Macular circulation in patients with diabetes mellitus with and without arterial hypertension

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Abstract

Background—Previous fluorescein angiographic studies have shown alterations in the macular microcirculation in patients with diabetes mellitus and arterial hypertension. In both diseases capillary blood velocity was reduced and capillary density decreased. These changes were more pronounced in diabetic patients. We have examined the influence of arterial hypertension in combination with diabetes mellitus.

Methods—62 patients with diabetes mellitus and arterial hypertension (group 1) were matched with patients with diabetes mellitus but without arterial hypertension (group 2, match criteria: ETDRS stage of retinopathy). In all subjects fluorescein angiograms were performed with a scanning laser ophthalmoscope. Macular capillary blood velocity (CBV), perifoveal intercapillary area (PIA), the coefficient of variation of both parameters, the area of the foveal avascular zone (FAZ), and the arteriovenous passage time (AVP) were assessed by digital image analysis.

Results—Systolic and diastolic blood pressures were significantly increased in the patients with arterial hypertension (systolic p=0.0008; diastolic p=0.003). Neither dynamic measures (AVP: 1.64 (0.49) seconds (group 1), 1.72 (0.58) seconds (group 2); CBV: 1.98 (0.39) mm/s (group 1), 2.09 (0.43) mm/s (group 2)) nor morphological measures (PIA: 7985 (3137) µm² (group 1), 8338 (3376) µm² (group 2); FAZ: 0.319 (0.206) mm² (group 1), 0.363 (0.237) mm² (group 2)) were significantly different between the two groups of diabetic patients.

Conclusion—Arterial hypertension did not result in more severe macular capillary dropout than diabetes without hypertension. This might be explained by the fact that most of the patients were being treated with antihypertensive drugs.

With the introduction of the scanning laser technology,1 angiograms of high spatial and temporal resolution can measure simultaneously both dynamic and morphological parameters. In the past, fluorescein angiographic studies in patients with diabetes or hypertension13 have shown reduced capillary blood velocity and decreased capillary density. Enlargement of the area of the foveal avascular zone and the perifoveal intercapillary area, as measures of capillary density, are related to decreased visual acuity4 and contrast sensitivity.5 Furthermore, in early diabetic angiopathy capillary blood velocities are reduced and the perifoveal intercapillary area is increased before microaneurysm formation occurs.6 Thus, digital fluorescein angiography identifies passage of dynamic and morphological changes in the retinal microcirculation of diabetic and hypertensive patients.

Several studies have examined circulatory changes in diabetic patients8–10 but the effect on the ocular circulation of diabetes mellitus combined with arterial hypertension has not been studied to date. From epidemiological data11 one might expect that capillary perfusion is further decreased and capillary density reduced in these patients. Previous microcirculatory studies12–14 have shown that measurement of capillary density is a valuable diagnostic tool for differentiating capillary loss. In this study we have used digital fluorescein angiograms to quantify the retinal microcirculation in diabetic patients with and without arterial hypertension. By matching for stage of retinopathy, the effect of diabetes mellitus induced capillary closure has been eliminated and an attempt has been made to define the influence of obstructive hypertensive microangiopathy.

Materials and methods

Digital recordings of scanning laser videofluorescein angiograms (Scanning Laser Ophthalmoscope; Rodenstock Instruments, Munich, Germany) and image analysing technology allow measurements of arteriovenous passage times (AVP), mean capillary blood velocity (CBV), the perifoveal intercapillary area (PIA), and the foveal avascular zone (FAZ). In brief, the CBV is determined by measuring the velocities of hypofluorescent particles through the parafoveal vasculature (PC, self-developed software). These particles are presumed to be rouleaux formations of red blood cells.12 The AVP time characterises the shortest passage from the dye arriving in the artery, passing through the capillary vasculature, and arriving in the corresponding vein.13 The AVP time is correlated with the macular...
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The two groups were matched for stage of hypertension (group 2, 20 IDDM, 42 NIDDM). Dependent diabetes mellitus (NIDDM) and non-dependent diabetes mellitus (IDDM) and 51 with non-insulin dependent diabetes mellitus showing means and standard deviations.

Patients

Fluorescein angiograms were performed in 62 diabetic patients with arterial hypertension (group 1; 11 with insulin dependent diabetes mellitus (IDDM) and 51 with non-insulin dependent diabetes mellitus (NIDDM) and in 62 diabetic patients without arterial hypertension (group 2, 20 IDDM, 42 NIDDM). The two groups were matched for stage of retinopathy. On the basis of the ETDRS classification the patients were assigned by standardised fundus photography to the following groups: S10 (no retinopathy), n=4; S20 (microaneurysms only), n=6; S35 (mild non-proliferative diabetic retinopathy (NPDR)), n=8; S43 (moderate NPDR), n=18; S53 (severe NPDR), n=9; S61 (mild proliferative retinopathy), n=8; S71 (proliferative retinopathy with high risk characteristics), n=9.

The patients with severe non-proliferative or proliferative retinopathy underwent the angiographic study before pan-retinal photocoagulation. The diagnosis of arterial hypertension was based on repeated readings of >160 mm Hg systolic BP and >95 mm Hg diastolic BP. The patients with arterial hypertension exhibited only mild vascular alterations corresponding to stages 0 to II described by Scheie. Forty three (70%) patients in group 1 were treated with an antihypertensive drug, 31 (72%) with a single drug (β blocker, n=3; diuretics, n=11; calcium channel blocker, n=11; ACE inhibitor, n=6), eight (19%) with a combination of two drugs, and four (9%) with three or more agents. A total of 19 patients (30%) had no antihypertensive drug therapy. To determine the influence of antihypertensive medication these 19 patients (group A) were compared with matched patients without arterial hypertension (group B). The match criterion again was the stage of diabetic retinopathy.

Informed consent was obtained from all patients before participation in the study. The protocol was approved by the human study committee of the Technical University of Aachen and followed the tenets of the Helsinki declaration. Exclusion criteria included lenticular or corneal diseases precluding detailed angiographic study. In addition, patients with allergic disease or history of sensitivity to fluorescein were excluded.

Best corrected visual acuity was determined by an ophthalmologist followed by a complete ophthalmological examination. The studied eye was selected at random if both qualified for the study. These eyes were then studied by fluorescein angiography using the scanning laser ophthalmoscope. Blood pressure (BP) and heart rate were measured before examination with an automatic device (Criticare Vital Datal Monitor, Criticon Inc, Tampa, FL, USA) in the sitting position after 5 minutes of rest. The mean arterial pressure was calculated as one third pulse pressure plus the diastolic (diast) pressure (BP<sub>diast</sub> + (BP<sub>syst</sub>−BP<sub>diast</sub>)/3). Data were corrected for individual refractive error using axial length (A scan ultrasonography) and keratometry.

Data analysis

Mean values and standard deviations are given for all samples with normal distribution (Kolmogorov-Smirnov test). The Student’s t test was used for paired and unpaired samples with normal distribution. Findings with an error probability of <0.05 were considered to be statistically significant. Pearson correlation coefficients were calculated to evaluate the relationship between the parameters. p Values were obtained after carrying out Fisher’s r to z transformations.

Results

The clinical and demographic data of the two groups of patients are shown in Table 1. The patients in group 1 had a higher mean age (p<0.0001; 24%), higher systolic (p=0.0008; 12%) and diastolic BP (p=0.03; 10%), and higher mean arterial pressure (p=0.002; 8%)
Table 1  Mean (SD) clinical and demographic data of diabetic patients with (group 1) and without arterial hypertension (group 2).

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Significance*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>36/26</td>
<td>36/26</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>54.5 (10)</td>
<td>41.4 (13)</td>
<td>p&gt;0.0001</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.4 (1.6)</td>
<td>8.6 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>108 (13)</td>
<td>100 (14)</td>
<td>p=0.03</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>150 (21)</td>
<td>132 (13)</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>87 (13)</td>
<td>78 (9)</td>
<td></td>
</tr>
<tr>
<td>Mean glycosylated haemoglobin (HbA1c) (8.0 (2.1)%</td>
<td>8.3 (1.4)%</td>
<td>p=0.0001</td>
<td></td>
</tr>
<tr>
<td>Mean systolic blood pressure (mm Hg)</td>
<td>143 (23) mm Hg</td>
<td>143 (23) mm Hg</td>
<td></td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
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<tr>
<td>Duration of diabetes (years)</td>
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<tr>
<td>HbA1c (%)</td>
<td>8.4 (1.6)</td>
<td>8.6 (1.6)</td>
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*Unpaired Student’s t test.

Figure 2  Regression curve of the size of the foveal avascular zone (FAZ) and the systolic blood pressure in patients with diabetes with arterial hypertension.

Discussion

The increased risk of cerebral, cardiovascular, and renal disease resulting from arterial hypertension in patients with diabetes mellitus has been described in various studies.31-34 However, these studies reached different conclusions with regard to the effect of reducing systolic and diastolic BP and the influence of the type of diabetes. The impact of arterial hypertension on diabetic retinopathy is either an increased rate of progression31-35 or it has little or no effect.20-23

Past studies using scanning laser fluorescein angiography have shown decreased capillary density in patients with arterial hypertension5 (PIA 5591 (838) µm2) and in those with diabetic retinopathy.4 Furthermore, capillary perfusion in the macula region is decreased in diabetic5 and in hypertensive7 patients. A decrease in perfusion occurs early in diabetes when no microaneurysms are visible and is associated with increased perfioveal intercapillary area as a sign of decreased capillary density.4 Various studies have found hyperperfusion or hypoperfusion to be pathogenic in patients with diabetes mellitus.11-14-16-17-20-22-25-26-27-28 The effect of decreased perfusion can be explained by progressive capillary closure with increased resistance and decreased perfusion.29 Capillary closure is a well established angiographic and histopathological sign of diabetic retinopathy.37-38 Capillary loss, as reflected by the
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were only moderately increased (systolic receiving antihypertensive medication. How-
no changes occurred because the patients were
perfusion was found, one could speculate that
between age and any of the parameters
did not influence the results. Correlation
the hypertensive group was significantly older
or without arterial hypertension. The fact that
vascular patterns seen in diabetic patients with
confirm this trend, but it supports the similar
ing was low and further studies are needed to
arterial pressure in diabetic patients with arte-
pressurisation and induction of humoral factors.
may be explained by shear stress of the vessel
wall and induction of humoral factors.

Vascular changes resulting from arterial hypertension include a range of changes in the vessel wall15 and can result in capillary rarefaction.38 In a 2 year angiographic follow up study of hypertensive patients the capillary density remained unchanged.40

The present study was designed to examine
whether progressive retinal capillary closure with attenuated circulation occurs in patients with diabetes mellitus and arterial hyper-
tension. Both patient groups had prolonged
 times with decreased CBV and increased
FAZ and PIA compared with reference data
from healthy subjects.5,13 With increasing stage
of diabetic retinopathy there was a significant increase in PIA and FAZ but no interaction was seen between the presence or absence of arterial hypertension and any of the morpho-
logical or dynamic parameters measured. This suggests that the capillary closure associated with diabetes mellitus is so dominant that the arterial hypertension results in no additional
perfusion or capillary density resulting from
the presence of arterial hypertension.

Correlation analysis revealed a decrease in
FAZ with increasing systolic BP and mean
arterial pressure in diabetic patients with arte-
rial hypertension. The significance of this find-
ing was low and further studies are needed to
confirm this trend, but it supports the similar vascular patterns seen in diabetic patients with
or without arterial hypertension. The fact that
the hypertensive group was significantly older
did not influence the results. Correlation
analysis showed no significant correlation
between age and any of the parameters measured.

Since no additional effect on capillary perfusion was found, one could speculate that no changes occurred because the patients were receiving antihypertensive medication. How-
never, no difference in retinal perfusion or capil-
lary density was seen between a group of newly
diagnosed hypertensive patients with diabetes
mellitus not receiving antihypertensive treatment
and a matched population of diabetic patients without arterial hypertension.

In this study the systolic and diastolic BP’s
were only moderately increased (systolic 150 mm Hg; diastolic 87 mm Hg). The
UKPDS study12 found that a reduction in
systolic BP to <150 mm Hg and in diastolic
BP to <85 mm Hg led to a significant reduc-
ton the risk of deterioration in visual acuity
and retinopathy. Norgaard et al38 found that
arterial hypertension per se is not associated
with increased retinal changes, but it may
worsen these changes in patients with clinically
apparent nephropathy. This suggests that
future angiographic studies should be per-
formed in diabetic patients with associated
nephropathy or with more severe arterial hypertension.

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