat genetic abnormality has been localized in a chromosomal domain that also contains growth-related hormones and elements of the renin-angiotensin system.

In conclusion, this study demonstrates that maximal capillary density with venous occlusion is significantly lower in hypertensive subjects than in normotensive controls. This strongly suggests that much of the reduction in capillary density in hypertension is due to the anatomic absence of capillaries rather than their functional reduction.

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References


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