CLINICAL STUDY

A prospective evaluation of the Heidelberg retina flowmeter in diagnosing ischaemia following branch retinal vein occlusion: a masked, controlled comparison with fluorescein angiography

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Abstract

Purpose **To evaluate the use of the Heidelberg retina flowmeter (HRF) in diagnosing retinal ischaemia following macular branch retinal vein occlusion.**

Methods **Ten patients with ischaemic macular branch retinal vein occlusion, as determined by strict fluorescein angiographic criteria, were examined with the HRF. Blood flow, blood volume and blood velocity characteristics from areas of ischaemic and non-ischaemic retina were recorded and the results between the normal and ischaemic areas of retina compared with paired *t*-test analysis. Ten healthy volunteers were similarly examined and acted as a control group.**

Results **Compared with normal retina the HRF recorded a statistically significant reduction in blood flow within the ischaemic retina in 7 of the 10 study patients. In 2 patients the HRF actually recorded a statistically significant increase in blood flow in the area of ischaemic retina; there was no significant difference in the blood flow recorded in the normal and ischaemic retina in the remaining patient. HRF examination of the control group revealed a significant difference in the blood flow between two areas of apparently normal retina in 3 of the 10 volunteers.**

Conclusion **The HRF is not a reliable tool for diagnosing retinal ischaemia following branch retinal vein occlusion. Our results may suggest that the HRF blood flow recordings are not derived from the retinal circulation alone, but represent the cumulative blood flow through the combined circulations of the retina and choriocapillaris.**

Key words Branch retinal vein occlusion, Heidelberg retina flowmeter, Retinal ischaemia

Doppler flowmetry is a reliable and well-established technique for measuring blood flow within vascularised tissues.[1] The technology of Doppler flowmetry has now been successfully incorporated into the confocal scanning laser ophthalmoscope and the development of these confocal scanning laser Doppler flowmetry (cSLDF) systems has, for the first time, facilitated the direct measurement of blood flow within the vascularised tissues of the eye. Such systems are now used routinely to investigate the haemodynamic properties of the optic nerve head and peripapillary retina in glaucoma,[2,3] but the potential applications of this technology for investigating the choroidal[4,5] and retinal[6,7] circulations are only now being explored.

We wished to investigate the potential value of one such system, the Heidelberg retina flowmeter (HRF), as a diagnostic tool in the evaluation of retinal ischaemia after macular branch retinal vein occlusion. We report the findings of a controlled, prospective study in which we compared the haemodynamic properties of the ischaemic and non-ischaemic retina in patients with ischaemic macular branch retinal vein occlusions.

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Table 1. *Demographic details of the 10 patients with macular branch retinal vein occlusion analysed in this study*

Patient no.	Age (years)	Sex	Visual acuity at entry into study
1	76	M	6/36
2	79	F	6/24
3	72	M	6/24
4	63	F	2/60
5	69	M	3/60
6	72	M	6/36
7	65	F	6/36
8	86	F	6/24
9	46	M	6/36
10	70	F	6/60

Patients and methods

Ethics approval was obtained before commencement of this study. Twenty subjects were included in the final data analysis: 10 patients with ischaemic macular branch retinal vein occlusions (BRVO) and 10 volunteers with normal fundi.

Patient recruitment

All patients who presented acutely with macular BRVO were recruited. Patients with a visual acuity of less than 6/9 in their fellow eye were excluded as it was felt that they would not be able to cooperate with the cSLDF examination. Patients with diabetes or any other recognisable retinal vaso-occlusive disease were also excluded from the study. All patients were first examined with cSLDF and only if they had been compliant with this investigation was a fluorescein angiogram performed. The fluorescein angiogram was then reviewed and the patient was only included in the final data analysis if the angiogram demonstrated all the following features of macular ischaemia: (1) confluent capillary non-perfusion greater than or equal to 5 disc areas extending from the horizontal raphe to the macular arcades, (2) staining of the walls of the larger retinal vessels, (3) loss of the foveal arcade in the affected retina. Ten normal volunteers were also recruited to act as a control group. The demographic details and visual acuity on presentation of the patients with macular BRVO are detailed in Table 1.

Data acquisition

All patients were first scanned with the Heidelberg retina tomograph (HRT). The HRT is a confocal scanning system which can produce a reproducible cross-sectional topographic map of the macula.[8] This system was used to establish the position of the internal limiting membrane and this landmark was then used as the reference plane for HRF examination. Once the reference plane of the retina under investigation had been established the central macula was scanned with the HRF; two identical images of the central macula centred on the fovea were obtained from all patients. The imaging sequence was conducted by an ophthalmic photographer who was trained in the use of the scanning laser ophthalmoscope. Once an image of appropriate quality had been obtained it was stored digitally for subsequent analysis.

The technical details of the HRF have been described previously.[6] The HRF analyses a total area of retina $2560 \times 640\ \mu m^2$ and for the purposes of data analysis this rectangular area of retina is divided into a grid comprising 64 horizontal lines each containing 256 sampling points. When acceptable alignment, focus and brightness have been achieved the operator initiates a process that, within 2.048 s, scans each of the 64 lines 128 times (each point on this grid is therefore sampled 128 times). The measurement of blood flow, velocity and volume by scanning laser Doppler flowmetry (SLDF) is based on the optical Doppler effect (laser light scattered by a moving particle is shifted in frequency by an amount proportional to the velocity of the moving particle). The principles utilised in the HRF have already been described in detail.[9] SLDF uses the ability of a laser scanning ophthalmoscope to measure the backscattered light at different locations in the tissue of interest in a short period of time. For a single picture line one sample from each point of the line is taken and this measurement is repeated several times for the same point with a high repetition rate. The backscattered intensities for each point scanned can therefore be obtained as a function of time (intensity–time curve). After the scan is complete the operator initiates a fast Fourier transform to extract the individual frequency components of the reflected light. A spectrum analysis from the data of each location is then performed and the power spectrum of the Doppler shift of each retinal point is calculated. On the x-axis of the spectrum, each frequency location represents a blood velocity and the height of the spectrum at that frequency represents the number of blood cells required to produce that intensity. Integrating the spctrum yields total blood flow. (Blood 'flow' therefore describes the distance travelled by all moving cells inside the sample volume per unit time.) Once this analysis has been completed the HRF displays a pictorial representation of blood flow in the form of a perfusion map. Blood flow, blood velocity and blood volume can be calculated for selected areas of retina by placing a cursor of variable size onto this perfusion map. A 10×10 pixel box was used for all haemodynamic analysis in this study.

Image analysis

Prior to image analysis the appropriate fluorescein angiogram was examined and the area of retinal ischaemia marked out on the perfusion map. An identical area was also marked out in the area of the unaffected, normal retina. Analysis of the perfusion map was performed by an observer (D.E.) who was unaware of the angiographic features of the retina he was asked to process.

Table 2. *Data obtained after examination of the central macula with the Heidelberg retina flowmeter (mean value of the parameter listed is shown)*

Case	Pathology	Blood flow			Blood volume			Blood velocity		
		Inferior	Superior	p value	Inferior	Superior	p value	Inferior	Superior	p value
1	Ischaemic inferior	139	226	***<0.001***	9.51	12.52	***0.01***	0.52	0.84	***0.01***
2	Ischaemic inferior	288	300	0.13	9.47	11.26	0.23	0.98	1.19	0.13
3	Ischaemic inferior	174	204	***0.02***	12.58	12.35	0.15	0.64	0.77	***0.01***
4	Ischaemic inferior	234	292	***<0.001***	11.34	12.70	0.27	0.87	1.08	0.13
5	Ischaemic inferior	123	274	***<0.001***	7.49	11.75	***0.01***	0.47	1.02	***<0.001***
6	Ischaemic superior	222	196	***<0.001***	8.94	9.60	0.16	0.84	0.74	0.14
7	Ischaemic superior	164	237	**<0.001**	8.34	11.25	**<0.001**	0.64	0.89	0.01
8	Ischaemic superior	200	246	**0.04**	10.14	13.45	0.07	0.79	0.86	0.10
9	Ischaemic superior	183	157	***<0.001***	10.34	11.00	0.50	0.69	0.66	0.70
10	Ischaemic superior	274	215	***<0.001***	13.40	12.31	0.33	1.01	0.76	***0.01***
11	Normal	256	275	0.60	9.54	9.75	0.80	0.96	1.03	0.42
12	Normal	478	325	**0.03**	29.33	19.40	**0.01**	1.67	1.15	**0.03**
13	Normal	355	371	0.80	24.14	24.25	0.96	1.26	1.34	0.76
14	Normal	257	321	0.33	17.10	18.01	0.68	0.94	1.19	0.30
15	Normal	408	374	0.67	19.51	16.17	0.16	1.48	1.40	0.37
16	Normal	380	440	0.35	16.67	19.46	0.16	1.40	1.60	0.37
17	Normal	342	259	0.10	18.98	16.71	0.25	1.24	0.95	0.10
18	Normal	444	400	0.50	21.55	17.32	0.05	1.60	1.43	0.43
19	Normal	369	245	**0.03**	19.92	14.98	**0.01**	1.34	0.90	**0.03**
20	Normal	243	197	**0.01**	14.97	11.80	**<0.001**	0.89	0.73	**0.04**

p values shown in ***bold italic*** represent those patients in whom a reduction in blood flow, blood velocity or blood volume was found in the area of retina deemed ischaemic using the fluorescein appearances.
p values shown in **bold** represent those patients in whom a reduction in blood flow, blood velocity or blood volume was found in an area of retina which was not deemed ischaemic using the fluorescein appearances.

Each perfusion map was analysed by way of a superimposed grid which was centred on the fovea. The grid therefore straddled both normal and ischaemic retina. The grid itself comprised 24 points (2 horizontal lines, each of 12 points) and each point on the grid was vertically aligned with a corresponding point on the fellow line. If a retinal vessel was found to lie underneath one of the points to be tested both it and its corresponding point were moved horizontally, so ensuring that only the retinal capillary bed was analysed. At each point on the grid the retina was analysed using the 10×10 pixel box and the three parameters – blood volume, blood flow and blood velocity – were recorded.

To reduce errors that may have been caused by variations in the haemodynamic properties of the retinal capillary bed during the cardiac cycle the vertical distance (measured in pixels) between the two lines of points was synchronised with the cardiac cycle. The vertical distance between the top and bottom horizontal lines of the grid was therefore determined by the patient's heart rate at the time of HRF examination. The scan takes approximately 2.05 s to cover a vertical distance of 64 pixels and the vertical distance (measured in pixels) between the two horizontal lines of points on the grid is therefore determined by the equation:

$$\text{Vertical distance (in pixels)} = \frac{64 \times \text{Heart rate (beats per minute)}}{2.05 \times 60}$$

This exercise ensured that our analysis was restricted to two areas of retinal capillary bed (one normal, one ischaemic) that were in the same phase of the cardiac cycle.

Data analysis

Six data sets were obtained from each individual examined in this study: two for each of the three parameters measured (blood volume, blood velocity and blood flow). One data set for each of these parameters was derived from those grid points that were located within the ischaemic retina; the other data set was derived from those grid points that were located within the unaffected 'normal' retina. In the case of the normal controls the data sets simply refer to normal areas of retina above and below the fovea. The haemodynamic properties of the two areas of retina were analysed by comparing the data set obtained from those points within the retina affected by the vein occlusion with the data set obtained from those points within the retina which was unaffected by the vein occlusion. Comparisons between the data sets derived from the affected and unaffected retina were made for each of the three parameters using two-tailed, paired t-tests, with $p < 0.05$ regarded as significant.

Power calculation

The purpose of the power calculation was to estimate the number of points we should sample in the affected and unaffected retina of the same individual to be reasonably certain of detecting a predetermined drop in blood flow in that part of the retina affected by the vein occlusion.

At the time the study was designed there was little published data regarding the measurement of macular blood flow using cSLDF. Before commencing this study we therefore had to assess the variability of blood flow readings (as recorded by the HRF) in the retinal capillary bed of healthy volunteers. A pilot study of 12 healthy

volunteers revealed that the perifoveal blood flow ranged from 310 units to 420 units, with a standard deviation within individual patients of 60 units. Having established the variability of blood flow in healthy volunteers we then had to arbitrarily define the degree of capillary hypoperfusion we wanted the HRF to detect. For the purposes of this study we arbitrarily defined ischaemia as a reduction in blood flow of 30% compared with that recorded in the unaffected (and thus normal) half of the macular capillary bed in that same eye. From these data we estimated that we would need to analyse 24 points (12 in the affected half of the macular capillary bed and 12 in the unaffected half) to detect a 30% reduction in blood flow using cSLDF with a power of 95%.

Results

Analysis of the blood flow data gathered from the retinal capillary bed in the affected and unaffected retina revealed that the HRF recorded a significant difference in blood flow between the two halves of the retinal capillary bed in 9 of the 10 patients in the BRVO group (Table 2). Compared with normal retina, the HRF recorded a statistically significant reduction in blood flow within the ischaemic retina (as judged by fluorescein angiogram) in 7 of the 10 patients with macular BRVO. The converse (increased blood flow in the ischaemic compared with normal retina) was observed in 2 patients; there was no significant difference in blood flow across the ischaemic and normal areas of retina in the remaining patient. The outcome data from the HRF examination specifically relating to blood flow are summarised in Table 3. Analysis of the blood volume data revealed that the HRF recorded a significant difference between the affected and unaffected retina in 3 patients, but again in only 2 of the 3 did the differences coincide with the fluorescein appearances. Analysis of the blood velocity data revealed similar findings.

Analysis of the data obtained from the control group revealed that the HRF recorded significant differences between the blood flow in the superior and inferior halves of an apparently normal macular capillary bed in 3 of the 10 individuals examined. It also recorded significant differences in blood volume (3 of 10 individuals) and blood velocity (2 of 10 individuals) across these two adjacent areas of normal retinal capillary bed.

Discussion

Retinal blood flow in any one eye may be influenced by a multitude of local and systemic factors and there are therefore difficulties in comparing the blood flow readings obtained from one individual with another. We chose instead to examine the effectiveness of the HRF by comparing how well it predicted 'ischaemia' in any one individual who was known to have an ischaemic macular branch vein occlusion. We hypothesised that if the systemic influences on the retinal circulation could be controlled, any differences in the HRF analysis of the normal and ischaemic retina would be due to local influences resulting from the vein occlusion. We attempted to eliminate the systemic influences on retinal capillary blood flow by two measures: firstly by comparing identical territories of normal and ischaemic retinal capillary bed in the same patient and secondly by ensuring that we only compared areas of retina during the same phase of the cardiac cycle. The latter was a necessary precaution as it has been reported that retinal capillary blood flow (as measured by the HRF) may vary by as much as 30–50% during the cardiac cycle.[7] An estimate of how useful a diagnostic tool the HRF was for detecting ischaemia could then be derived by determining the number of patients who had the area of abnormal retina correctly predicted by the HRF. We further controlled the study by conducting an identical examination in a group of volunteers with normal fundi. As there should be no gross local differences in blood flow across the two areas of capillary bed examined, any difference found by HRF examination would have to be explained by factors beyond the retinal capillary bed itself.

Table 3. *Summary of the blood flow outcome data in all 20 subjects*

Outcome of examination with the HRF	No. of subjects ($n = 20$)
Ischaemic retina correctly identified	7
Normal retina correctly identified	7
Erroneous result from HRF examination	6

A review of the mathematical methods of how the HRF derives the parameters blood flow, blood velocity and blood volume reveals that all three are dependent upon one measured parameter, namely the frequency shift in laser light that occurs after being scattered by a particle (in this case a red blood cell) moving at a particular velocity.[9] The parameters blood flow, blood velocity and blood volume are therefore dependent variables. As the effective Doppler shift of the scattered laser light is most accurately represented by the equation from which blood flow is developed, we shall concentrate on this variable alone for the remainder of this discussion.

Our results indicate that the HRF cannot be relied upon to give an accurate description of retinal blood flow. We found that the HRF not only failed to predict all the hypoperfusion abnormalities we expected, but in two cases of angiographic ischaemia it found that blood flow was significantly lower in the normal half of the retinal capillary bed. Overall the HRF recorded an erroneous finding in 6 of 20 patients studied (blood flow data), as the HRF also recorded a significant difference in blood flow in 3 of the healthy volunteers where none was expected.

We made two key assumptions whilst designing this study that will influence the interpretation of our data. The first is that we defined ischaemia on the basis of the findings of the fluorescein angiogram. Crucially fluorescein angiography produces a morphological

description of the retinal capillary bed and this does not necessarily correspond to physiological function. Nevertheless fluorescein angiography remains the gold standard for investigating the retinal capillary bed and the criteria we chose for labelling a branch retinal vein occlusion as 'ischaemic' are those which most clinicians would regard as indicative of ischaemia.[10] The second important assumption we made was that an 'ischaemic vein occlusion' is associated with impaired blood flow within the retinal capillary bed. This assumption is open to debate because as yet our knowledge of retinal capillary bed function is based upon anatomical fluorescein angiographic studies. Evidence that these fluorescein angiographic findings are associated with hypoperfusion of the retinal capillary bed is, however, slowly emerging. It has been reported that blood flow in both the branch retinal arteries[11,12] and veins[13] are reduced compared with that in the fellow eye after ischaemic retinal vein occlusions. These data support our assumption that, after retinal vein occlusion, the capillary bed lying between these two sets of larger vessels may also be hypoperfused.

Our study produced a number of unexpected results in both the BRVO and control groups which require explanation. Considering the BRVO group alone, even if we assume that the capillary bed after an 'ischaemic' retinal vein occlusion is not necessarily hypoperfused this only accounts for one of the false results in the BRVO group, this being case 2 in Table 2. In the remaining 'false positives' (cases 7 and 8) the HRF indicated that the ischaemic retina was actually hyperperfused in comparison with the retina which had not been affected by the vein occlusion, and physiologically this is difficult to explain. One possible explanation may be that it reflects the development of shunt vessels within the microcirculation of the territory affected by the vein occlusion; however, it seems unlikely that we consistently happened to examine an area of retina that contained a shunt vessel rather than a shut-down capillary bed. Another possibility is that metabolic autoregulatory mechanisms may have skewed the findings, as both hypoxia and hypercapnia can exert profound influences on the retinal precapillary arterioles.[14,15] Whilst the shunt and autoregulatory hypotheses may offer a theoretical explanation for the anomalous results in the BRVO group, neither explains why a third of our control group were found to have a significant difference in blood flow across what was a normal retinal capillary bed. Histological studies of the macula's retinal vasculature reveal that the capillary beds immediately above and below the fovea are identical;[16] the results from our control group therefore suggest that the explanation for our findings may lie beyond the retinal capillary bed.

The claim that the perfusion map generated by the HRF is derived solely from the retina is based on two assumptions: firstly that the analysis is limited to a tissue depth of 300 μm and secondly that the wavelength of the laser light used (670 nm) cannot penetrate the retinal pigment epithelium (RPE).[9] It is argued that if the laser cannot penetrate the RPE then the backscatter Doppler effect can only be generated by the movement of blood cells within the retinal capillary bed alone, with no contribution from the choriocapillary meshwork. The assertion that cSLDF systems such as the HRF record blood flow from the retinal capillary bed alone is now being questioned.[17,18] The belief that laser light of wavelength of 670 nm cannot penetrate the RPE is incorrect and recently Gunwald *et al.*[19] have actually used a 670 nm diode laser system to measure the choroidal circulation at the fovea. The fovea was chosen as the neurosensory retina is avascular at this point and thus any measurements recorded must have been derived from the choroidal circulation alone. Moreover, the HRF system that is available commercially employs an infrared laser of 795 nm[20] and this can penetrate the RPE. Technically it is therefore possible that the perfusion map generated by the HRF may not be derived from the retinal circulation alone and may, after all, be derived from the combined circulations of the retina and choriocapillaris. If this is the case then it is almost certain to influence our results as it has been estimated that the relative vascularity of the retina and choriocapillaris at the macula is in the order of 1:10.[21] If the HRF is recording a block of tissue which includes both retina and choriocapillaris it is possible that any differences in the blood flow between the two halves of an ischaemic and non-ischaemic retinal capillary bed are simply too subtle for the HRF to detect with accuracy. One other consideration is that the choroidal circulation is not visible on the perfusion map generated by the HRF. There is a high probability, therefore, that at least one of the points we analysed may have inadvertently coincided with an underlying choroidal vessel. Whilst it is difficult to predict what influence this may have on our results, it is possible that it would further distort the blood flow readings generated by the HRF, making analysis between different parts of the perfusion scan invalid. This latter factor may explain why there was a significant difference in blood flow between two areas of apparently normal retina in 3 of the control group.

In summary, our results suggests that the Heidelberg retina flowmeter cannot be relied upon to give an accurate description of retinal capillary blood flow. Our findings add weight to the hypothesis that the existing generation of confocal scanning laser Doppler flowmetry systems scan deeper than has been assumed and may actually analyse both the retinal and choroidal capillary beds. Indocyanine green (ICG) imaging allows an accurate description of the choroidal vascular bed to be obtained and further studies comparing the results obtained from confocal scanning laser Doppler flowmetry systems with ICG may help answer this question.

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