Effects of Aging and Hypertension on the Microcirculation

Martin A. James, Jayne Tullett, Anthony G. Hemsley, Angela C. Shore

Abstract—Alterations of structure and function of the microcirculation in hypertension in the elderly and changes with normotensive aging have not been fully clarified. We studied capillary pressure, density, and skin microvascular function in 46 subjects in 3 groups: elderly subjects (aged >60 years) with untreated hypertension (n=16), elderly normotensive subjects (n=16), and young normotensive subjects (age <45 years, n=14). In a subgroup of 19 subjects, we also studied resistance artery function in the isometric myograph. Capillary pressure was higher in both elderly groups (elderly hypertensives: 18.6±4.7 mm Hg, elderly normotensives: 17.6±4.0 mm Hg) compared with young normotensives (13.9±2.6 mm Hg, P<0.05), but capillary density did not differ between the groups. Skin vasodilating responses to acetylcholine were greater in young normotensives compared with both elderly groups (P<0.05). In isolated resistance arteries, there was a greater inhibitory effect from blockade of the L-arginine-NO pathway in elderly normotensives (P<0.05) and a reduction in the maximal inhibitory effect of combined blockade of NO, prostanoids, and endothelium-derived hyperpolarizing factor in elderly hypertensives (P<0.05). This study has demonstrated a significant effect of aging but no additional effect of hypertension on capillary pressure and no effect of either on capillary density. Our findings with both in vivo and in vitro methods suggest that normotensive aging may depend on relative preservation of NO-dependent vasodilatation in resistance arteries at the expense of a rise in capillary pressure.

Key Words: microcirculation ■ capillaries ■ endothelium ■ endothelium-derived relaxing factors ■ aging

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Key Words: microcirculation ■ capillaries ■ endothelium ■ endothelium-derived relaxing factors ■ aging

Study Protocol

Subjects attended the laboratory for assessment of capillary pressure and density and functional studies of the cutaneous microcirculation. Subjects acclimatized to a temperature-controlled laboratory (21.5°C to 22.5°C) while resting supine for 30 minutes before the introduction of glass micropipettes (tip diameter: 5 to 10 μm) into the apex of between 4 and 12 nailfold capillary loops, usually in the left ring finger. Capillary pressure was measured by a method described elsewhere.15 Mean capillary pressure, capillary pulse pressure, and precapillary and postcapillary zero values were obtained, together with skin temperature. The time from the ECG-R wave to the foot of the systolic upstroke of the capillary pressure trace was

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derived (the systolic arrival time, SAT). In this laboratory, this technique for capillary pressure measurement is highly reproducible, with a coefficient of variation of ~5%.

Capillary density on the dorsum of the middle finger of the left hand was measured by a video-microscopy technique.\(^1\)\(^2\) Recordings were made before and after venous occlusion with a 40-mm Hg sphygmomanometer cuff applied to the finger.\(^3\)\(^4\) Capillaries were counted during playback of the videotape and expressed as density per mm². Drug iontophoresis was performed on the volar aspect of the right arm using a technique described previously.\(^5\) Briefly, preparations of acetylcholine (ACh; 1%; Miochol, Iolab) and sodium nitroprusside (SNP, 0.01%; Nipride, Roche) or inactive vehicle were placed in an iontophoresis chamber applied to several sites on the forearm and attached to an iontophoresis controller (Moor Instruments). Microampere currents of increasing duration were applied to the chamber to deliver charges of 1, 2, 4, and 8 mCb after an escalating ACh or SNP dose protocol. Red blood cell flux was measured with a laser Doppler perfusion imager (Lisca PIM; Lisca Development AB). Dose-response curves were derived for each agonist with increasing iontophoretic charge (mCb) plotted against arbitrary flux units.

A subgroup of 19 subjects (7 elderly hypertensives, 6 elderly normotensives, and 6 young normotensives) underwent biopsies of subcutaneous gluteal fat under local anesthesia for the harvesting of small resistance arteries by a method described previously.\(^6\)\(^7\) Resistance arteries of mean internal diameter 308 μm (range, 234 to 453 μm) were mounted on parallel 40-μm stainless steel wires in an isometric myograph (JP Trading) and maintained in physiological salt solution at 37°C and pH 7.4 and gassed with 95% O₂/5% CO₂. We studied 31 vessels from the 19 subjects.

**Laboratory Methods**

In studying isolated resistance arteries, an initial cumulative dose-response curve was obtained to norepinephrine, and the EC₅₀ was derived for each vessel preparation. Cumulative dose-response curves were then obtained (after vessels were preconstricted with norepinephrine at EC₅₀ dose) to ACh (0.1 mmol/L to 10 μmol/L), the stable NO donor diethylylammonium(Z)-1-((N,N-diethylamino)diazen-1-IM1.2-diolate (DEANO; 1 mmol/L to 10 μmol/L), ACh in the presence of the nonselective inhibitor of Ca²⁺-activated K⁺ channels, tetraethylylammonium (TEA; 100 μmol/L), ACh after 60 minutes of preincubation with the NO-synthase inhibitor N⁵-nitro-L-arginine (L-NOARG; 100 μmol/L), and ACh in the presence of TEA after 60 minutes of preincubation with L-NOARG and the cyclo-oxygenase inhibitor indomethacin (30 μmol/L).

Plasma lipid subfractions and glucose were measured by analyzer. Fasting insulin was measured in triplicate by specific radioimmunoassay. Insulin sensitivity was estimated from homeostasis model assessment and expressed as a percentage of standardized data.\(^8\)

**Statistical Methods**

Group data are described either by mean±SD or by median (interquartile range) for nonparametric data. Dose response curves from the iontophoresis procedure were compared from the maximum response and area under the curve and by ANOVA for repeated measures. For the resistance artery studies, within-group effects of the various inhibitors were assessed using the paired test. Comparison of dose-response curves was made by ANOVA for repeated measures. Between-group comparisons were made using 1-way ANOVA with Tukey’s post-hoc correction or the Kruskal–Wallis test for nonparametric data. Statistical significance was taken at P<0.05.

**Results**

Clinical and metabolic data for the 3 study groups are shown in Table 1. SBP and DBP were not significantly different between the young and elderly normotensive groups. SBP and DBP and ambulatory daytime SBP were higher in the elderly hypertensive group (P < 0.001), but there were no differences between all 3 of the groups in daytime DBP. Compared with the young group, the elderly normotensives had a higher total and low-density lipoprotein cholesterol, but no other factors linked to the insulin resistance syndrome. By contrast, the elderly hypertensives had significantly higher body mass index, cholesterol, and fasting glucose but no significant reduction in insulin sensitivity.

**Capillary Pressure and Density**

The capillary data are presented in Table 2. Capillary pressure was higher in both elderly groups compared with the young reference group. Capillary pulse pressure was also higher in the elderly. SAT in the elderly normotensive group was significantly longer than in the elderly hypertensive group. Skin temperature was not different between the groups.

Basal capillary density was not different between the 3 groups (Table 2). Venous occlusion led to an increase of between 0% and 29% in capillary numbers, but both the postocclusion capillary density and the percentage change were not different between the 3 groups.

**Microvascular Function**

Iontophoresis of ACh led to significantly greater increases in skin perfusion in the young normotensive group than in either of the elderly groups (Figure 1 and Table 2; ANOVA F = 3.65; P = 0.006). The ACh responses in the 2 elderly groups did not differ. No differences were seen between the endothelium-independent relaxations induced by SNP (Figure 2).

In the resistance artery subgroup, there were no significant differences in the BP or metabolic data between the subgroups and their larger parent groups (data not shown). There

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**TABLE 1. Baseline Characteristics for the 3 Groups**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Young Normotensive</th>
<th>Elderly Normotensive</th>
<th>Elderly Hypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>14</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Age, y</td>
<td>36±7</td>
<td>65±8</td>
<td>69±6</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.5±3.0</td>
<td>26.0±3.6</td>
<td>26.5±4.0*</td>
</tr>
<tr>
<td>Clinic SBP</td>
<td>119±14</td>
<td>121±8</td>
<td>159±18†</td>
</tr>
<tr>
<td>Clinic DBP</td>
<td>72±9</td>
<td>72±6</td>
<td>81±5†</td>
</tr>
<tr>
<td>Daytime ambulatory SBP</td>
<td>119±8</td>
<td>118±11</td>
<td>139±14†</td>
</tr>
<tr>
<td>Daytime ambulatory DBP</td>
<td>78±6</td>
<td>74±10</td>
<td>80±10</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.8±1.1</td>
<td>5.8±0.8‡</td>
<td>6.2±1.1*</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>2.9±1.0</td>
<td>3.8±0.7‡</td>
<td>3.9±1.0*</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.4±0.5</td>
<td>1.4±0.3</td>
<td>1.6±0.3</td>
</tr>
<tr>
<td>Fasting triglycerides, mmol/L</td>
<td>1.1±1.0</td>
<td>1.4±0.5</td>
<td>1.5±0.6</td>
</tr>
<tr>
<td>Fasting plasma glucose, mmol/L</td>
<td>4.6±0.3</td>
<td>4.7±0.5</td>
<td>5.0±0.4*</td>
</tr>
<tr>
<td>Insulin sensitivity, %</td>
<td>93±43</td>
<td>111±56</td>
<td>114±39</td>
</tr>
</tbody>
</table>

Data are mean±SD. LDL indicates low-density lipoprotein; BMI, body mass index; HDL, high-density lipoprotein.

*P<0.05 for elderly hypertensive vs young normotensive.
†P<0.05 for elderly hypertensive vs elderly normotensive.
‡P<0.05 for elderly normotensive vs young normotensive (ANOVA).
were no significant differences between the groups in the contractile response to norepinephrine (data not shown), and all of the vessels relaxed near maximally to ACh and to DEANO, again with no differences among the 3 groups (Table 3). NO blockade with L-NOARG (Figure 3) produced a similar effect in both normotensive groups of a statistically significant shift in the dose-response curves equivalent to a /\text{10-fold}\text{,}^{*}\text{221} reduction in sensitivity, but the reduction in sensitivity with NO blockade in the elderly hypertensive group was smaller and did not reach statistical significance (Table 3). Blockade of NO synthase also led to significant reductions in the maximum relaxation achieved but with a significantly greater inhibitory effect from L-NOARG in the elderly normotensives than in either of the other 2 groups ($P<0.05$).

Nonspecific inhibition of K$^+$ channels with TEA led to statistically significant reductions in sensitivity in all of the groups of between $\approx$24-fold and 38-fold, but no change in the maximum relaxation was seen, and no effect of aging or hypertension on the responses (Figure 4) was found. With the combined blockade of NO synthase, K$^+$ channels, and prostanoids, there was a significant reduction in sensitivity to ACh in all of the groups of between $\approx$75-fold and 268-fold and significant reductions in the maximum relaxation of $\approx$41% in the young normotensives, 36% in the elderly normotensives, and 22% in the elderly hypertensives (Table 3). When the effect of combined blockade on the entire relaxation curve was considered, there was a significant difference between the responses in the elderly hypertensives and the 2 normotensive groups ($P=0.027$; Figure 5).

### Table 2. Structural and Functional Parameters in the Microcirculation for the 3 Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Young Normotensive</th>
<th>Elderly Normotensive</th>
<th>Elderly Hypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capillary pressure, mm Hg</td>
<td>13.9±2.6</td>
<td>17.6±4.0†</td>
<td>18.6±4.7*</td>
</tr>
<tr>
<td>Capillary pulse pressure, mm Hg</td>
<td>1.6 (1.0 to 3.3)</td>
<td>4.1 (1.4 to 6.8)</td>
<td>4.9 (1.6 to 8.2)*</td>
</tr>
<tr>
<td>No. of capillaries cannulated</td>
<td>6.4 (range, 4 to 10)</td>
<td>6.8 (range, 5 to 9)</td>
<td>8.3 (range, 6 to 12)</td>
</tr>
<tr>
<td>Systolic arrival time, ms</td>
<td>213 (200 to 224)</td>
<td>213 (195 to 230)</td>
<td>190 (180 to 200)*†</td>
</tr>
<tr>
<td>Capillary density</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal, mm$^2$</td>
<td>98±14</td>
<td>100±17</td>
<td>108±20</td>
</tr>
<tr>
<td>Postocclusion, mm$^2$</td>
<td>104±16</td>
<td>107±18</td>
<td>117±25</td>
</tr>
<tr>
<td>% Increase postocclusion</td>
<td>6±5</td>
<td>7±6</td>
<td>9±8</td>
</tr>
<tr>
<td>Skin microvascular function, flux units</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACh maximum response</td>
<td>2.5±0.6</td>
<td>1.9±0.5‡</td>
<td>1.9±0.6*</td>
</tr>
<tr>
<td>ACh AUC</td>
<td>697±211</td>
<td>502±164‡</td>
<td>511±165*</td>
</tr>
<tr>
<td>SNP maximum response</td>
<td>2.0±0.7</td>
<td>1.9±0.5</td>
<td>1.8±0.8</td>
</tr>
<tr>
<td>SNP AUC</td>
<td>363±164</td>
<td>366±146</td>
<td>354±185</td>
</tr>
</tbody>
</table>

Data are mean±SD or median (interquartile range). $^*P<0.05$ for elderly hypertensive vs young normotensive. $^†P<0.05$ for elderly hypertensive vs elderly normotensive. $^‡P<0.05$ for elderly normotensive vs young normotensive.
Discussion

In this study, we have sought to clarify the changes in the microcirculation that are associated with aging and, in the elderly subjects, to separate these from the changes observed with hypertension. The only other published comparison of capillary pressure in hypertension observed an increase in capillary pressure closely correlated with the measured increase in brachial artery BP. The mean capillary pressure in the young normotensive subjects in the present study, at 13.9 mm Hg, agrees closely with the normotensive group in the earlier study (13.0 mm Hg). Other workers have observed higher pressures (20.5±3.7 mm Hg) in nailfold capillaries among younger normotensive men (28±5 years) using a slightly different technique.

However, this study has demonstrated no separate effect of systemic BP on capillary pressure among elderly subjects. Indeed, when the elderly normotensives are compared with the young group with similar clinic and daytime ambulatory BP, a significant increase in capillary pressure is observed. When potential metabolic factors are considered, there appears to be no effect from glucose/insulin metabolism, but an increase in total and low-density lipoprotein cholesterol levels with age is seen. Alterations in vascular homeostasis in the precapillary segment with increasing serum cholesterol have been observed, leading to an increase in the wall:lumen ratio in small arteries and reduced vasorelaxation. Although it might be expected that these changes would reduce capillary pressure with higher cholesterol levels, the regulation of capillary pressure is the net effect of the relative resistance in both precapillary and postcapillary segments, and the effects on the postcapillary segments are not clearly elucidated. Our observation of impaired vasodilatation of the microcirculation

<table>
<thead>
<tr>
<th>Agonist Response</th>
<th>Young Normotensive</th>
<th>Elderly Normotensive</th>
<th>Elderly Hypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessel diameter, μm</td>
<td>292±55</td>
<td>309±35</td>
<td>324±62</td>
</tr>
<tr>
<td>ACh EC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>31.7±41.0</td>
<td>15.2±17.5</td>
<td>19.0±21.8</td>
</tr>
<tr>
<td>ACh max</td>
<td>97±2</td>
<td>95±4</td>
<td>98±2</td>
</tr>
<tr>
<td>DEANO EC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>136±63</td>
<td>220±190</td>
<td>199±144</td>
</tr>
<tr>
<td>DEANO max</td>
<td>98±2</td>
<td>98±2</td>
<td>98±2</td>
</tr>
<tr>
<td>ACh+NOARG EC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>181±111</td>
<td>187±166</td>
<td>71±74</td>
</tr>
<tr>
<td>ACh+NOARG max</td>
<td>87±4</td>
<td>75±3*‡</td>
<td>82±10</td>
</tr>
<tr>
<td>ACh+TEA EC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>753±605</td>
<td>575±276</td>
<td>421±343</td>
</tr>
<tr>
<td>ACh+TEA max</td>
<td>88±15</td>
<td>94±6</td>
<td>97±2</td>
</tr>
<tr>
<td>ACh+NOARG+TEA+indomethacin EC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>6239±2463</td>
<td>2741±1154</td>
<td>1836±852‡</td>
</tr>
<tr>
<td>ACh+NOARG+TEA+indomethacin max</td>
<td>56±22</td>
<td>59±12</td>
<td>76±6</td>
</tr>
</tbody>
</table>

Data are mean±SD.

*P <0.05 elderly normotensive vs young normotensive.
†P <0.05 elderly normotensive vs elderly hypertensive.
‡P <0.05 elderly hypertensive vs young normotensive.
to ACh with aging is compatible with impairment of the venular component causing a raised postcapillary resistance, a reduced arteriolar capacity to buffer the effect of altered resistance artery function, or elements of both.

Capillary pressure in elderly hypertensives in the current study (18.6±4.7 mm Hg) is similar to that described in hypertensive subjects of a similar age and BP in another recent study from our group3 (median: 17.2 mm Hg; interquartile range: 15.1 to 19.8). However, the latter study did not include nondiabetic elderly normotensive subjects. It is worth noting that the BP profile of the hypertensives in the original study of Williams et al2 differs from that in our study. As would be expected in our older sample, elevation of DBP is less prominent, with no difference in ambulatory daytime DBP among our 3 groups. DBP measured in conduit arteries is principally related to the total peripheral resistance, mediated through structural and functional alterations in small arteries and arterioles, whereas SBP reflects large artery rigidity.14 In the current study, the shorter SAT and increased pulse wave velocity in the elderly hypertensives reflect this increased rigidity. Younger subjects with mainly diastolic hypertension might, therefore, be expected to have a greater precapillary resistance. By contrast, the older subjects in our study, with DBP and resistance artery diameter identical to that in the younger normotensive group, may not have developed such “protective” changes in their precapillary segment. This may contribute to the higher capillary pulse pressure that was seen in both elderly groups in the current study, although, in the elderly hypertensive group, a raised capillary pulse pressure amplitude may reflect their greater systemic pulse pressure. The lack of capillary rarefaction in our group of elderly hypertensives would minimize any potential rise in capillary pressure because of altered capillary surface area.

We studied the function of the vasculature using both transcutaneous iontophoresis of endothelium-dependent (ACh) or -independent (SNP) vasodilators to the cutaneous microcirculation and the of resistance arteries in vitro. With the iontophoresis method, we observed significant reductions in microvascular endothelium-dependent relaxations as a function of aging but not of hypertension, whereas NO-mediated, endothelium-independent relaxation with SNP was unaffected by either
(Figures 1 and 2). This is in contrast to a recent study, which suggested that endothelium-independent skin vasodilatation declined significantly with age but not with BP.23

Findings from other authors in this area have differed, with some showing a significant effect of hypertension on endothelium-dependent relaxation in resistance arteries, and others not.7,24 In human in vitro studies, Coats et al25 observed near-maximal relaxation with ACh in subcutaneous resistance arteries from a group of older subjects, some of whom had hypertension, much as we have seen with all 3 of the groups. In the study by Coats et al,25 this relaxation response was inhibited by between 20% and 25% by incubation with L-NOARG, comparable to the 16% to 20% reduction with NO synthase inhibition in the older subjects seen in the present study, but these findings contrast with the near-total inhibition of relaxation with L-NOARG seen in a previous study,11 which may be accounted for by methodological differences. Our current results suggest that subjects who reach old age without developing hypertension show a relative preservation of the NO pathway in small subcutaneous arteries, as shown by their significantly greater inhibitory response with NO-synthase blockade. This enhanced NO component may reflect the ability of this group to compensate for the decline of other vasodilatory pathways or an increase in a vasoconstrictor pathway by modifying the NO pathway, thereby maintaining normotension. This relatively preserved vasodilatation effect may, on the one hand, mitigate a rise in peripheral resistance and BP with age, but it may increase the delivery of a raised pressure to the microvasculature. A rise in capillary pressure and capillary pulse pressure without a corresponding rise in conduit artery BP may be a feature of normotensive aging, and our current and previous findings with both the in vivo and in vitro methods suggest that changes in endothelium-dependent mechanisms seen with aging appear to contribute little to the pathophysiology of the mainly systolic hypertension seen among older subjects.11

Recent studies have suggested that with hypertension there is a shift away from the L-arginine-NO pathway toward alternatives mediated via prostanoids and/or endothelium-derived hyperpolarizing factor.26 Our data showing substantial inhibitory responses with indomethacin and TEA confirm that these pathways are significant contributors to vasodilatation in isolated resistance arteries, and we have not observed differences in the role of these alternative pathways with aging. However, with full inhibition of NO, prostanoids, and endothelium-derived hyperpolarizing factor, we have observed a reduced inhibitory effect in the elderly hypertensive subjects, which may, if anything, suggest a lesser role for these alternative pathways among older hypertensives.

Capillary rarefaction as a feature of hypertension has been described by several authors, although principally among younger subjects.4,5,9 In contrast, we have not observed capillary rarefaction, either basal or after venous occlusion, in our study. Our study has included subjects of an older age than any previous study, but we were surprised by our finding that capillary rarefaction is not a feature of hypertension in older subjects. Again, this may relate to the differing BP profile of hypertension in the elderly, more than half of whom have no elevation or even a reduction in DBP.13 Structural changes within the peripheral bed, and capillary rarefaction in particular, may not be implicated to the same extent as they are in younger hypertensives with predominant diastolic elevations. In a recent study,2 capillary rarefaction among hypertensive subjects was related to elevation of the DBP, but not the SBP, and inversely related to age.

The current study has a number of limitations that need to be considered. We set out to examine the separate effects of both aging, on the one hand, and BP among the elderly on the other, and we, therefore, have not included a fourth group of young hypertensives. As discussed above, this may account for some of the differences between our study findings and those of others who have confined their study to younger age groups. The study of the function of the microvasculature with laser Doppler fluximetry precludes the study of the separate components (arterioles, capillaries, and venules) of the microcirculation. However, our study is the first, to our knowledge, to combine the study of microvascular function in vivo with resistance artery function in vitro, and, as such, it
suggests that functional abnormalities may differ between specific parts of the vasculature. We cannot assume, however, that the changes in the dermal circulation that we have described apply to the microvasculature in other vascular beds, but the nailfold remains the only site at which it is possible to measure capillary pressure in human subjects.

**Perspectives**

This study of the structure and function of the microcirculation in elderly hypertensive and normotensive subjects, with a comparison to a young, normotensive reference group, indicates an effect of aging but no additional effect of hypertension on both capillary pressure and microvascular function, together with no contribution of capillary rarefaction to the predominantly systolic hypertension of elderly subjects. Subjects who reach older age without developing hypertension appear to have a relative preservation of the microvasculature, but the nailfold remains the only site at which it is possible to measure capillary pressure in human subjects.

**Acknowledgments**

This study was supported by project grant 97184 from the British Heart Foundation. A.G.H. was supported by a Clinical Fellowship at the expense of a rise in capillary pressure.

**References**


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