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

O Arend, M Rüffer, A Remky

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=0.03). 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 hypertension2–3 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 patients7–9 but the effect on the ocular circulation of diabetes mellitus combined with arterial hypertension has not been studied to date. From epidemiological data10 one might expect that capillary perfusion is further decreased and capillary density reduced in these patients. Previous microcirculatory studies11–14 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 (PC) 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.15 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.16 The AVP time is correlated with the macular...
Circulation in patients with diabetes and arterial hypertension

1393

14 ultrasonography) and keratometry.14 refractive error using axial length (A scan patient. All data were corrected for individual distribution of PIA and CBV in a single

retinopathy. On the basis of the ETDRS classi-

tation (72%) with a single drug (β blocker, n=3; diu-

retics, n=11; calcium channel blocker, n=11; ACE inhibitor, n=6), eight (19%) with a com-

bination 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 arte-

rial 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 examina-
tion with an automatic device (Criticare Vital Daten 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 (BPdiast + (BPsyst−BPdiast)/ 3)).17

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%)

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 hyper-
tension (group 2, 20 IDDM, 42 NIDDM). The two groups were matched for stage of retinopathy. On the basis of the ETDRS classifica-
tion17 the patients were assigned by stand-
ardised 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 retin-

opathy 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 hyper-
tension exhibited only mild vascular alterations corresponding to stages 0 to II described by Scheie.14 Forty three (70%) patients in group 1 were treated with an antihypertensive drug, 31 (72%) with a single drug (β blocker, n=3; diu-

retics, n=11; calcium channel blocker, n=11; ACE inhibitor, n=6), eight (19%) with a com-

bination 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 arte-

rial 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 examina-
tion with an automatic device (Criticare Vital Daten 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 (BPdiast + (BPsyst−BPdiast)/ 3)).17

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%)

www.bjophthalmol.com
than patients in group 2. The number of patients with IDDM or NIDDM in the two groups did not differ significantly from each other ($\chi^2$ test).

Correlation analysis of the microcirculatory data (AVP, CBV, CV(CBV), PIA, CV(PIA), FAZ) with age, systolic BP, diastolic BP, mean arterial pressure, and heart rate showed a weak significant negative correlation between the size of the FAZ and systolic BP ($r = -0.29$, $p = 0.03$; Fig 2) and mean arterial BP ($r = -0.3$, $p = 0.03$) only in patients in group 1. With increasing stage of diabetic retinopathy there was a significant increase in PIA ($p = 0.0002$) and FAZ ($p = 0.03$), but no interaction was seen between the presence or absence of arterial hypertension and any of the morphological or dynamic parameters measured (ANOVA).

No significant differences were seen between patients in groups 1 and 2 in either the dynamic (AVP 1.64 (0.49) seconds $\pm$ 1.72 (0.58) seconds; CBV 1.98 (0.39) mm/s $\pm$ 2.09 (0.43) mm/s; CV(CBV) 16.9 (7.9) % $\pm$ 17 (7.9) %) or the morphological parameters (PIA 7985 (3137) $\mu$m $^2$ $\pm$ 8338 (3376) $\mu$m $^2$; CV(PIA) 66 (33) % $\pm$ 70 (32) %; FAZ 0.319 (0.206) $\mu$m $^2$ $\pm$ 0.363 (0.237) $\mu$m $^2$).

Compared with reference data in healthy subjects, $^{15}$ AVP 1.58 (0.4) seconds, CBV 2.83 (0.3) mm/s, CV(CBV) 12 (5) %; PIA 0.363 (0.237) $\mu$m $^2$, CV(PIA) 66.8 (43.1) %, FAZ 0.205 (0.062) $\mu$m $^2$, both groups with diabetic retinopathy showed significantly prolonged AVP times ($p < 0.0001$), decreased CBV ($p < 0.0001$), increased coefficients of variation (CV(CBV): $p = 0.0001$ (group 1), $p = 0.0007$ (group 2); CV(PIA): $p < 0.0001$), as well as increased FAZ area ($p < 0.0001$) and PIA ($p < 0.0001$).

The effect of antihypertensive medication on retinal circulation was studied in 19 diabetic patients with arterial hypertension receiving no antihypertensive medication (group A) and a group of 19 normotensive diabetic patients matched for stage of retinopathy (group B). There were no significant differences between the two groups for age (54 (9) $\pm$ 47 (18) years), duration of diabetes (9.6 (5.7) $\pm$ 13.1 (7.7) years), mean glycosylated haemoglobin (HbA$_1c$) (8.0 (2.1) % $\pm$ 8.3 (1.4) %), and systolic BP (148 (24) $\pm$ 143 (23) mm Hg) but significant differences were found in diastolic BP (93 (16) $\pm$ 81 (17) mm Hg; $p = 0.04$). There were no significant differences in the microcirculatory data tested between the patients in groups A and B (Table 2).

### Table 1. Microcirculatory results of diabetic patients with untreated arterial hypertension (n=19; group A) and matched normotensive diabetic patients (n=19; group B)

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (years)</th>
<th>Sex (M/F)</th>
<th>Systolic BP (mm Hg)</th>
<th>Diastolic BP (mm Hg)</th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Duration of diabetes (years)</th>
<th>HbA$_1c$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>54.5 (10)</td>
<td>36/26</td>
<td>150 (21)</td>
<td>87 (13)</td>
<td>108 (13)</td>
<td>15 (8)</td>
<td>8.4 (1.6)</td>
</tr>
<tr>
<td>Group B</td>
<td>41.4 (13)</td>
<td>36/26</td>
<td>132 (13)</td>
<td>78 (9)</td>
<td>100 (14)</td>
<td>16 (6)</td>
<td>8.6 (1.6)</td>
</tr>
</tbody>
</table>

*Significance: $p < 0.05$ NS $p > 0.05$.

### Table 2. Clinical and demographic data of diabetic patients with arterial hypertension

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (years)</th>
<th>Sex (M/F)</th>
<th>Systolic BP (mm Hg)</th>
<th>Diastolic BP (mm Hg)</th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Duration of diabetes (years)</th>
<th>HbA$_1c$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>54.5 (10)</td>
<td>36/26</td>
<td>150 (21)</td>
<td>87 (13)</td>
<td>108 (13)</td>
<td>15 (8)</td>
<td>8.4 (1.6)</td>
</tr>
<tr>
<td>Group B</td>
<td>41.4 (13)</td>
<td>36/26</td>
<td>132 (13)</td>
<td>78 (9)</td>
<td>100 (14)</td>
<td>16 (6)</td>
<td>8.6 (1.6)</td>
</tr>
</tbody>
</table>

*Significance: $p < 0.05$ NS $p > 0.05$.

**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. 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 progression or it has little or no effect.

Past studies using scanning laser fluorescein angiography have shown decreased capillary density in patients with arterial hypertension, $^{1}$ (PIA 5591 (838) $\mu$m $^2$) and in those with diabetic retinopathy. $^{4}$ Furthermore, capillary perfusion in the macula region is decreased in diabetic and in hypertensive patients. A decrease in perfusion occurs early in diabetes when no microaneurysms are visible and is associated with increased peri-foveal intercapillary area as a sign of decreased capillary density. Various studies have found hyperperfusion or hypoperfusion to be pathogenic in patients with diabetes mellitus. $^{7} 10–31$ The effect of decreased perfusion can be explained by progressive capillary closure with increased resistance and decreased perfusion. $^{36}$ Capillary closure is a well established angiographic and histopathological sign of diabetic retinopathy. $^{37} 38$ Capillary loss, as reflected by the

---

**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.
Circulation in patients with diabetes and arterial hypertension

UKPDS study\(^1\) found that a reduction in systolic BP to <150 mm Hg and in diastolic BP to <85 mm Hg led to a significant reduction in the risk of deterioration in vision acuity and retinopathy. Nørgaard \textit{et al.}\(^8\) 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 performed in diabetic patients with associated nephropathy or with more severe arterial hypertension.


Supported by Start 4-96 (OA, AR) and Hochschulsonderprogramm III Nordrhein-Westfalen (MR).

Proprietary interests: None


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

O Arend, M Rüffer and A Remky

Br J Ophthalmol 2000 84: 1392-1396
doi: 10.1136/bjo.84.12.1392

Updated information and services can be found at:
http://bjo.bmj.com/content/84/12/1392

These include:

References
This article cites 33 articles, 14 of which you can access for free at:
http://bjo.bmj.com/content/84/12/1392#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/