Follow up by colour Doppler imaging of 102 patients with retinal vein occlusion over 1 year

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Background/aim: Retinal vein occlusion (RVO) is one of the most frequent ocular vascular diseases and leads to severe vision impairment. Colour Doppler imaging (CDI) is the first method which allows distinct evaluation of arterial and venous velocities in RVO. CDI is valuable for diagnosis of RVO and shows the effects of isovolaemic haemodilution. Patients with RVO were monitored by CDI for 1 year in order to clarify venous and arterial involvement in the pathogenesis of this disease.

Methods: Patients with RVO were monitored prospectively for 1 year with clinical examinations, fluorescein angiography, and CDI every 3 months. 102 adults referred for RVO for less than 2 months were enrolled. Unaffected eyes were used as control. The maximum systolic and diastolic flow velocities and the resistance index (RI) were measured in the central retinal artery (CRA) and the maximum and minimum blood flow velocities in the central retinal vein (CRV).

Results: During the year of observation, branch retinal vein occlusion (BRVO), ischaemic central retinal vein occlusion (CRVO), and non-ischaemic CRVO had a distinct pattern of venous velocity changes. BRVO had a similar profile to that observed in controls. Venous velocities were continuously lower in central forms, with the lowest values in ischaemic occlusion. In contrast, a brief decrease in arterial diastolic velocity was observed in ischaemic CRVO at presentation, correlated with arteriovenous passage time on fluorescein angiography, but with rapid normalisation.

Conclusions: CDI findings were correlated with the type of RVO at all times during follow up. CDI showed persistent impairment of central venous velocity in CRVO whereas there was a fast initial velocities recovery of the arterial velocity. These results using CDI show strong evidence of a primary venous mechanism in RVO.

R etinal vein occlusion (RVO) is one of the most frequent ocular vascular diseases, and is conventionally divided into non-ischaemic and ischaemic types. Ischaemic RVO leads to severe vision impairment. Non-ischaemic RVO has an unpredictable course with a possible switch to the ischaemic form even several months after onset of the disease. The physiopathology is complex and unclear, with several factors involved such as arteriosclerosis, hyperviscosity, or coagulation disorders. As risk factors for arteriosclerosis are known to be important in RVO patients, it has been assumed by some investigators that the first event was an end artery obstruction. Another explanation is direct compression of central veins by a rigid arteriosclerotic central artery. Hyperviscosity appears to be caused predominantly by abnormal erythrocyte aggregation. This hypothesis supports the concept of isovolaemic haemodilution or troxerutin therapy. Such treatments have shown positive effects in controlled trials. Complete venous obstruction by thrombosis has been ruled out by fluorescein angiography and the role of coagulation disorders remains hypothetical.

Colour Doppler imaging (CDI), which allows easy location of the orbital vessels, has previously provided major contributions regarding the initial characterisation of RVO and in the evaluation of the effects of isovolaemic haemodilution. Arterial and venous flows are modified at the outset of the disease, and CDI helps in differentiating ischaemic from non-ischaemic types of CRVO with a minimum velocity (CRVmin) in the central retinal vein of less than 2 cm/s in non-ischaemic types with a sensitivity of 0.67 and specificity of 0.65. The effect of isovolaemic haemodilution is clearly demonstrated on arterial and venous velocities, with significant improvement from prehaemodilution to post-haemodilution velocities. In a previous study we showed that eyes of patients without RVO and contralateral eyes in RVO patients are similar, with no difference in arterial and venous velocities, thus allowing us to use unaffected eyes as controls.

The natural course of RVO is long and unpredictable, with possible occurrence of ischaemia several months after onset of the disease. Arterial and venous flow changes during this evolution remain unknown. The purpose of this study was to assess prospectively the haemodynamic course in the first year of RVO follow up.

MATERIAL AND METHODS

Patients
One hundred and two adults referred for RVO of less than 2 months’ duration were included between January 1993 and December 1997. Patients underwent a complete ophthalmological examination, including measurement of best corrected visual acuity (Snellen scale), ocular tonometry, anterior segment examination, and fundus biomicroscopy. The diagnosis of RVO was confirmed by fluorescein angiography. CRVO required for inclusion the presence of retinal haemorrhages in all four quadrants. Branch retinal vein occlusion (BRVO) was defined as haemorrhages in the area of an occluded vein at an arteriovenous overlap. Ischaemic type occlusion was diagnosed when fluorescein angiography disclosed an area of capillary non-perfusion of 10 disc diameters or more in patients with CRVO and four disc diameters for BRVO. In addition, measurement of the time of maximal venous filling on fluorescein angiography was used as an indirect parameter for flow velocity in retinal vessels. The normal arteriovenous passage time (AVT) was between 5 and 12 seconds.

Abbreviations: AVT, arteriovenous passage time; BRVO, branch retinal vein occlusion; CRA, central retinal artery; CRV, central retinal vein; CRVO, central retinal vein occlusion; EDV, end diastolic velocity; ICRA, ischaemic central retinal artery occlusion; ICRCVO, ischaemic central retinal vein occlusion; NICRVO, non-ischaemic central retinal vein occlusion; PSV, peak systolic velocity; RI, resistance index; RVO, retinal vein occlusion

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Sixty three men and 39 women (mean age 61 (SD 14.6) years, range 21–84 years) were included in the study. Fourteen of these patients had previously experienced a CRVO event. Forty seven patients had a history of arterial hypertension, 15 patients had a history of diabetes, and nine a history of glaucoma. The occlusion was considered to be central type in 69 cases and branch type in 33 cases. Fluorescein angiography identified ischaemic type CRVO in 18 cases of CRVO (ICRVO) and non-ischaemic type CRVO in 51 cases (NICRVO). Angiography identified ischaemic type occlusion in 13 of the 33 cases of BRVO, and we did not separate ischaemic and non-ischaemic types in this group (BRVO).

The interval from the onset of CRVO to the date of examination was 20.3 (17.4) days (range 2–60 days). Eighty five patients (26 BRVO, 42 NICRVO, 17 ICRVO) were monitored over 1 year.

**Colour Doppler imaging**

CDI was performed with an Acuson 128 XP (Acuson, Mountain View) with a 7 MHZ probe. Eye and orbit scans were performed by the same examiner who was unaware of the diagnosis, with the patient lying with eyes closed in a supine position. The transducer was applied to the closed upper lid using acoustic gel with the examiner’s hand resting on the orbital margin in order to minimise the pressure on the globe. CDI was performed with a gain adjusted to avoid artefactual colour noise, thus allowing detection of low velocities. The highest coded velocity was only 0.06 m/s. The Doppler sample volume (3 mm) was then placed without angle correction on the detected vessel in order to record blood flow signals in the retinal central artery and vein of both affected and unaffected fellow eyes.

A spectral analysis pulsed Doppler signal was used to assess the blood flow velocity waveform from these vessels. Because the angle between the ultrasound beam and the vessel remains very low in orbital vessels, we assumed that the frequency shift could be used as the velocity measurement. Peak systolic velocity (PSV) and end diastolic velocity (EDV) were determined in the central retinal artery by averaging the readings from three consecutive waveforms, and the resistance index (RI) was then calculated according to the formula defined by Pourcelot to assess changes in local blood flow resistance. We determined the maximum (CRVmax) and minimum velocities (CRVmin) in the central retinal vein during each of three consecutive cardiac cycles in the same way.

Ultrasound examinations were performed on the day of admission (D0) and then 3 months (M3), 6 months (M6), and 1 year (M12) later. Fluorescein angiography were performed on the same days. The control eye for each patient was the unaffected eye.

### Isoloxaemic haemodilution

None of the patients presented a contraindication to isoloxaemic haemodilution (age over 85 years, patients with retinal or disc neovascularisation at presentation; medical conditions including renal, respiratory, or cardiac failure; myocardial infarction or stroke within the past 6 months; unstable angina and ischaemic heart disease diagnosed by electrocardiogram) and each gave their informed consent before being included in the isoloxaemic haemodilution protocol. Isoloxaemic haemodilution was performed using an aphaeresis machine (Cobe Spectra; Cobe BCT, Lakewood, CO, USA), which is a continuous flow system. The extracorporeal volume was reduced by about 200 mL. A red blood cell exchange procedure was used, with a target haematocrit of 32%. Red blood cells were collected in a bag, autologous plasma was returned to the patient, and the red blood cell volume was simultaneously balanced with human 4% serum albumin.

### Statistical analysis

Results were expressed as the mean (SD). A Spearman correlation coefficient was estimated in order to assess the relation between RI in the CRA and AVT. Paired Student’s t tests were performed to assess differences in Doppler data between affected and unaffected eyes within each group. The results from each form of RVO were then compared by using a one way analysis of variance. Data were analysed using SAS (SAS Institute Inc, Carry, NC, USA).

### Table 1 Evolution and comparison of arteriovenous passage times (AVT) in patients with RVO over 12 months

<table>
<thead>
<tr>
<th>Group</th>
<th>AVT D0</th>
<th>AVT M6</th>
<th>M6/D0* p value</th>
<th>AVT M12</th>
<th>M12/D0† p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NICRVO</td>
<td>14.27</td>
<td>10.82</td>
<td>0.0001</td>
<td>10.79</td>
<td>0.0002</td>
</tr>
<tr>
<td>ICRVO</td>
<td>17.89</td>
<td>14.69</td>
<td>0.013</td>
<td>16.06</td>
<td>0.607</td>
</tr>
<tr>
<td>BRVO</td>
<td>13.06</td>
<td>10.52</td>
<td>0.011</td>
<td>10.36</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

Data expressed as mean (SD).

*Wilcoxon signed rank test comparing AVT M6 to AVT D0 and †comparing AVT M12 to AVT D0 within each group. Subjects lost to follow up were excluded.

NICRVO = non-ischaemic central retinal vein occlusion; ICRVO = ischaemic retinal vein occlusion; BRVO = branch retinal vein occlusion; AVT = arteriovenous passage time measured by fluorescein angiography in seconds; D0 = day of admission; M6 = 6 months later; M12 = 12 months later.

### Table 2 CDI characteristics in patients with retinal vein occlusion at presentation

<table>
<thead>
<tr>
<th>Central retinal vein occlusion</th>
<th>Branch retinal vein occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic (n=18)</td>
<td>Ischaemic + non-ischaemic; (n=33)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Affected eye</td>
<td>Unaffected eye</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>RI (CRA)</td>
<td>0.89 [0.11]</td>
</tr>
<tr>
<td>CRVmin</td>
<td>1.83 [0.94]</td>
</tr>
<tr>
<td>CRVmax</td>
<td>2.94 [5.84]</td>
</tr>
</tbody>
</table>

Data expressed as mean (SD).

*Wilcoxon signed rank test to compare affected and unaffected eyes. Tests performed within each group.

**One way ANOVA to compare the mean value of affected eyes over the three groups.

RI = resistance index in the central retinal artery; CRVmax = maximum venous flow velocity in the central retinal vein (cm/s); CRVmin = minimum venous flow velocity in the central retinal vein (cm/s); AVT = arteriovenous passage time measured by fluorescein angiography in seconds.
RESULTS

Arteriovenous passage time

Compared to the normal, the AVT at presentation was prolonged in the three groups of patients with RVO. The longest time was observed in the ICRVO group. The mean RI in the central retinal artery for the ICRVO group was significantly correlated to AVT at presentation ($r = +0.54; 95\% \text{ CI} = 0.10 \text{ to } 0.80); p = 0.02$). At 6 months, AVT was significantly improved in the NICRVO, BRVO, and ICRVO groups. Improvement in AVT remained significant only in the NICRVO and BRVO groups at 1 year (Table 1).

CDI haemodynamic characteristics at presentation

Using CDI at presentation, each form of RVO had a distinct profile for all haemodynamic characteristics measured and velocity reductions were related to the clinical severity of RVO. The mean CRVmax, CRVmin, and the mean RI in the central retinal artery of BRVO were not significantly different from those of unaffected eyes. Central arterial and venous velocities for CRVO were significantly different from unaffected eyes and the worst results were for ICRVO (Table 2). These results on the first 60 patients have already been published.

Changes in RI in the central retinal artery

During the 1 year follow up the mean RI in the central retinal artery decreased in ICRVO and NICRVO. The mean RI in the central retinal artery for CRVO, BRVO, and unaffected eyes were similar after 6 months’ evolution (Fig 1). One year later there was no significant difference in arterial velocity measured by mean RI in the central retinal artery in BRVO, ICRVO, and NICRVO. Moreover, for all forms of RVO there was no significant difference between affected and unaffected eyes (Table 3).

Changes in venous velocity in central retinal vein

BRVO had a similar profile to that observed in controls. At 1 year, venous blood flow velocities in CRVO were significantly worse than in unaffected eyes except for minimal venous blood flow velocities in NICRVO (Table 3). The pattern of venous velocities remained distinct for the three groups over the year of observation (Fig 1). ANOVA analysis of venous blood flow velocities in BRVO, ICRVO, and NICRVO showed significant differences between each group of RVO at 1 year with the lowest values for CRVO (Table 3).

DISCUSSION

As the physiopathology of CRVO has not been fully established, extensive research has been undertaken to develop atraumatic methods to clarify the underlying mechanisms. Two vascular mechanisms are regularly presented: firstly, the changes in central retinal artery velocity (related to atherosclerosis) predate the onset of CRVO and have a crucial role in the development of CRVO and, secondly, the changes in central retinal artery velocity are the consequence of a venous obstacle. CDI is the first method which allows easy and non-invasive distinct evaluation of arterial and venous velocities at the onset and during follow up of RVO.

This study is, to our knowledge, the first large prospective report of long term follow up by CDI of RVO occlusion. We showed a persistent impairment of central venous flow velocities correlated with the ischaemic or non-ischaemic CRVO, whereas arterial velocity in the central retinal artery was briefly modified in ischaemic CRVO.

A concomitant increase in RI in the central retinal artery was more marked in ICRVO at presentation than in NICRVO and BRVO. This RI value appears to be a discriminating
isovolaemic haemodilution was observed for venous blood was more severe in ICRVO than in NICRVO. Moreover, this lower velocities in affected eyes. BRVO had a similar profile to flow velocity reductions in all CRVO at the onset of RVO, with passage times were progressively reduced for NICRVO but not retinal artery at presentation. During follow up arteriovenous passage times were progressively reduced for NICRVO but not for IRVO. In contrast, CDI showed an improvement in RI in the central retinal artery at presentation. These results demonstrated clearly central venous blood flow velocity reductions in all CRVO at the onset of RVO, with lower velocities in affected eyes. BRVO had a similar profile to that observed in controls. The impairment of venous velocity was more severe in ICRVO than in NICRVO. Moreover, this difference remained constant at all times of measurement by CDI throughout the year of follow up. Improvement following isovolaemic haemodilution was observed for venous blood flow velocities in the central retinal vein as for RI in the central retinal artery, but this appeared transient. Despite improvement in arteriovenous passage time, notably in NICRVO, we observed persistent low flow velocities in the central retinal vein in affected eyes. Together, our results showed three distinct patterns of venous flow change correlated with the type and severity of RVO.

For NICRVO, this persistent significant change in venous flow in the central retinal vein could explain the risk of switching from a non-ischaemic form to an ischaemic form, even several months after the first occlusive event, and suggesting that improvement in RI in the central retinal artery and AVT was mostly related to the development of collateral channels rather than recanalisation of central veins.

The CDI results suggested predominantly venous involvement in the RVO process. In both unaffected eyes of patients with RVO and normal eyes there was no change in arterial velocities. Although arterial blood flow velocities improved in our study, even in ICRVO, venous blood flow velocities remained significantly decreased in ICRVO and NICRVO. Thus, RVO appeared to be caused by changes in venous flow and the severity of disease seemed to be correlated with the degree of occlusion causing the initial deterioration in arterial flow in IRVO.

Baxter et al followed 20 patients with CRVO by CDI over 1 year and observed an improvement in venous velocities but this appeared transient. Despite improvement in arteriovenous passage time, notably in NICRVO, we observed persistent low flow velocities in the central retinal vein in affected eyes. Together, our results showed three distinct patterns of venous flow change correlated with the type and severity of RVO.

Table 3 CDI characteristics at one year in patients with retinal vein occlusion

<table>
<thead>
<tr>
<th>Central retinal vein occlusion</th>
<th>Branch retinal vein occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ischaemic (n=17)</strong></td>
<td><strong>Non-ischaemic (n=42)</strong></td>
</tr>
<tr>
<td><strong>Affected eye</strong></td>
<td><strong>Unaffected eye</strong></td>
</tr>
<tr>
<td>RI (CRA)</td>
<td>0.81 (0.10)</td>
</tr>
<tr>
<td>CRVmin</td>
<td>2.05 (0.54)</td>
</tr>
<tr>
<td>CRVmax</td>
<td>3.14 (1.38)</td>
</tr>
<tr>
<td>AVT</td>
<td>16.06 (6.07)</td>
</tr>
</tbody>
</table>

Data expressed as mean (SD). Patients lost to follow up at 1 year were excluded from the analysis.

**Wilcoxon signed rank sum test to compare the affected and unaffected eyes. Tests performed within each group.**

**One way ANOVA to compare the mean values of affected eyes over the three groups:**

RI = resistance index in the central retinal artery; CRVmax = maximal venous flow velocity in the central retinal vein, in cm/s; CRVmin = minimum venous flow velocity in the central retinal vein, in cm/s; AVT = arteriovenous passage time measured by fluorescein angiography in seconds.

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