Experimental retinal branch vein occlusion in rhesus monkeys. I. Clinical appearances

A. M. HAMILTON,1 E. M. KOHNER,2 D. ROSEN,* A. C. BIRD,1 AND C. T. DOLLEY2

From the 1Institute of Ophthalmology, Judd Street, London, and the 2Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London

SUMMARY Branch and hemisphere vein occlusion were produced in rhesus monkeys by argon laser photoocoagulation. The following observations were made: (1) Immediately after occlusion there was venous dilatation, delayed filling of the artery, delayed drainage by the occluded vein, and capillary leakage. (2) Two patterns of evolution were identified within the first week. In some animals the fundus changes resolved and the retina returned to normal, while in others there was progressive retinal capillary closure. (3) Those animals destined to have capillary closure had diffuse or cluster retinal haemorrhages at 24 hours. (4) Capillary closure took place over 1 week and was usually complete over large areas of retina. (5) Retinal atrophy and major vessel changes occurred over several weeks. (6) Retinal revascularisation occurred in those areas of closure, though this was often limited. It was concluded that the early changes mimicked those seen in human retinal vein occlusion, though persistent retinal oedema and preretinal neovascularisation were not identified.

The morphological changes which follow retinal branch vein occlusion in man have been well documented (Foster-Moore, 1924; Jensen, 1936; Wise, 1957; Gass, 1968; Archer et al., 1974). Occlusion may occur close to the optic disc edge, causing disease in a retinal hemisphere; at a major arteriovenous crossing, resulting in changes within a quadrant; or at a minor crossing, in which case a small sector of the retina is affected. Retinal haemorrhages, infarcts, and oedema may be seen soon after occlusion; capillary closure with new vessel formation and persistent oedema occur as late complications and are largely responsible for persistent visual loss (Archer et al., 1976).

The pathogenesis of these phenomena following venous occlusion have been studied in animal homologues (Becker and Post, 1951; Campbell, 1961; Linner, 1961; Okun and Collins, 1963; Voipio and Riatta, 1964; Mutlu, 1966; Kohner et al., 1970; Archer et al., 1974).

In this paper we report the results of a further study which was designed to define in more detail the fundus changes following venous occlusion and in particular to identify those factors which may be more important in the genesis of capillary closure. Flow measurements and histopathological studies were also undertaken and are reported separately (Rosen et al., 1979; Hockley et al., 1979).

Methods

Rhesus monkeys were chosen as the experimental animal because of the close resemblance of the retinal vasculature to that of the human. Forty-five retinal vein occlusions were produced in 31 healthy monkeys of varying age.

ANAESTHESIA

The monkeys were all anaesthetised by intravenous thiopentone (4·6 ml of 2·5% solution) and intubated with a cuffed endotracheal tube; anaesthesia was maintained by oxygen and nitrous oxide in the proportion of 1:2 and fluothane.

PHOTOGRAHY

Pupillary dilatation was produced with the topical applications of 10% phenylephrine drops and 1% cyclopentolate drops. The cornea was irrigated intermittently with normal saline, a lid speculum being used to maintain good exposure.
Photographs were taken with a vertically mounted Zeiss (Oberkochen) camera with Kodachrome II for colour photographs and Ilford FP4 for fluorescein angiography. Colour and fluorescein photographs were taken several days prior to occlusion and then at intervals after occlusion. Fluorescein angiograms were taken after the injection of 1 ml of 10% solution of sodium fluorescein through a scalp vein needle in a superficial leg vein.

PHOTOCOAGULATION
The argon laser (Coherent Radiation 800) was chosen to produce the occlusion because it was possible to place high-energy burn of small diameter accurately and directly on a retinal vein with the minimum amount of heat diffusion to the surrounding retina, thus minimising the effects on the adjacent retinal vessels. The argon laser beam was delivered through a vertically mounted Zeiss slit lamp, so facilitating its application on the anaesthetised monkey. The laser was directed through a Worst unflanged scleral contact lens, with normal saline between the lens and the cornea.

METHODS OF OCCLUSION
The type and position of the vessel for occlusion was selected prior to the occlusion by examination of fluorescein angiographs. The site chosen for occlusions was well away from neighbouring arteries, and at least 1 disc diameter in length of vein was required for application of the laser. It was found that occlusion of the vein was greatly facilitated by intravenous injection of 1 to 2 ml of 10% sodium fluorescein just before the start of laser application. During this injection the site for occlusion was once more examined and finally confirmed to be free of adjacent arterioles. Argon laser energy was then applied to the vein with either the 50- or 100-μm spot size, an exposure of 0:20 second, and a power setting of 100 to 450 mW. A segment of vein and the immediately adjacent pigment epithelium was blanched by low-intensity burns, and then with increasing power the segment of the vein furthest from the optic disc was occluded. Laser was then applied to the more proximal part of the vein. The end point of laser application was when the occluded segment appeared either salmon pink or white in colour. Finally total occlusion and the absence of patent small vessels adjacent to the occlusion was confirmed by a further injection of fluorescein.

The maximum power required to produce an occlusion never exceeded 450 mW. The number of burns required to effect occlusion was similar in all the large veins occluded, but in the 2 macular tributary veins much less laser energy was required.

The site of the vessel occluded varied. In 2 cases small macular tributaries were chosen; the remainder were either hemisphere or quadrant tributaries.

In 11 monkeys the vein reopened and was re-occluded by further photococoagulation within 1 week. The duration of occlusion was calculated from the time of the permanent occlusion.

Results
A total of 45 occlusions in 31 monkeys were produced, comprising small tributary occlusions (2), branch vein occlusions (14), and hemisphere vein occlusions (29). The details of animals and the lengths of follow-up are shown in Table 1.

The morphological changes and the subsequent outcome were similar irrespective of whether the occlusion was a tributary, a branch vein, or a hemisphere vein occlusion. In view of this the results are not subdivided into these groups (Table 2).

ACUTE STAGE (1 TO 24 HOURS)
Immediately after occlusion there was a marked dilatation of the vein peripheral to the site of occlusion with narrowing and occasionally collapse of the vein proximal to the occlusion. Veins showed increased tortuosity, and there were arteriovenous crossing changes, the angle between the artery and vein at arteriovenous crossing points becoming much more acute (Fig. 1).

Haemorrhages were not a prominent feature immediately after occlusion. In 1 eye (M9) there
### Table 2: Results of occlusion (key to abbreviations at end of Table)

<table>
<thead>
<tr>
<th>Eye number</th>
<th>Vein occluded</th>
<th>Period of observation after final occlusion</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RSTBVO</td>
<td>1 h 15 min</td>
<td>Slight retinal oedema, deep haemorrhages, no capillary closure</td>
</tr>
<tr>
<td>2</td>
<td>LSHVO</td>
<td>1 h 30 min</td>
<td>Retinal oedema + + + no haemorrhages, fluorescein leakage from capillaries and terminal venules + + +, capillary and terminal venular dilatation, no closure</td>
</tr>
<tr>
<td>3</td>
<td>RIHVO</td>
<td>2 h</td>
<td>Retinal oedema + + +, no haemorrhages, fluorescein leakage from capillaries and terminal venules + + +, capillary and terminal venular dilatation, no closure, immediate delay in filling of affected half of retina, early capillary collaterals temporal to the macula</td>
</tr>
<tr>
<td>4</td>
<td>RSHVO</td>
<td>2 h</td>
<td>Retinal oedema + + +, small deep haemorrhage below and nasal to macula, fluorescein leakage from capillaries and terminal venules + + +, capillary and terminal venular dilatation, no closure, immediate delay in filling of affected half of retina, early capillary collaterals temporal to macula</td>
</tr>
<tr>
<td>5</td>
<td>RSHVO</td>
<td>2 h</td>
<td>Retinal oedema + + +, few scattered superficial haemorrhages, fluorescein leakage, no closure</td>
</tr>
<tr>
<td>6</td>
<td>RIHVO</td>
<td>2 hr</td>
<td>Retinal oedema + + +, no haemorrhages, fluorescein leakage + + +, capillary and terminal venular dilatation, no closure</td>
</tr>
<tr>
<td>7</td>
<td>RIHVO</td>
<td>2 h 30 min</td>
<td>Retinal oedema + + +, no haemorrhages, fluorescein leakage + + +, capillary and terminal venular dilatation, no closure</td>
</tr>
<tr>
<td>8</td>
<td>LIHVO</td>
<td>2 h 30 min</td>
<td>Retinal oedema + + +, no haemorrhages, focal capillary and terminal venular leakage, capillary and terminal venular dilatation, no closure</td>
</tr>
<tr>
<td>9</td>
<td>RSTBVO</td>
<td>3 h</td>
<td>Vitreous haemorrhage shortly after occlusion, nil else seen</td>
</tr>
<tr>
<td>10</td>
<td>RSTBVO</td>
<td>3 h</td>
<td>No retinal oedema, no leakage, capillary and terminal venular dilatation, no closure</td>
</tr>
<tr>
<td>11</td>
<td>LIHVO</td>
<td>3 h 30 min</td>
<td>Retinal oedema + + +, no fluorescein photographs</td>
</tr>
<tr>
<td>12</td>
<td>RIHVO</td>
<td>4 h</td>
<td>Retinal oedema + + +, few scattered superficial haemorrhages below macula, capillary and terminal venular leakage dilatation, no closure, delayed filling of affected half of retina</td>
</tr>
<tr>
<td>13</td>
<td>LIHVO</td>
<td>4 h</td>
<td>Retinal oedema + + +, no fluorescein photographs</td>
</tr>
<tr>
<td>14</td>
<td>RIHVO</td>
<td>5 h 30 min</td>
<td>Retinal oedema + + +, few superficial haemorrhages, capillary and terminal venular leakage + + +, dilatation, capillary closure, immediate delay in filling of affected half of retina, reversal of flow in major vessels</td>
</tr>
<tr>
<td>15</td>
<td>RSHVO</td>
<td>7 h</td>
<td>Retinal oedema + + +, few superficial retinal haemorrhages, no fluorescein photographs</td>
</tr>
<tr>
<td>16</td>
<td>LIHVO</td>
<td>24 h</td>
<td>Retinal oedema + + +, preferential haemorrhage at macula, a few scattered haemorrhages, capillary and terminal venule leakage, dilatation, no capillary and terminal venule closure</td>
</tr>
<tr>
<td>17</td>
<td>LSTBVO</td>
<td>2 days</td>
<td>Retinal oedema +, haemorrhages temporal to macula, no fluorescein photographs</td>
</tr>
<tr>
<td>18</td>
<td>LSTBVO</td>
<td>3 days</td>
<td>Retinal oedema +, extensive haemorrhages and cotton-wool spots, capillary and terminal venule leakage, dilated capillaries, capillary closure</td>
</tr>
<tr>
<td>19</td>
<td>LSTBVO</td>
<td>5 days</td>
<td>Retinal oedema + + +, scattered haemorrhages, capillary and terminal venular leakage +, dilated capillaries, collaterals larger than capillaries, temporal to macula, no closure</td>
</tr>
<tr>
<td>20</td>
<td>LSTBVO (macular tributary spared)</td>
<td>5 days</td>
<td>Retinal oedema +, scattered haemorrhages temporal to macular, capillary and terminal venular leakage +, dilated capillaries, no closure, collaterals temporal to macula</td>
</tr>
<tr>
<td>21</td>
<td>LIHVO</td>
<td>6 days</td>
<td>Retinal oedema + + +, extensive haemorrhages, haemorrhages at the site of occlusion and at macula, no fluorescein photographs</td>
</tr>
<tr>
<td>22</td>
<td>LIHCO</td>
<td>7 days</td>
<td>Retinal oedema + + +, extensive retinal haemorrhages, capillary and terminal venular leakage + + +, dilated capillaries and capillary closure, very slow flow in veins with granular flow, leakage from large vein</td>
</tr>
<tr>
<td>23</td>
<td>LSHVO</td>
<td>7 days</td>
<td>Retinal oedema + + +, extensive haemorrhage, cotton-wool spots, capillary and terminal venule leakage + + +, dilated capillaries, capillary closure, dilated capillaries temporal to macula</td>
</tr>
<tr>
<td>24</td>
<td>L Small macular tributary</td>
<td>7 days</td>
<td>Retinal oedema +, multiple superficial haemorrhages, no fluorescein photographs</td>
</tr>
<tr>
<td>25</td>
<td>L Small macular tributary</td>
<td>7 days</td>
<td>No fluorescein photographs</td>
</tr>
<tr>
<td>26</td>
<td>LSTBVO</td>
<td>7 days</td>
<td>Retinal oedema + + +, multiple massive haemorrhages, multiple areas of capillary nonperfusion, collaterals temporal to macula</td>
</tr>
<tr>
<td>27</td>
<td>LSTBVO</td>
<td>7 days</td>
<td>Few retinal haemorrhages, no fluorescein photographs</td>
</tr>
</tbody>
</table>

Continued
<table>
<thead>
<tr>
<th>Eye number</th>
<th>Vein occluded</th>
<th>Period of observation after final occlusion</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>LSTBVO</td>
<td>14 days</td>
<td>After 6 days no retinal oedema and multiple haemorrhages lateral to macula, 7 capillary and terminal venular closure, after 14 days unchanged, but no capillary closure</td>
</tr>
<tr>
<td>29</td>
<td>LITBVO</td>
<td>14 days</td>
<td>No retinal oedema, preretinal haemorrhage lateral to macula, capillary and venular dilatation, capillary closure ++</td>
</tr>
<tr>
<td>30</td>
<td>RIHVO</td>
<td>14 days</td>
<td>At 7 days no retinal oedema, multiple haemorrhages, capillary and terminal venular dilatation, no leakage, no capillary closure, marked delay in arterial filling, at 14 days appearance unchanged, well-formed collaterals temporal to macula</td>
</tr>
<tr>
<td>31</td>
<td>LSHVO</td>
<td>14 days</td>
<td>No haemorrhages, capillary and terminal venular dilatation, no leakage, no closure, large collateral formation</td>
</tr>
<tr>
<td>32</td>
<td>LIHVO</td>
<td>14 days</td>
<td>No oedema, extensive haemorrhages and cotton-wool spots adjacent to site of occlusion, capillary and terminal venular leakage, large areas of peripheral capillary nonperfusion</td>
</tr>
<tr>
<td>33</td>
<td>RIHVO</td>
<td>14 days</td>
<td>3 days after occlusion retinal oedema ++++, extensive deep haemorrhages, capillary nonperfusion ++++, 1 week after occlusion appearance unchanged but no oedema and veins seen as white lines, 2 weeks unchanged appearance but large-diameter collaterals temporal to macula nasally</td>
</tr>
<tr>
<td>34</td>
<td>LSHVO</td>
<td>21 days</td>
<td>No retinal oedema, extensive deep haemorrhages and preretinal haemorrhage, nonperfusion peripherally ++++</td>
</tr>
<tr>
<td>35</td>
<td>LSTBVO</td>
<td>21 days</td>
<td>No retinal oedema, multiple haemorrhages, 1 CWS large diameter, collaterals temporal to macula, no capillary closure</td>
</tr>
<tr>
<td>36</td>
<td>LSTBVO</td>
<td>21 days</td>
<td>No retinal oedema, haemorrhages and dilated capillaries temporal to macula</td>
</tr>
<tr>
<td>37</td>
<td>LIHVO</td>
<td>28 days</td>
<td>At 2 days retinal oedema ++++, scattered haemorrhages, 2 CWS near macula, leakage from capillaries and terminal venules ++++, no capillary closure, delayed perfusion of affected hemisphere, at 7 days no retinal oedema, marked collateral temporal to macula, at 28 days no oedema, well established large-diameter collaterals temporal to macula</td>
</tr>
<tr>
<td>38</td>
<td>RSHVO</td>
<td>28 days</td>
<td>No retinal oedema, multiple haemorrhages and CWS, capillary and terminal venule dilatation ++++, no leakage, large-diameter collaterals lateral to macula and in nasal periphery, sheathing and narrowing of arteries, pallor of superior half of optic disc</td>
</tr>
<tr>
<td>39</td>
<td>RSHVO</td>
<td>28 days</td>
<td>At 2 days retinal oedema ++++, multiple haemorrhages and CWS At 28 days no retinal oedema, multiple haemorrhage, capillary closure ++++, large-diameter collaterals lateral to macula, sheathing and narrowing of arteries, pallor of superior half of optic disc</td>
</tr>
<tr>
<td>40</td>
<td>RSHVO</td>
<td>28 days</td>
<td>7 days extensive haemorrhages 28 days no retinal oedema, multiple haemorrhages, extensive peripheral closure</td>
</tr>
<tr>
<td>41</td>
<td>LIHVO</td>
<td>35 days</td>
<td>2 days, retinal oedema, multiple haemorrhage, capillary and terminal venular leakage, capillary closure 7 days, appearance unchanged 35 days, no oedema, multiple haemorrhages, capillary closure ++++, venous and arterial narrowing and sheathing</td>
</tr>
<tr>
<td>42</td>
<td>LIHVO</td>
<td>42 days</td>
<td>7 days, retinal oedema, few haemorrhages, capillary and terminal venule dilatation and leakage +++ 28 days, widespread capillary and terminal venule dilatation, no capillary closure, venous sheathing and arterial narrowing 42 days, appearance unchanged, pallor of lower half of disc</td>
</tr>
<tr>
<td>43</td>
<td>LIHVO</td>
<td>56 days</td>
<td>28 days, extensive haemorrhages and CWS, sheathing of retinal veins and arteries, capillary closure ++++ 35 days, large preferential haemorrhage at macula, corkscrew collaterals temporal to macula, large vein leaks as it passes through an area of capillary nonperfusion 56 days, as above, intraretinal new vessel formation, beading of veins and extensive collaterals, and widespread vascular sheathing and occlusion</td>
</tr>
<tr>
<td>44</td>
<td>LIHVO</td>
<td>56 days</td>
<td>7 days, multiple haemorrhages and CWS, capillary dilatation and leakage from terminal venules and veins, capillary closure +++ 35 days, intraretinal new vessels with leakage from tip of growing vessels, large areas of capillary closure, occlusion of veins and arteries 56 days, regression of intraretinal new vessels, progressive retinal vascular closure, large collateral vessels formation</td>
</tr>
<tr>
<td>45</td>
<td>LSTBVO</td>
<td>63 days</td>
<td>7 days, multiple haemorrhages, capillary closure +++ 14 days, widespread capillary closure, peripherally extensive collateral 63 days, remodelling collaterals, intraretinal new vessel formation</td>
</tr>
</tbody>
</table>

Key to abbreviations: R = Right. L = Left. STBVO = Superior temporal branch vein occlusion. ITBVO = Inferior temporal branch vein occlusion. SHVO = Superior hemisphere vein occlusion. IHVO = Inferior hemisphere vein occlusion. CWS = Cotton-wool spots
Experimental retinal branch vein occlusion in monkeys. I. Clinical appearances

was a massive vitreous haemorrhage at the time of the occlusion due to inadvertent coagulation of the dilated distal segment of the vein. The few haemorrhages that occurred were superficial, flame-shaped, and were usually close to the site of occlusion (Nos. 1, 4, 5, 12, 14, 15, 16).

Within minutes of the occlusion the retina within the territory of venous drainage became swollen, fluorescein angiography showed delayed appearance of dye in arterioles supplying the affected area, and there was prolonged transit time in the retina drained by the occluded vein (Nos. 3, 4, 12, 14, 30, 37). The capillaries in the distribution of the occluded vein were dilated, and within 5 minutes of fluorescein injection there was dye leakage from the dilated retinal capillaries and terminal venules (Fig. 2). (Nos. 2, 3, 4, 5, 6, 7, 8, 11, 12, 14, 15, 16, 17, 18, 19, 29, 36, 45). In only 1 monkey's eye (No. 10) was there capillary dilatation without leakage.

The retinal oedema persisted for 24 hours in most animals, and limited oedema was still present at 7 days in some. In no monkey was there persistent macular oedema.

Within hours of the occlusion the capillaries in the horizontal meridian between the affected and unaffected quadrants became dilated; this phenomenon was more obvious temporal to the macula than nasal to the optic disc (Fig. 3). Reversal of flow in larger veins was sometimes demonstrated (No. 14) owing to the flow of fluorescein through the preferential channels temporal to the macula (Fig. 4). In only 1 monkey eye (No. 14) with a hemisphere occlusion was capillary closure demonstrated within 24 hours of occlusion. This occurred 5½ hours after occlusion, and the capillary nonperfusion was confined to the area below and temporal to the macula.
The subsequent pattern of retinal changes following vein occlusion fell into two broad groups. In the first there was complete resolution of the changes identified whilst in the second there was progression characterised by capillary closure and retinal atrophy. These two patterns of evolution will be described separately.

**Resolution of Disease After 24 Hours**

Retinal oedema slowly subsided, and the amount of leakage from the terminal venules and capillaries diminished. In this group of monkeys the retinal haemorrhages, which were few and superficial (Nos. 16, 17, 19, 20, 24, 27, 42), were gradually absorbed over the subsequent weeks. The fine multiple collateral channels which had formed between the affected quadrants were replaced by larger, fewer, and sometimes tortuous blood vessels temporal to the macula (Fig. 5). These collateral channels did not leak fluorescein at any stage.

The capillary pattern appeared normal on fluorescein angiography, and there was no evidence of any secondary arteriolar or venular changes. In this group the nerve fibre layer remained intact, and there was no pallor of the optic disc.

**Progression of Disease After 24 Hours**

In this group of monkeys the haemorrhages were extensive and darker and in all layers of the retina (Nos. 18, 21, 22, 23, 26, 28, 30, 33, 37, 38, 39, 40, 41, 44, 45). The amount and extent of retinal haemorrhages was a reliable indication of the presence of capillary nonperfusion. In some monkeys the haemorrhages were confluent, occupying the entire retina between the major blood vessels; in others the haemorrhages were arranged in a cluster fashion in the deep retina. Over the subsequent weeks there was gradual absorption of the haemorrhages, but intraretinal blood could be identified up to 8 weeks after occlusion.

In this group of monkeys the retinal vascular changes were characterised by capillary closure. In the most severely affected, closure was seen throughout the entire affected quadrant or hemisphere (Nos. 39, 41, 43, 44), while in others it was confined to the posterior pole or the peripheral retina (Fig. 6) (Nos. 40, 45). Closure was usually complete over large parts of the affected retina, and small patches of retinal nonperfusion within otherwise normally

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**Fig. 4 a and b** Fluorescein angiograms to show reversal of flow in major retinal vein following occlusion (arrowed)
perfused retina was seen rarely. Retinal capillary closure was identified as early as 5 hours (No. 14) and appeared to be a progressive phenomenon during the first 7 days following occlusion. After this period no increase of capillary closure was identified, but progressive changes occurred within the retina and major retinal vessels (No. 33).

Confluent closure of the peripheral capillaries was followed by nonperfusion of the major arteries and veins supplying that area (Fig. 7).

Closure of major retinal vessels was first identified 7 days after occlusion and was progressive over a subsequent period of 9 weeks. In 1 monkey slow perfusion in the quadrant was associated with an irregular calibre of venous lumen giving the appearance of 'beading' (No. 43). Major vessels crossing nonperfused retina showed accumulation of dye within the vessel wall during fluorescein angiography (No. 43), and these vessels subsequently became sheathed (Fig. 8) (Nos. 38, 39, 42); this change was limited to that length of vessel which crossed the ischaemic retina.

Within 28 days of the occlusion there was growth of vessels from the retinal veins into nonperfused retina (Fig. 9) (Nos. 41, 43, 44, 45). These 'intra-retinal new vessels' first appeared as small outgrowths from the veins at right-angles to the main channel. Leakage was seen from the terminal ends of these growing vessels only (No. 44).

Revascularisation was seen in all monkeys with capillary nonperfusion. In most the revascularisation was extremely limited, while in others there was progressive growth of these vessels until the whole area of nonperfused retina became vascularised. During the period of growth there was constant remodelling of the capillary bed, and in 1 monkey closure of the newly formed vessels was observed (No. 44). All new vessels were within the neuroretina and did not grow through the internal limiting membrane.
Fig. 7  Capillary closure with a secondary venular (arrowed a) and arteriolar occlusion (arrowed b)

Fig. 8  Black-and-white print of a colour photograph showing sheathing of retinal arteries and veins in the same area as Fig. 7. Retinal vein arrowed a and retinal artery arrowed b

Fig. 9  Fluorescein photograph 28 days after occlusion to show early growth of 'new vessels' into areas of capillary nonperfusion and subsequent appearance some 3 months later to show the progressive change
Experimental retinal branch vein occlusion in monkeys. I. Clinical appearances

There was progressive alteration in the appearance in the neuroretina over the subsequent weeks. At an early stage the retina was swollen, and in 4 monkeys multiple infarcts were seen (Nos. 18, 37, 39, 44). Within 4 weeks with absorption of the haemorrhages the retina became thin and atrophic, with loss of ganglion cell axons and segmented pallor of the optic disc, corresponding to the occluded quadrant or hemisphere.

In the monkeys that were observed for longer than 3 weeks there was progressive change within the pigment epithelium, with decrease in pigment content so that part of the fundus took on an orange colour. There was no pigment migration into the retina. Fluorescein angiography at no time showed evidence of any abnormality in the choroid except at the site of the laser occlusion.

Discussion

In order to study the pathogenesis of disease following venous obstruction experimental occlusion of retinal veins in animals has been undertaken by several workers. Becker and Post (1951), and Mutlu (1966) caused venous occlusion with the aid of transvitreal diathermy probes, and other workers used photococagulation with xenon (Campbell, 1961; Linner, 1961; Okun and Collins, 1963; Voipio and Riatta, 1964; Kohner et al., 1970; Archer et al., 1974) or argon laser energy (Hamilton et al., 1974; Coscas and Sterkers, 1977).

That permanent occlusion could be achieved in one session of photococagulation in a majority of animals (34 of 45) differs from the experiences of Coscas and Sterkers (1977). It was certainly our impression that the presence of intravascular fluorescein aided occlusion, and this may account for the different observations. The closure rate was also better than that following xenon (Kohner et al., 1970). Laser also had the advantage of the more accurate delivery system and small aperture, so that more precise lesions were created, and the arteries could be avoided more easily than with xenon.

The vein selected for occlusion was chosen well away from any adjacent arteries, so that the changes produced could be considered to be related to venous occlusion only. Inevitably some energy was absorbed within the choroid, but fluorescein angiography, both soon after occlusion and in the subsequent weeks, showed no apparent abnormality of the choroidal circulation. Delayed arrival of dye in the artery of the affected retina, slow capillary perfusion, capillary dilatation, and dye leakage were a constant feature in those monkeys examined within hours of occlusion. It was rare at this stage to see many retinal haemorrhages. These observations conform well with those in previous reports (Campbell, 1961; Okun and Collins, 1963; Kohner et al., 1970; Archer et al., 1976), and indicate that venous occlusion alone may produce the clinical appearance of "acute retinal branch vein occlusion". This conclusion is not new (Kohner et al., 1970; Archer et al., 1976; Coscas and Sterkers, 1977) but is at variance with the opinions expressed by Heyreh following his experimental (Heyreh, 1965) and clinical studies (Heyreh, 1971) of central vein obstruction. The circumstances which Heyreh has stated are necessary to produce the clinical appearance are high intraluminal pressure and ischaemia. Clearly both these are produced by venous occlusion due to the increased resistance to outflow, and arterial obstruction is not an essential prerequisite for such haemodynamic changes to occur. It might be argued that xenon photococagulation is likely to cause coincident arterial lesions as was observed by Kohner et al. (1970) in some cases, but with the argon laser no arterial lesions could be detected clinically.

After the first 24 hours following venous occlusion the evolution of retinal disease fell into two distinct patterns. In the first, in which there was complete restoration of the retinal appearance and blood vessels to normal, relatively few haemorrhages were seen at 24 hours. By contrast in the second deep or cluster haemorrhages occurred throughout the affected retina, and these monkeys developed progressive capillary closure. That the subsequent evolution of change could be predicted accurately on the basis of the retinal appearance soon after venous occlusion corresponds precisely with human disease (Hamilton, 1976).

The presence of capillary closure as a late phenomenon was implied by the observations of Okun and Collins (1963), and Mutlu (1966). The latter reported that after the initial retinal changes two patterns of evolution could be seen. In some animals large collaterals formed between the affected part of the retina and its neighbours within 5 days, and the retina reverted to a normal appearance; in the others no collaterals were seen and progressive atrophy of the retina followed, with narrowing or closure of the large vessels and slow resorption of the haemorrhages. Kohner et al. (1970) studied in more detail the phenomenon of closure. Of the 11 pigs observed for more than 1 week there was closure in 1, and out of 8 monkeys there was closure in 5. However, in some of the animals the veins reopened after the initial closure and had to be reclosed, and in several (3 of 5 monkeys with closure) the neighbouring artery was also closed. Failure to avoid the artery was probably related to the use of a xenon photococagulator. Although they
observed closure between 21 and 64 days after the initial occlusion, the relatively small number of observations make it impossible to identify the temporal profile of closure and those factors associated with this phenomenon. Curiously, Coscas and Sterkers (1977) failed to observe capillary closure despite using similar techniques. They considered that the closure was a late result of venous occlusion and that longer observation would have shown this change (Coscas and D’Hermy, 1978), but our results do not support this conclusion, since closure is an early change. Their failure to produce nonperfusion remains unexplained.

Our observations indicate that the process of closure took place during the 7 days after occlusion and rarely progressed beyond this time, and furthermore was usually complete over large areas of retina. Small areas of closure within otherwise normally perfused retina was unusual. It appears that capillary closure was a progressive and self-perpetuating phenomenon during the early and critical period of haemodynamic instability.

Kohner et al (1970) considered two possible factors which might influence capillary closure: firstly, that capillary endothelial damage due to a combination of high intraluminal pressure and ischaemia may induce intravascular thrombus formation; secondly, that the presence of tissue oedema may result in a rise in tissue pressure sufficient to cause capillary collapse. In addition, the rapid escape of plasma from the capillaries in the presence of slow flow may create intraluminal plugs of red cells and platelets (Hockley et al., 1976), which would increase resistance to flow within the capillary bed and compound the ischaemia. It is difficult to judge the relative importance of these influences. The fact that capillary intraluminal pressure is raised and that capillaries do not reopen after resolution of retinal oedema argues against the concept that capillary collapse in response to raised tissue pressure is important. However, the presence of thrombi and cellular plugs within the vessels may reduce flow within the capillary bed and consequently reduce intraluminal pressure down stream from the obstruction. Moreover, widespread collapse would result in ischaemia and the consequent endothelial damage would mitigate against reopening of the vessel.

The presence of diffuse haemorrhage as a presage of closure may represent an indication of endothelial dysfunction whereby red cells are allowed to escape from the vessel lumen, and the presence of a static plug of erythrocytes within the capillary may also be important in the production of this phenomenon. That haemorrhage is common and widespread indicates that closure cannot be due to external pressure alone. It is possible that all three factors are relevant to the pathogenesis of capillary closure and that each may enhance the influence of the other.

If the cessation of flow and the height of intraluminal pressure were important in the production of closure, the rate of formation of efficient collateral channels would be critical, as has been suggested by Mutlu (1966). Because we undertook no formal measurement of the small collateral channels during the critical first week following venous obstruction it is possible that differences existed between the 2 groups of animals at this stage, but large collaterals were seen in animals of both groups 3 weeks or more after occlusion.

Changes in the major vessels occurred as a secondary phenomenon determined by capillary closure. Dye leakage occurred from both veins and arteries as they crossed areas of nonperfused retina and became sheathed during the subsequent weeks. This change in the major vessel wall appeared to be a response to local tissue ischaemia, since the major vessel appeared normal on either side of the ischemic region. Progressive closure of the major vessels serving an area of nonperfused retina was also observed and took several weeks. That sheathing and closure of the major vessels followed some weeks after venous occlusion show that this change was purely a secondary phenomenon as it may be in man (Kohner and Shilling, 1976) and when observed after vein obstruction in man cannot be adduced as evidence of pre-existing arterial disease (Paton et al., 1964).

New vessels arising at right-angles from retinal veins with leakage from the growing tip were seen consistently in monkeys with capillary nonperfusion and appear to be an attempt at retinal revascularisation. This appearance is identical to that described recently in human disease (Shilling and Kohner, 1976). In man these changes frequently precede the growth of vessels anterior to the limiting membrane, but in experimental animals this phenomenon was not observed.

Persistent oedema, which is a prominent cause of visual loss in human retinal vein occlusion did not occur; this accords with the observation of Coscas and Sterkers (1977).

Progressive atrophy of the inner retina can be accounted for by failure of retinal perfusion, but the retinal pigment epithelial changes are more difficult to explain. There was no evidence that choroidal perfusion was significantly altered, and it is unlikely that retinal vessel disease caused outer retinal ischaemia. Retinal haemorrhages were certainly extensive in these animals, and this may have influenced the outer retina and pigment epithelium, though progressive pigment epithelial changes were
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seen in areas without macroscopic haemorrhage and progressed for a long time after intraretinal blood had disappeared.

Retinal vein occlusion in rhesus monkeys produces acute changes which simulate precisely those in man, and the evolution of the disease is similar to that seen in many patients. However, it was disappointing that persistent oedema and preretinal neovascularisation, which are the two major sight-threatening complications of venous occlusion in man, did not appear. These obvious differences may be due to differences between the circumstances of spontaneously occurring venous occlusion in man and the experimental homologue in primates. In man the problem arises in patients with coexistent vascular disease (Kohner et al., 1975) as opposed to the young healthy monkeys. The behaviour of blood vessels is certainly modified by age and by vascular disease. It should be emphasised that spontaneous retinal venous occlusion has not yet been achieved in experimental animals by manipulating systemic dysfunction.

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References


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A M Hamilton, E M Kohner, D Rosen, A C Bird and C T Dollery

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