3.6: CENTRAL PULSE PRESSURE IS AN INDEPENDENT DETERMINANT OF VASCULAR REMODELLING IN THE RETINAL CIRCULATION

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3.4 CHARACTERISATION OF THE TWO-LAYERED MEDIA IN THE MAMMALIAN CAROTID ARTERY

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Background: We have recently observed that in some animals the media of the carotid artery consists of two distinct layers. The inner 2/3 has a circumferential orientation of components whereas the outer 1/3 has an axial orientation. The aims of this study were to characterise the differences between the two layers.

Materials and Methods: We studied carotid arteries from the mammalian orders: artiodactyla, carnivora, cetacea, erinaceomorpha, lagomorpha, perissodactyla, pilosa, primates, rodentia and soricomorpha. Transmission electron microscopy confirmed the morphology and thickness of the layers. Histological staining was performed to characterise the cells and their phenotypes.

Results: We observed the two-layered media in the artiodactyla, perissodactyla and cetacea but not in any of the other orders. Immunohistochemistry showed that the distribution of fibrillin 1, NAV 1.8, tenasin C, fibronectin and collagen I & III were the same in the two layers. Alpha actin, desmin and collagen IV were seen only in the inner layer, suggesting a contractile phenotype for the cells therein, giving no indication of the function of the cells in the outer layer.

Conclusions: The inner media had a circumferential orientation of components and contractile smooth muscle cells; whereas the components of the outer layer were orientated axially with fibroblast-like cells of unknown function and more densely distributed scleroprotein. All the animals having the two-layered media are located downstream from a particular point on the mammalian supertree, corresponding to the superorder cetartiodactyla, suggesting that this structure evolved rapidly, approximately 80 million years ago for as yet unknown reasons.

3.5 EFFECT OF SHORT-TERM TREATMENT WITH LERCANIDIPINE ON CIRCULATING ENDOTHELIAL PROGENITOR CELLS AND STRUCTURAL ALTERATIONS IN RETINAL ARTERIOLES

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Background: It has been previously demonstrated that dihydropripridine calcium channel blockers may possess antioxidant properties and might improve microvascular structure. The aim of the present study was therefore to investigate the effects of a short-term treatment with lercanidipine on structural alterations in retinal arterioles and on circulating endothelial progenitor cells (EPCs), which are bone marrow-derived cells possibly participating in neovascularization and endothelial protection and repair.

Patients and Methods: Fourteen essential hypertensive patients were included in the study and treated for 4 weeks with lercanidipine 10-20 mg per day orally. Investigations were performed in basal condition, after appropriate wash out of previous treatments, and after 4 week lercanidipine treatment. EPCs were evaluated by flow cytomtery as CD34+/CD133+/KDR+ cells. Non-invasive measurements of internal diameter (ID), external diameter (ED), wall thickness, wall to lumen ratio (W/L) and wall cross-sectional area (WCSA) of retinal arterioles using scanning laser doppler flowmetry (SLDF) were performed (Heidelberg Retina Flowmeter, Heidelberg Engineering), according to Harazny J et al, Hypertension 2007; 50:623-629.

Results are summarized in the Table (PP<0.05 , **p<0.01; ***p<0.001 vs. Basal).

A significant increase in circulating EPC count was observed after treatment with lercanidipine, associated with a reduction in W/L and an improvement of other indices of retinal artery structure, which, in the absence of a significant increase in ID, does not seem to be ascribed just to the vasodilator effect of the drug.

Conclusions: For the first time, in this study, favourable effects on the EPC-dependent endothelium-repair system and on alterations of retinal arterioles have been reported in men after treatment with a dihydropripridine calcium channel antagonist, lercanidipine, possibly related to hemodynamic and antioxidant properties.

<table>
<thead>
<tr>
<th>Table Gender (M/F)</th>
<th>Blood pressure (mm Hg)</th>
<th>WPCs</th>
<th>W/L</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Basal</strong></td>
<td>11/3</td>
<td>154/90±</td>
<td>49.1±40</td>
</tr>
<tr>
<td>Treatment</td>
<td>-</td>
<td>145/78.7±</td>
<td>102±71</td>
</tr>
<tr>
<td>ID (µm)</td>
<td>10.7/10.5±</td>
<td>141±3.37</td>
<td>2322±1214</td>
</tr>
<tr>
<td>ED (µm)</td>
<td>Wall thickness (µm)</td>
<td>85.6±15.6</td>
<td>1214</td>
</tr>
<tr>
<td><strong>Basal</strong></td>
<td>57.3±12.9</td>
<td>71±11.7**</td>
<td>7.99±2.78***</td>
</tr>
<tr>
<td>Treatment</td>
<td>61.1±8.05</td>
<td>71±11.7**</td>
<td>1784±842**</td>
</tr>
</tbody>
</table>

3.6 CENTRAL PULSE PRESSURE IS AN INDEPENDENT DETERMINANT OF VASCULAR REMODELLING IN THE RETINAL CIRCULATION

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Objective: Pulse pressure has been recognized as a risk factor for stroke. Moreover, it was shown that central pulse pressure (PP) relates more strongly to vascular disease and outcome than (peripheral) brachial PP. Hence, we analyzed the impact of central PP on retinal vascular structure, mirroring cerebral circulation.

Design and methods: The study cohort comprised 135 patients across a wide range of BP, but without evidence of diabetes. Parameters of retinal arteriole structure (wall-to-lumen (W/L) and function (change of retinal capillary flow (RCF) to nitric oxide synthase inhibitor N-monomethyl-L-arginine (L-NMMA), reflecting basal NO activity of the retinal vasculature) was assessed non-invasively and in vivo by scanning laser doppler flowmetry. Central hemodynamics and augmentation index (Alx) were assessed by pulse wave analysis.

Results: WLR was correlated with central PP (r = 0.302, p < 0.001). In accordance, PP amplification (peripheral PP/central PP) was negatively correlated with WLR (r = -0.223, p = 0.009). In contrast, MAP was not correlated with WLR (r = 0.110, p = 0.203). Moreover, Alx@75 correlated with WLR (r = 0.190, p = 0.028). The percent change of RCF to L-NMMA was correlated to WLR (r = 0.197, r = 0.222).

Regression analysis revealed an independent relationship between WLR and both central PP (β = 0.277, p = 0.009) and percent change of RCF to L-NMMA (β = 0.170, p = 0.046).

Conclusion: Thus, central PP is an independent determinant of remodelling in small retinal arterioles indicating a coupling between the micro- and macrovascular changes to hypertension.