Experimental occlusion of the central artery of the retina.* I. Ophthalmoscopic and fluorescein fundus angiographic studies

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SUMMARY Transient experimental occlusion of the central artery of the retina (OCAR), lasting from 15 to 270 minutes, was produced by clamping the artery in the orbit in 63 eyes of rhesus monkeys. Ophthalmoscopic and fluorescein angiographic studies were performed before and during clamping of the artery, as well as periodically after unclamping, for periods of up to 22 weeks. The effects of transient retinal ischaemia on the retina, optic disc, and retinal vascular bed were studied. 89% of the eyes showed a variable amount of residual retinal circulation on angiography during CAR clamping, but this did not exercise any protective action against ischaemic damage. Duration of the ischaemia was the principal factor determining severity of damage. OCAR for up to 98 minutes produced no significant permanent neural damage, but OCAR for 105 minutes or longer produced irreversible permanent neural damage. There was no significant permanent damage to the retinal vascular bed, though a transient fluorescein leakage was seen after OCAR for $2\frac{1}{2}$ –3 hours or longer. The findings revealed that the normal red colour of the optic disc represents retinal vascular filling in the surface layer of the disc and not deeper vascular filling. The various factors influencing the retinal circulation and neural damage in OCAR are discussed.

Von Graefe¹ in 1859 was the first to diagnose occlusion of the central artery of the retina (OCAR) ophthalmoscopically, and he wrote a classical description of the appearance of the fundus which is still well worth reading. In spite of the tremendous amount written about OCAR since then the essential question of how long it takes for the retinal ischaemia to produce irreversible damage remains unanswered; so do many other related questions. The subject has been investigated experimentally in the rat, cat, rabbit, squirrel, monkey, and man.^{2–11} These studies gave conflicting results. Moreover, the methods of producing retinal ischaemia in no way duplicated clinical OCAR in man. For example, raising the intraocular pressure to supra-arterial blood pressure^{3–7 9 10} not only stops the retinal circulation but also stops the choroidal circulation, which almost never occurs in clinical OCAR. In all

the previous studies the retinal integrity was evaluated either by electroretinography (ERG) or by histology, or in a few cases by both these techniques. In none of the studies was there a systematic evaluation of the retinal circulation by fluorescein fundus angiography or by fundus ophthalmoscopy during OCAR or serially thereafter during the follow-up period. It is well known that ERG, while a good indicator of the functional integrity of the photoreceptors and bipolar cells, does not give us any information about the functional status of the ganglion cells or most of the inner part of the retina, which is essentially the area involved in OCAR in man. Since it is vital for the management of this visually crippling condition to have exact information about the time that it takes for retinal ischaemia to produce irreversible damage, the present studies in rhesus monkeys were designed to find an answer to this important problem, using techniques which should duplicate as nearly as possible the natural occurrence of embolism in the CAR in man. In addition we wished to get more information on the transient acute retinal ischaemia caused by temporary OCAR, by ophthalmoscopic, angiographic, electrophysiological, and morpho-

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Table 1 Duration of retinal ischaemia and follow-up

Duration of retinal ischaemia (minutes)	Total no. of eyes	Duration of follow-up		
		Eyes with acute experiments	Chronic experiments	
			No. of eyes	Duration (weeks)
15-16	4	3 (Nos. 1-3)	1 (No. 4)	13½
20	2	1 (No. 5)	1 (No. 6)	14
30	1	1 (No. 7)	—	—
45	6	3 (Nos. 8-10)	3 (Nos. 11-13)	10, 13, 21
52	2	—	2 (Nos. 14-15)	20, 20
60	6	2 (Nos. 16-17)	4 (Nos. 18-21)	2*, 12, 14, 22
75	7	2 (Nos. 22-23)	5 (Nos. 24-28)	½*, 4*, 20, 20, 22
90	6	3 (Nos. 29-31)	3 (Nos. 32-34)	12, 13, 14
97	8	4 (Nos. 35-38)	4 (Nos. 39-42)	17, 17, 19, 19
102	4	4 (Nos. 43-46)	—	—
105	6	2 (Nos. 47-48)	4 (Nos. 49-52)	13, 14, 14, 16
135	6	3 (Nos. 53-55)	3 (Nos. 56-58)	13, 14, 14
270-280	5	2 (Nos. 59-60)	3 (Nos. 61-63)	3*, 13, 14
Total no. of eyes	63	30	33	

*The 4 animals died unexpectedly.
Numbers in parentheses denote the serial numbers of eyes in this study.

logical studies. This paper deals with the ophthalmoscopic and fluorescein angiographic aspects of the study. The electrophysiological and morphological studies are presented in subsequent papers.^{12 13}

Materials and methods

This study was carried out in 63 eyes of rhesus monkeys. All the eyes had stereoscopic colour fundus photography and fluorescein fundus angiography, and electroretinography (ERG) and visual evoked response (VER) recorded in their normal state.

Lateral orbitotomy was performed under general anaesthesia, with intravenous Nembutal (pentobarbitone sodium), and complete surgical asepsis. Under an operating microscope the central artery of the retina (CAR) was exposed and isolated from the attached central retinal vein and sheath of the optic nerve near its entry into the optic nerve. A microclamp was applied to the CAR. No other ocular vessel (central retinal vein or anterior or posterior ciliary arteries) was interfered with, so that the rest of the ocular circulation was normal. The wound was temporarily closed. ERG and VER were recorded within a few minutes after applying the clamp. Then fluorescein fundus angiography was performed, and in a number of eyes, colour fundus photography was done at variable intervals after clamping the CAR.

After the desired length of CAR occlusion (OCAR) (Table 1) the orbitotomy wound was opened and the clamp removed. The moment the

clamp was removed recording of ERG and VER was started, and this was usually carried on till there was recovery in the various electrophysiological functions or no further improvement was expected. The wound was stitched in layers; then colour fundus photography and fluorescein fundus angiography were repeated. In some eyes, however, the photography and angiography were performed earlier to get some information about the pattern of resolution of the fundus changes following restoration of the CAR circulation. A few hours thereafter 30 eyes were enucleated for histopathological studies. The remaining 33 eyes were followed up, mostly for about 12-22 weeks (Table 1) by serial stereoscopic colour fundus photography and fluorescein angiography, and recording of ERG and VER. After this period the eyes were enucleated either before or after the animal was perfused with a fixative solution via the heart. The eyes were examined by light microscopy and some by electron microscopy. Electrophysiological and morphological findings are reported in our subsequent papers.^{12 13}

Results

TERMINOLOGY

Before describing the results it is essential to clarify certain terms used in the description.

Posterior retina. This includes the part of the retina lying between the superior and inferior temporal retinal vessels and nasal peripapillary retina. The ophthalmoscopically apparent changes in OCAR were mostly limited to this region. Also,

Fig. 1 Fluorescein angiograms of left eye (No. 60) 36 minutes after clamping CAR: (a) 19 seconds after injection of dye shows normal filling of disc and choroid but not of the retinal vessels which show cattle-trucking of blood column; (b) 408 seconds after the injection partial filling of main retinal arterioles seen posteriorly.

on fluorescein fundus angiography only this part of the retina could be examined satisfactorily.

Macular region. This consists of an area with a diameter of 5.25 mm, with the centre at the foveola.

Fovea. This is the central part of the macular region and is about the size of an optic disc.

Foveola. This is the central tiny spot, with avascular zone. It showed a punched-out dark brown or yellowish-brown appearance when the macular region became opaque due to ischaemia.

Retinal opacity. The ophthalmoscopic appearance of the retina soon after acute ischaemia has been described by different names, e.g., retinal oedema, milky, cloudiness, or opacity. We prefer the term 'retinal opacity', as appropriate to describe ophthalmoscopic findings, although light and electron microscopy may show oedema as one of the changes.

On ophthalmoscopy and fluorescein fundus angiography all eyes were perfectly normal before occlusion of the CAR.

OCULAR CIRCULATION

I. During CAR clamping. Fluorescein angiography was performed in all the eyes 5–9 minutes after the clamping.

Choroidal circulation. In all the eyes the choroidal vascular bed filled normally, demonstrating that

the posterior ciliary artery (PCA) circulation was intact and normal (Figs. 1a, 2a).

Optic disc circulation. Since the major blood supply to the disc is derived from the PCA circulation the disc showed a normal vascular filling of PCA origin (Figs. 1a, 2a).

Retinal circulation. The detailed findings from each eye are given in Table 2. A summary of the results follows.

(a) **The cilioretinal arterioles.** Six eyes showed the presence of cilioretinal arterioles extending temporally from the optic disc for $\frac{1}{4}$, $\frac{1}{3}$, $\frac{1}{2}$, $\frac{2}{3}$, and $\frac{3}{4}$ of the distance to the fovea, with 1 eye having the upper $\frac{1}{3}$ of the retina supplied by the cilioretinal arteriole (Fig. 2).

(b) **The retinal arterioles.** These started to fill from the optic disc in all except 7 eyes (Fig. 1), starting anywhere from <4 to >120 (38 ± 56) seconds after the injection of intravenous fluorescein (Table 2). In 42 eyes the arterioles filled completely in the posterior retina (Fig. 2b), taking from 3 to 275 (81 ± 65) seconds. In 14 eyes where the arterioles started to fill 14–100 (58 ± 32) seconds after the injection, they showed a partial filling for only 1/2–2 disc diameters' distance from the disc margin in 65–376 (164 ± 82) seconds (Fig. 1b). There was no definite relationship between the time it took for the retinal arterioles to start filling (after the

Table 2 Fluorescein fundus angiographic findings during CAR clamping

Animal number	Duration of ischaemia (minutes)	Main retinal arteriolar filling (seconds)			Capillary filling at posterior pole of retina	Miscellaneous
		Start	Complete	Partial		
2	5	20	110	—	None	None
3	6	20	—	150	None	V filling from disc in 180 s
7	6	8	<19	—	F filling in 107 s	V filling from disc
1	7	None	None	None	None	—
8	8	20	60	—	F filling in 60 s	CRA fills up to nasal margin of F
6	9	20	75	—	At 178 s fill except in F	—
9	9	33	150	—	None	—
12	10	None	None	None	None	—
61	10	100	—	250	None	—
20	11	20	70	—	None	—
10	11	23	150	—	D-F fill at 150 s	CRA fills up to 1/3 of D-F V fill at 150 s
4	12	43	—	120	None	—
56	12	20	150	—	None	—
5	13	Gradual	70	—	In PP only	—
55	14	20	62	—	None	—
57	15	50	200	—	None	V fill from optic disc
24	16	15	130	—	None	—
40	17	None	None	None	None	—
54	17	12	50	None	None	Nasal retina filled well
62	17	20	110	—	None	—
21	18	10	26	—	Post pole fill at 60 s	—
52	18	17	24	—	Mac fill at 70 s	Normal retinal vascular bed filling at 180 s
58	18	20	26	—	Post pole fill at 50 s	—
14	19	6	14	—	Some perimac fill by 196 s	—
13	20	12	27	—	None	—
41	20	50	—	132	None	—
47	20	100	—	260	None	—
48	20	7	14	—	Post pole fill	CRA fills up to 1/3 retinal vascular bed
26	20	31	125	—	None	CRA fills up to 1/4 D-F
42	21	6	20	—	Post pole fill by 75 s	CAR fills slowly with complete V fill in 75 s
18	22	20	200	—	None	—
39	23	30	250	—	Some fill in PP	—
59	23	None	None	None	None	—
53	24	20	85	—	Up to centre of F by 5 min	—
16	25	None	None	None	None	—
17	25	14-37	128	—	In PP up to 2/3 D-F	—
27	25	21	120	—	None	—
19	26	20	—	191	None	—
50	26	14-33	300	—	None	Main and branch A fill
25	26	40	—	250	None	—
15	27	36	72	—	In PP up to F margin by 100 s	—
28	27	None	None	None	None	—
63	28	20	180	—	None	—
32	31	38	—	120	None	—
29	33	100	—	300	None	—
30	35	20	?	—	None	Cattle-trucking in A. Small vessels fill in mac
34	35	>26	<154	—	In mac except F fill at 154 s	—
31	35	20	140	—	None	—
49	35	30	200	—	None	—
60	36	60	—	436	None	Cattle-trucking in A
51	38	14	—	185	None	CRA fills up to 1/2 D-F
33	41	Very slow	?	—	None	—
22	45	100	—	350	None	—
23	45	30	100	—	None	—
36	70	12	26	—	PP fill by 200 s	CRA fills up to 2/3 D-F
38	71	20	140	—	None	—
37	75	40	150	—	None	—
35	81	60	—	230	None	—
44	85	None	None	None	None	—
43	90	30	130	—	None	—
45	90	<4	6	—	Post pole except central F at 10 s and F at 20 s	V fill completely at 60 s
46	90	10	20	—	None	—
11	? <30	60	—	125	None	—

A = Retinal arterioles. V = Retinal veins. CRA = Cilioretinal artery. Post = Posterior. PP = Peripapillary region. S = Seconds. D-F = Disc to foveolar region. F = Foveal region. Mac = Macular region.
All the time for filling of vessels from intravenous injection of fluorescein.

intravenous injection of fluorescein) and the time that elapsed before the complete/partial filling was finished.

(c) *The retinal capillary bed at the posterior pole.* This filled completely in 9 eyes (in 16–280 (80 ± 85) seconds) (Fig. 3) and partially in 9 more eyes (in 64–220 (147 ± 52) seconds). There were cilioretinal

arterioles in 2 of the former and 2 of the latter group, while in the other 2 eyes with cilioretinal arterioles there was no appreciable filling of the retinal capillaries (Fig. 2). In the remaining eyes the fluorescein usually filled only the main retinal arterioles without any extension to their smaller branches.

(d) *The retinal veins.* There was no retinal venous

Fig. 2 Fluorescein angiograms of right eye (No. 26) 25 minutes after clamping CAR: (a) 7 seconds after injection of dye shows normal filling of choroid, disc and a cilioretinal artery but empty retinal vessels; (b) 125 seconds after the injection shows filling of the main retinal arterioles only.

Fig. 3 Composite fluorescein angiogram of left eye (No. 8) 8 minutes after clamping CAR showing complete filling of the retinal vascular bed 206 seconds after injection of dye.

Fig. 4 Fluorescein angiograms of a right eye (No. 63) with OCAR for 4½ hours: (a, b) 50 minutes after unclamping CAR shows normal filling of retinal vascular bed and fluorescein leakage—mainly from the fine arterial vessels. (c) 47 days later shows slow filling of attenuated arterioles and partial unmasking of the choroidal fluorescence.

filling except in 6 eyes. In 3 of these (Nos. 10, 42, 45) the veins filled completely (Table 2) and in the remaining 3 eyes (Nos. 3, 7, 57) retrograde filling of the retinal veins from the optic disc was seen (most probably due to some compression of the central retinal vein in the orbit of these eyes).

II. *After unclamping CAR.* The retinal circulation was evaluated in all eyes immediately after unclamping the CAR. The time intervals between removing the clamp and the angiography varied in different eyes, but it was usually about 5 minutes after taking the colour fundus photographs (Table 4 below).

In all the eyes the retinal circulation was restored to its normal preclamping state with normal

filling of the retinal arterioles, capillaries, and veins (Figs. 4a, 5a). No abnormality of any kind was detected in eyes with OCAR up to 105 minutes. Two eyes (Nos. 56, 58) with ischaemia for 2¼ hours showed a very mild fluorescein leak from the capillaries at the tips of some of the macular vessels, with no other abnormality. In eyes with OCAR for 4½ hours angiography ¾–1¾ hours after unclamping the CAR showed marked fluorescein leakage from the macular vessels in all eyes, being mostly along the retinal venules in 2 eyes (Nos. 59, 62) arterioles in 2 (Nos. 60, 63), and both venules and arterioles in one (No. 61) (Figs. 4, 5).

On follow-up, in all but 2 eyes with retinal ischaemia up to 97–98 minutes, the retinal circulation

Fig. 5 Fluorescein angiograms of a right eye (No. 62) with OCAR for 4½ hours: (a, b) 1¾ hours after unclamping CAR shows normal filling of retinal vascular bed and fluorescein leakage—mainly from the fine venous vessels. (c) 3 months later shows some retinal capillary atrophy although no focal obliteration.

remained perfectly normal throughout with retinal capillaries normally outlined; there was no other angiographic abnormality. In 2 eyes with 75 minutes' ischaemia, however, the retinal capillaries were poorly defined, and their overall population was reduced.

In eyes with retinal ischaemia of 105 minutes or longer the retinal capillaries and retinal pigment epithelium showed abnormalities. In the 2 eyes with OCAR for 2¼ hours (Nos. 56, 58) and fluorescein leakage soon after unclamping the artery the leak disappeared the next day. In eyes with retinal ischaemia of 4½ hours' duration the fluorescein leakage seen in the macular region (see above) was either less or had almost vanished on the day

following unclamping; it disappeared in all cases in 4–5 days, leaving normal filling of the retinal capillaries. In all eyes with retinal ischaemia of 105 minutes or more the retinal capillaries were normally outlined during the initial follow-up of 2–3 weeks, but after this period the capillaries were progressively less well outlined, though no localised capillary closure was seen in any eye. With longer follow-up it seemed that there was an overall narrowing of the capillary lumen, and their population was somewhat reduced (Fig. 5c), and there was some delay in filling of the CAR (Fig. 4c).

OPHTHALMOSCOPIC APPEARANCES

I. *During CAR clamping.* Table 3 gives the details

Table 3 Ophthalmoscopic findings during CAR clamping

Animal number	Duration of ischaemia (minutes)	Posterior retinal opacity	Opacity of foveal retina	Brown spot	Retinal vessels	Optic disc
40	7	Mild	Slight	None	Full, mild cyanosis	Pale
24	13	Mild	Mild	±	Full, slight narrowing	Pale
13	15	Moderate	Mild	±	Normal-looking	Normal
26	15	Moderate	Moderate	±	Full and narrow	Pale
41	16	Moderate	Mild	±	Full, cyanotic, narrow	Pale
15	17	Slight	Slight	None	Normal-looking	Normal
42	18	Slight	Almost normal	None	Full, normal-looking	Normal
16	19	Slight	Slight	None	Full, normal-looking	Normal
28	20-22	Marked	Marked	—	Marked narrowing, A and V cattle-trucking	Pale
27	15-20	Mild-Moderate	Mild	None	Full, slight-narrowing	Pale
25	20	Moderate	Moderate	+	Full, slight narrowing	Pale
39	20	Mild	Slight	None	Full, normal-looking	Mild pallor
14	24	Marked	Marked	+	Full, normal-looking	Pale
31	25	Marked	Marked	+	A and V cattle-trucking	Pale
23	30	Moderate	Moderate	—	Full, normal-looking	Pale
22	35	Marked	Marked and ILMW	+	Full and narrow	Pale
36	60	Marked	Severe	+	Normal-looking	Almost normal-looking
37	70-75	Severe	Severe	+	A-marked narrowing, V cattle-trucking	Pale
38	70	Marked	Severe	+	Full and narrow	Pale
43	70-75	Severe	Severe	—	Marked narrowing, V cattle-trucking	Pale
44	75	Severe	Severe and ILMW	—	Extremely narrow, A and V cattle-trucking	Pale
46	78	Severe	Severe and foveal star	—	Full, normal-looking, Markedly sheathed main A	Pale
29	78	Severe	Severe	—	A-extremely narrow, A and V cattle-trucking	Pale
35	71-77	Severe	Severe	+	As above	Pale
45	90	Moderate*	Marked*	+	A normal-looking, V engorged	Hyperaemic
58	113	Severe	Severe	—	Pariarterial sheathing	Pale

A = Retinal arterioles. ILMW = Internal limiting membrane wrinkling. V = Retinal veins.

*With Christmas tree pattern of normal-looking retina around arterioles.

of findings in 26 eyes of the present series arranged in order of duration of retinal ischaemia. When the earliest fundus examination was performed, 7 minutes after OCAR, the posterior retina already showed a mild degree of opacity with a pale disc; the retinal vessels were full of blood and mildly cyanotic. Thirteen minutes after OCAR the picture was almost similar. In 3 eyes 15-16 minutes after OCAR the retinal opacity was of moderate degree with a pale disc. However, in 3 eyes 17-19 minutes after OCAR there was only a slight retinal opacity of the posterior pole with a normal-looking optic disc. In 4 eyes about 20 minutes after OCAR the retinal opacity varied from mild to marked with a pale disc, though on angiography there were no gross differences except that the eye with marked

retinal cloudiness had no retinal circulation at all compared to some arterial filling in the rest. Twenty-four to 60 minutes after OCAR the opacity was marked in the posterior retina, with almost normal-looking peripheral retina, and the disc was pale. Seventy minutes and longer after OCAR there was a severe degree of opacity of the posterior retina, with a pale optic disc (Fig. 6a). The severity of retinal opacity increased with the increase in duration of ischaemia, and was usually greatest in the foveal zone, which in severe cases was swollen, and in some cases also showed wrinkling or other changes of the internal limiting membrane (ILM). The central foveola always showed a well-defined punched-out brown spot after an ischaemia of 20 minutes or longer with marked or severe opacity of

Fig. 6 Composite fundus photographs of a left eye (No. 38): (a) 66 minutes after clamping CAR shows retinal opacity with a well-defined brown spot at the foveola. (b) $3\frac{1}{2}$ hours after unclamping the CAR (after 97 minutes' OCAR) shows almost normal-looking fundus.

the foveal retina (Fig. 6a) and not always so distinct a brown spot with moderate opacity; the brown spot is equivalent to the classical cherry red spot in OCAR in Caucasians. The retinal vessels showed narrowing (more marked in the arteries than in the veins) which was most marked with severe retinal opacity, so much so that in the latter group the arteries were reduced to extremely thin lines. The longer the ischaemia, the narrower the vessels became, most probably due to retinal oedema compressing the vessels. In eyes with severe opacity there was usually segmentation of the blood column ('cattle-trucking') in both arteries and veins—more often in the latter than the former. However some eyes showed the cattle-trucking with less marked

opacity as well (Fig. 1). Periarterial sheathing of the main retinal arteries was seen in 2 eyes (Nos. 46 and 58). In some eyes the retinal vessels appeared almost normal in spite of mild to marked retinal opacity (Nos. 13–16, 23, 36, 39, 42, 45).

II. After unclamping CAR.

(A) Within a few hours after unclamping the CAR. Detailed findings in the various eyes are shown in Table 4. The fundus appeared normal when seen $\frac{1}{2}$ –1 hour after restoration of circulation in eyes with retinal ischaemia of up to 20 minutes. In an eye with ischaemia for 30 minutes the fundus was normal when seen $1\frac{1}{2}$ hours after unclamping the CAR. Ischaemic changes following 45–52 minutes of OCAR had disappeared $2\frac{1}{4}$ – $3\frac{1}{4}$ hours later,

Table 4 Ophthalmoscopic findings soon after unclamping CAR

Animal number	Duration of ischaemia (minutes)	Time since CAR unclamping (minutes)	Retina	Foveal region	Brown spot	Retinal vessels	Optic disc
1	15	60	Normal	Normal	None	Normal	Normal
2	15	30	Normal	Normal	None	Normal	Normal
3	15	40	Normal	Normal	None	Normal	Normal
4	16½	26	Normal	Normal	None	Normal	Normal
6	20	60	Normal	Normal	None	Normal	Normal
7	30	105	Normal	Normal	None	Normal	Normal
11	45	1 day	Normal	Normal	None	Normal	Normal
8	45	10	Opacity in PP and post pole	Opaque	None	Normal	? Pale
12	45½	1 day	Normal	Normal	None	Normal	Normal
13	45	195	Almost normal	Normal	None	Normal	Normal
10	45	135	Normal	Normal	None	Normal	Normal
14	52	68	Slight opacity ST and IT to disc	Mild opacity	None	Normal	Normal
15	53	195	Normal	Normal	None	Normal	Normal
20	60	60	Mild opacity post pole	Yellowish	None	Normal	Normal
16	60	135	As above	Mild opacity	None	Normal	Normal
18	60	144	As above	Mild opacity	None	Normal	Normal
21	60	113	Mod opacity post pole	Mod opacity	?	Normal	Normal
19	60	101	As above	Mod opacity	?	Normal	Normal
17	60	130	As above	Mod opacity	?	Normal	Normal
26	75	135	As above	Mod opacity	?	Normal	Normal
22	75	180	Faint opacity ST and IT to disc	Mild opacity and ILM folds	?	Normal	Normal
28	75	165	As above	Very mild opacity	?	Normal	Normal
27	75	165	Opacity mainly along arc fib*	Mild opacity	?	Normal	Normal
23	75	240	Normal-looking	Normal-looking	None	Normal	Normal
25	75	180	Normal-looking	Normal-looking	None	Normal	Normal
24	74	180	Normal-looking	Normal-looking	None	Normal	Normal
32	90	16	Mild opacity	Mild opacity	None	Normal	Normal
29	90	180	Almost normal	Almost normal	None	Normal	Normal
33	90	180	Almost normal	Almost normal	?	Normal	Normal
30	90	180	Almost normal	Slight opacity	None	Normal	Normal
34	90	100	Some opacity	Slight opacity	None	Normal	Normal
31	90	135	Some opacity	Slight opacity	Yellow spot	Normal	Normal
35	97	270	Almost normal	Almost normal	None	Normal	Normal
36	97	270	Almost normal	Almost normal	None	Normal	Normal
37	97	270	Faint opacity	Almost normal	None	Normal	Hyperaemic
38	97	225	Normal-looking	Mild opacity	None	Normal	Normal
41	97	150	Mild opacity	Mild opacity	None	Normal	Normal
39	98	150	Mild opacity	Normal	None	Normal	Normal
42	97	150	Almost normal	Mild opacity and ILMW	None	Normal	Normal
40	97	150	Slight opacity	Slight opacity	None	Normal	Normal
43	102	285	Mild opacity	Mild opacity	None	Normal	Normal
44	102	270	Mild opacity	Mild opacity with ILMW	None	Normal	Normal
45	102	225	Mild opacity	Mild opacity	None	Normal	Normal
46	102	300	Mild opacity	Mild opacity	Present	Normal	Slightly blurred margins
52	105	138	Slight opacity	Slight opacity with ILMW	None	Normal	Normal
50	105	150	Slight opacity	Mild opacity	?	Normal	Normal
49	105	210	Mild-moderate opacity	Mild-moderate opacity	Present	Normal	Slightly hyperaemic
47	105	60	As above	As above	Present	Normal	Hyperaemic
51	105	210	Mod opacity	Mod opacity	Present	Normal	Hyperaemic
48	105	105	Mod opacity**	Mod opacity	Present	Normal	Normal
58	138	1 day	Marked opacity	Marked opacity with ILMW	Present	Normal	Hyperaemic
56	134	23	Marked opacity	Marked opacity	Present	Normal	Hyperaemic
54	135	150	Marked opacity	Marked opacity	Present	Normal	Hyperaemic
57	135	30	Marked opacity	Marked opacity	Present	Normal	Hyperaemic
55	146	135	Marked opacity	Marked opacity	Present	Normal	Hyperaemic
61	275	1 day	Marked opacity	Marked opacity with ILMW	Present	Normal	?
62	280	90	Marked opacity	Marked opacity and oedema with ILMW	—	Periarterial sheathing	Hyperaemic
59	270	68	Marked opacity	As above	—	—	Hyperaemic
63	270	45	Marked opacity	As above	Present	—	Normal
60	270	60	Marked opacity	Marked opacity and oedema	Present	—	Hyperaemic

ILM = Internal limiting membrane. ILMD = ILM detachment. ILMW = ILM wrinkling. Mod = Moderate. Post = Posterior. PP = Peripapillary region. IT = Inferior temporal. ST = Superior temporal. Arc fib = Arcuate fibers. Periar = Periarterial.

*Peripapillary retina normal. **Upper half of retina normal because of big cilioretinal artery.

except for some prominent white nerve fibre striation near the superior temporal and inferior temporal margin of the disc in some eyes. In eyes with OCAR lasting for 1 hour the retina still showed mild to moderate retinal opacity, especially along the arcuate fibres, $1\frac{3}{4}$ – $2\frac{1}{4}$ hours after unclamping the CAR though the optic disc looked normal. Retinal changes due to 75–90 minutes' ischaemia had recovered almost to normal $4\frac{1}{2}$ hours after restoration of the circulation and the optic disc was normal. In eyes with ischaemia of 97 minutes the fundus looked almost normal $3\frac{3}{4}$ – $4\frac{1}{2}$ hours after unclamping the CAR or showed faint retinal opacity with normal optic disc (Fig. 6b) while $2\frac{1}{2}$ hours after the release of the clamp it showed variable degrees of retinal opacity. In eyes with retinal ischaemia for 102 minutes mild retinal opacity was still evident $4\frac{1}{2}$ –5 hours after restoration of circulation, though the optic disc was normal-looking by then. Eyes with retinal ischaemia of 105 minutes, when seen $3\frac{1}{2}$ hours after unclamping the CAR, still showed mild to moderate retinal opacity and a normal-looking or hyperaemic optic disc. When retinal ischaemia was of $2\frac{1}{4}$ hours' duration the retina did not show much recovery that day and the optic disc was always hyperaemic. Eyes with OCAR of $4\frac{1}{2}$ hours showed marked retinal opacity, marked at the upper and lower poles of the optic disc, and there was detachment of the ILM in the foveal zone in 3 (Nos. 59, 62, 63) of the 5 eyes with marked oedema in that region and the disc was usually hyperaemic with slightly blurred margins. When the retinal oedema was marked the macular retina showed folding in the foveal region, producing a ridge or a cruciform elevation.

In summary, on restoration of circulation after OCAR (a) in eyes with 90 minutes' ischaemia or less the retina and optic disc looked normal within $4\frac{1}{2}$ hours, (b) eyes with occlusion for 97 and 102 minutes showed a normal-looking disc, but the retina showed mild opacity in the latter group and faint opacity or a normal appearance in the former group, and (c) in eyes with OCAR for 105 minutes or longer the ischaemic fundus changes did not resolve.

(B) *During follow-up period.* Thirty-three eyes were followed up for up to 22 weeks (Table 1). The findings fall naturally into the following 3 groups.

(a) *15–90 minutes' retinal ischaemia.* In eyes with retinal ischaemia of 90 minutes or less the retina and optic disc mostly remained normal during the entire period of follow-up except for a few eyes showing some unusual changes which were as follows:

1. One eye with 45 minutes' ischaemia developed during the 2nd–3rd week transient wrinkling of the

ILM in the macular region; this lasted a few weeks, leaving a normal retina after that.

2. One eye with 52 minutes' ischaemia showed some residual retinal opacity in the foveal zone after the first day; this cleared during the first week. This eye showed a slight pallor of the optic disc after about 2 weeks.

3. Two eyes after OCAR of 75 minutes developed pallor of the optic disc in about 2 weeks; this gradually progressed to optic atrophy which was maximum by about the fifth week, by which time the retina of these 2 eyes also looked atrophic.

4. In the eyes with retinal ischaemia of 90 minutes the fundus looked perfectly normal in 1 week, but 1 eye showed some doubtful optic disc pallor.

(b) *97 minutes' retinal ischaemia.* In all the eyes the retina was normal-looking throughout the period of follow-up (Fig. 7). In about 2–3 weeks the optic disc developed a slight pallor which did not progress.

(c) *105–270 minutes' retinal ischaemia.* In all these eyes the retinal opacity and oedema worsened on the day after the unclamping of the CAR, compared to what was seen a few hours after the unclamping. The retinal changes started to resolve before the end of the first week, leaving retinal opacity mainly in the macular region and along the superior and inferior arcuate fibres, with some radial wrinkling of the ILM. The retinal opacity and wrinkling of the ILM cleared within 2, 2–3, and 3 weeks after the ischaemia in eyes with retinal ischaemia of 105, 135, and 270 minutes respectively, leaving an atrophic retina and attenuated retinal vessels. In the second or third week fine crystalline deposits developed in the retina, mainly in the macular region, in half the eyes with 105 minutes' ischaemia and in all the eyes with 135 and 270 minutes' ischaemia. These crystalline deposits cleared after variable time intervals, usually in about 2 months, but persisted in a few eyes even up to the end of follow-up (Fig. 8). The detachment of the ILM in the foveal zone, seen in 3 of 5 eyes after ischaemia of 270 minutes, cleared in 4–5 weeks.

The optic disc started to develop pallor during the first week and marked optic atrophy was seen in the second or third week, without much change thereafter.

The retinal pigment epithelium showed granularity at the posterior pole in all eyes with retinal atrophy, i.e., 105 minutes' and longer ischaemia, and 2 eyes with 75 minutes' ischaemia. This usually developed gradually 3 weeks after the OCAR. It never developed into gross pigmentary disturbance.

(C) *The final ophthalmoscopic appearance at the end of follow-up.* This is given for each eye in Table 5. In all eyes with retinal ischaemia of up to 97–98

Fig. 7 Composite fundus photographs of a right eye (No. 42): (a) Normal fundus before clamping of CAR. (b) 4 months after 97 minutes' OCAR shows normal-looking fundus.

minutes (except 2 eyes with 75 minutes' ischaemia) the retina was normal-looking ophthalmoscopically (Fig. 7b). The optic disc was normal in all eyes except for a doubtful pallor of the disc in one eye with 90 minutes' ischaemia, and a slight pallor in 1, 1, and all 4 eyes with 52, 75, and 97 minutes' ischaemia respectively.

In 2 eyes with 75 minutes' ischaemia and in all eyes with ischaemia of 105 minutes or longer the retina and optic disc were markedly atrophic with attenuated retinal vessels; a few eyes showed fine crystalline deposits in the retina at the posterior pole (Fig. 8). However, 2 (Nos. 50, 52) of the 4 eyes with 105 minutes' ischaemia showed a more or less normal-looking retina; but this is an ophthalmo-

scopic artefact and deceptive, because the optic disc was markedly atrophic.

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This is an extremely important consideration and was especially investigated in the present study. Table 2 summarises the fluorescein angiographic findings on residual retinal circulation in each eye. Tables 4 and 5 summarise the ophthalmoscopic findings in each eye soon after unclamping the CAR and at the end of follow-up, respectively. A comparison of Table 2 with Table 4 or 5 revealed no well-defined correlation. Consider, for example, the

Fig. 8 Composite fundus photographs of right eye (No. 62): 7 weeks after $4\frac{1}{2}$ hours' OCAR showing complete atrophy of the disc and retina, sheathing of main retinal arterioles, crystalline retinal deposits, and foveal degeneration. Angiograms of this eye soon after unclamping CAR are shown in Fig. 5.

various eyes of the 75- and 105-minute groups.

This lack of correlation was found almost throughout the series, so that neither the absence of retinal circulation, nor the filling of the main retinal arterioles (complete or partial), nor the filling of retinal capillaries in a part or the entire posterior pole, made any significant difference to the final outcome of retinal ischaemia; nor did the presence of cilioretinal arterioles prevent damage to the part of the retina supplied by the occluded central retinal artery. In eyes with 105 minutes' OCAR or longer complete or partial filling of the retinal circulation as compared to minimal or no filling did not protect the retina from irreversible damage. This was the most unexpected finding of this study and contradicts all the previous assumptions.

Discussion

RESTORATION OF RETINAL CIRCULATION AFTER OCAR

For well over a century, in eyes with OCAR, filling of the retinal arteries on ophthalmoscopy has been described when the patient is first seen within a few days or sometimes even within a few hours after the onset of loss of vision. This has led to considerable controversy, not only about the mechanism responsible but also about the basic nature of the lesion causing OCAR. The residual retinal circulation after OCAR and its subsequent improvement have been thought to be due to (1) cilioretinal anastomoses in the optic nerve head,¹⁴⁻¹⁶ (2) the transient nature of systemic arterial hypotension in eyes with stenosed CAR producing OCAR,^{15 17}

(3) transient spasm of the CAR,¹⁸ (4) dislodging of an embolus in CAR¹⁹ or ophthalmic artery,²⁰⁻²² (5) incomplete OCAR,²³ and (6) retrograde flow from the anterior ciliary arteries.² The last possibility evidently is illogical while the others remain probabilities (except for the dislodging of an ophthalmic artery embolus).

In the present study occlusion of the CAR near its entry into the sheath of the optic nerve by the clamp was complete and indubitable, and yet fluorescein angiography performed immediately after clamping the artery revealed a variable amount of residual retinal circulation in 89% of the eyes. Hill,²⁴ in 10 patients with OCAR seen $\frac{1}{4}$ -4 days after the onset of occlusion, found on fluorescein angiography normal retinal circulation in 3 eyes (in $\frac{1}{2}$, 1, 4 days), slightly delayed circulation in 3 eyes (in 1, 1, 2 days), delayed in 2 (in $\frac{1}{2}$, 1 day), and no filling of the CAR in 2 eyes (in $\frac{1}{4}$, $1\frac{1}{2}$ day). If eyes with permanent OCAR are followed up in patients^{25 26} or in rhesus monkeys with experimental occlusion,^{27 28} a slow restoration to almost normal retinal circulation is seen in almost all eyes within a few days after the occlusion. Thus, the presence of retinal circulation on fluorescein angiography in eyes seen a few hours or days after OCAR is no proof of nonoccurrence or incompleteness of the occlusion.

It appears that the residual retinal circulation or its restoration in OCAR is most probably due to the following 2 anastomoses.

(1) *Cilioretinal capillary anastomoses.* The optic disc is supplied essentially by the posterior ciliary arterial (PCA) circulation in the lamina cribrosa and prelaminar regions (Figs. 1a, 2a), and by the retinal circulation in the surface layer.^{25 29} The 2

*Experimental occlusion of the central artery of the retina*Table 5 *Ophthalmoscopic findings at the end of follow-up in chronic experiments.*

<i>Animal number</i>	<i>Duration of ischaemia (minutes)</i>	<i>Follow-up period (weeks)</i>	<i>Optic disc</i>	<i>Retina</i>	<i>Macular region</i>	<i>Retinal vessels</i>
4	16½	13½	Normal	Normal	Normal	Normal
6	20	14	Normal	Normal	Normal	Normal
11	45	10	Normal	Normal	Normal	Normal
12	45½	13	Normal	Normal	Normal	Normal
13	45	21	Normal	Normal	Normal	Normal
14	52	20	Sl pallor	Normal	Normal	Normal
15	53	20	Normal	Normal	Normal	Normal
20	60	14	Normal	Normal	Normal	Normal
18	60	2*	Normal	Normal	Normal	Normal
21	60	22	Normal	Normal	Normal	Normal
19	60	12	Normal	Normal	Normal	Normal
26	75	20	Atrophic	Atrophic	ILM reflex	Normal
28	75	22	Sl pallor	Normal	Normal	Normal
27	75	20	Atrophic	Atrophic	ILM reflex	Normal
25	75	4*	Normal	Normal	Normal	Normal
24	74	½*	Normal	Normal	Normal	Normal
32	90	12	? Sl pallor	Normal	Normal	Normal
33	90	13	Normal	Normal	Normal	Normal
34	90	14	Normal	Normal	Normal	Normal
41	97	19	Sl pallor	Loss of NFS except in PMB	Yellow foveal discolouration	Normal
39	98	17	Sl pallor	Normal	Normal	Normal
42	97	19	Sl pallor	Normal	Normal	Normal
40	97	17	Sl pallor	Normal	Normal	Normal
52	105	16	Atrophic	Normal-looking	Normal	Normal
50	105	14	Atrophic	Normal-looking	Normal	Normal
49	105	13	Atrophic	Atrophic	Atrophic	Narrow
51	105	14	Atrophic	Atrophic	Atrophic	Narrow
58	138	14	Atrophic	Atrophic	Atrophic	Normal-looking
56	134	13	Atrophic	Atrophic	Atrophic	Narrow
57	135	14	Atrophic	Atrophic	Atrophic	Narrow
61	275	3	Atrophic	Atrophic	Atrophic	Narrow
62	280	13	Atrophic	Atrophic	Atrophic with old ILMD border markings	Narrow
63	270	14	Atrophic	Atrophic	Atrophic with old ILMD border markings	Narrow

*Animal died during follow-up. ILMD = Internal limiting membrane detachment. ILM = Internal limiting membrane. NFS = Nerve fibre striation. PMB = Papillomacular bundle. Sl = Slight.

circulations communicate via the capillaries of the optic disc, so that, in OCAR, capillaries on the surface of the optic disc (Fig. 1a), and even in the peripapillary retina, can fill from the ciliary circulation of the disc. Soon after OCAR, these anastomoses do not seem to contribute to the filling of the CAR to any appreciable extent, but after a few weeks these enlarge sufficiently.²⁵⁻²⁸

(2) *Anastomoses by the CAR.* The artery in man gives out pial branches in 95% and a variable number of branches within the optic nerve in 75% of cases.³⁰ The pial branches in the great majority of cases establish prominent anastomoses with other pial branches arising from other sources (described and illustrated in detail elsewhere).³⁰ At the lamina cribrosa the CAR gives no branches. In the present study, with the site of OCAR outside the optic nerve, all the pial collaterals would still be present and lead to filling of the CAR beyond the site of occlusion. This was strongly suggested by the fact that the CAR started to fill from its intra-neural course and that in a number of these eyes (e.g., Nos. 7, 13, 14, 21, 36, 42, 45, 46, 48, 52, 58) once the filling of the artery started the flow was fairly quick. These observations would strongly suggest that, clinically, when a residual retinal circulation is seen in OCAR, the site of occlusion is probably where the artery pierces the dura mater (i.e., the part of the artery with the narrowest lumen³¹) and in eyes with no residual circulation (except filling of the capillaries on the surface of the optic disc) the site of occlusion is likely to be in the lamina cribrosa.

EFFECT OF ISCHAEMIA ON RETINAL VASCULATURE

The present study provides important information on this subject. The findings show that acute transient ischaemia of up to 4½ hours does not produce retinal capillary obliteration, but an acute transient ischaemia of 6-7½ hours or longer can produce it.²⁷⁻²⁸ If the OCAR is permanent, no fluorescein leakage is seen at any stage.²⁷⁻²⁸

Retinal ischaemia is thought to upset the normal retinal-blood barrier in the retinal capillaries. Cunha-Vaz³² demonstrated in rats that temporary ischaemia of 70 minutes and longer increased permeability first of the retinal arterioles and later, at 24 hours, led to preferential involvement of the venous side. The permeability change was directly related to the changes in the endothelial cells and no passage of the tracer took place through the interendothelial junctions, which were always closed.³³ Reinecke *et al.*⁵ showed death of the endothelial cells and finally of the mural cells in cats after an experimental ischaemia of 1½ hours by

raised intraocular pressure. Our findings would indicate that in spite of severe endothelial cell damage by ischaemia it probably takes 2½-3 hours to produce fluorescein leakage with normal intraluminal blood pressure, and that too is only a transient phenomenon lasting at the most 4-5 days, with full recovery after that. This would also suggest that acute ischaemic damage to the retinal endothelial cells for up to 2½ hours does not seem to upset the retinal-blood barrier significantly. The subject of the retinal-blood barrier in retinal vascular occlusion is discussed at length elsewhere.²⁸

OPHTHALMOSCOPIC APPEARANCES DURING OCAR

The classical description of this by von Graefe¹ 120 years ago, and numerous other clinical reports, are essentially based on anecdotal observations, because it is very rarely that a patient comes to an ophthalmologist within an hour or two of the occlusion. There has been no systematic evaluation of the ophthalmoscopic appearances at different time intervals after the onset of angiographically confirmed OCAR in primates or man. The present study provides such information (see above) for transient retinal ischaemia up to 4½ hours, and our previous study²⁷⁻²⁸ on longer or permanent OCAR. One remarkable fact emerges from these 2 studies: *in spite of angiographically proved complete occlusion of the CAR, it was not at all uncommon to find on ophthalmoscopy normal-looking retinal vessels*, misleading an observer to believe that the retinal arteries had a normal or almost normal blood flow. This is a serious drawback in some of the observations reported in the preangiography era. *Normal-looking retinal vessels do not rule out a complete OCAR.* This study for the first time also provides us information on the resolution pattern of retinal ischaemic changes on restoration of retinal circulation.

The cherry red spot, which is pathognomonic of OCAR (Fig. 6a) is due to the normal red colour of the retinal pigment epithelium (which is mostly responsible for the normal colour of the fundus) seen through the normal avascular zone of the fovea (not supplied by retinal circulation), which is not involved by the retinal ischaemia and consequently the retinal opacity, while the surrounding opaque retina masks the normal red colour of the fundus background.

The peripheral fundus (around the posterior retina) looks normal in OCAR. In this peripheral part the retina is thin, with a thin nerve fibre layer and sparse ganglion cells, so that choroidal blood supply is probably sufficient to maintain the structural integrity of the retina.

Retinal pigment epithelial degeneration of the posterior retina was seen in all eyes with ischaemic retinal atrophy in spite of normal choroidal circulation, usually developing gradually 3 weeks after a prolonged OCAR in this study and in our previous experimental studies^{27 28} and also seen clinically with similar lesions. The exact mechanism of the pigmentary degeneration is not known. Possibly, ischaemic destruction of the Müller cells has some role to play in this.

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Watson³⁴ very well reflected the prevailing view that if there is even a minimal retinal circulation after OCAR it is possible to obtain a considerable recovery in these eyes. The present studies clearly showed that the existence of any small residual retinal circulation after OCAR does not seem to protect the retina, presumably because of its very low oxygen tension. *The duration of the retinal ischaemia was almost always the principal determining factor in the production of irreversible retinal damage, i.e., the longer the ischaemia the more marked the retinal damage.* An occasional eye, however, showed variation from this pattern and represented a normal biological variation in response.

WHAT DOES REDNESS OF A NORMAL OPTIC DISC REPRESENT?

The present study provides important information on the subject. During OCAR the optic disc was almost always pale. The main source of blood supply to the disc is by the PCA circulation, with the retinal arteries supplying only the surface nerve fibre layer of the disc.^{25 29} In these eyes with OCAR angiography showed perfectly normal PCA circulation and normal filling of the prelaminar part of the disc (Fig. 1a, 2a), and yet the disc was pale. Also in our recent experiments with rhesus monkeys a few minutes after all the PCAs were cut (but the CAR left intact) the optic disc remained perfectly normal in colour in the majority. A few showed some pallor, mostly of the temporal region, because of the PCA contribution to the surface nerve fibre layer capillaries in that region.^{25 29} It appears, then, that *the normal redness of the disc is essentially due to the filling of the capillaries in the surface layer of the disc and not due to its deeper vessels.* This further confirms our previous observations that in a normal optic disc redness of the disc is not a true guide to its vascularity.^{25 35}

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