

# PULSATILE OCULAR BLOOD FLOW IN EYES WITH UNTREATED CHOROIDAL MELANOMA

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## SUMMARY

**Purpose:** To investigate the effect of choroidal melanoma on pulsatile ocular blood flow (POBF).

**Methods:** Seventeen patients (10 men and 7 women) with unilateral untreated choroidal melanoma and 22 controls matched for age and sex were studied. Intraocular pressure (IOP), pulse amplitude (PA) and POBF were measured using the OBF Tonograph. In each patient, mean inter-ocular differences were analysed using the paired *t*-test. The correlation coefficient between tumour thickness and POBF was calculated. To assess the variation of this parameter, the coefficient of variation for three repeated readings was determined for healthy and affected eyes.

**Results:** In the control group, there was no significant difference between eyes in any parameter. In patients with melanoma, there was no significant difference in IOP and PA between affected and unaffected eyes. Mean POBF was significantly higher in affected eyes ( $1040 \mu\text{l min}^{-1}$ ) than unaffected eyes ( $876 \mu\text{l min}^{-1}$ ) ( $p = 0.003$ ). There was no correlation between tumour thickness and absolute POBF ( $r = -0.24$ ) or between tumour thickness and inter-ocular difference in POBF between affected and unaffected eyes ( $r = -0.17$ ). Mean coefficient of variation of three repeated readings of POBF was 7.76% in healthy eyes and 8.97% in affected eyes.

**Conclusions:** These findings suggest a high tumour blood flow or a global increase in choroidal blood flow in the presence of melanoma. POBF measurement may be useful in the clinical assessment of eyes with choroidal melanoma.

Measurements of tumour circulation may allow prediction of tumour responsiveness to chemotherapy or immunotherapy and may also be of prognostic value with respect to metastatic disease.<sup>1,2</sup> Histolo-

gical studies have shown a correlation between tumour vascularity and metastatic disease.<sup>3,4</sup>

Although qualitative data can be obtained on the tumour vascularity with techniques such as A- and B-mode ultrasonography, fluorescein angiography and indocyanine green angiography,<sup>5-8</sup> an accurate and non-invasive method of measuring circulation in a uveal melanoma may provide a valuable means of assessing tumour activity. Duplex ultrasound with colour Doppler imaging (CDI) has been used in several studies to quantify blood flow in choroidal melanoma.<sup>9,10</sup> In this method, the magnitude of pulsatile flow is expressed in terms of frequency shifts rather than velocity, as the angle between the ultrasound beam and the blood vessels imaged cannot be determined accurately.<sup>11</sup> As measurements are taken from a small sample area it is uncertain whether such measurements are representative and whether repeated measurements over time from different areas of a tumour can be reliably compared.<sup>11,12</sup>

Pulsatile ocular blood flow (POBF) estimation by tonography using the OBF system was first developed by Langham *et al.*<sup>13,14</sup> With this method, the ocular pulse is recorded and analysed mathematically to derive values of POBF in  $\mu\text{l min}^{-1}$ . Briefly, its principle is based on converting the pressure curve recorded to a volume curve from known values of pressure/volume relationships of the human globe. The slope of the volume curve, obtained by mathematical differentiation, describes the net flow rate with time. The POBF is then determined from the net flow curve.<sup>15-17</sup>

The aim of this study was to determine whether uveal melanomas cause a measurable change in POBF.

## METHOD

Seventeen patients (10 men and 7 women) with newly diagnosed unilateral choroidal melanoma and 22 age-matched controls (13 men and 9 women) were

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selected. All patients gave informed consent to participate in the study, which was approved by the Royal Liverpool University Hospital's Ethics Committee. All patients and control subjects received a full ophthalmic and systemic assessment. Patients with other ocular pathologies, and a history of diabetes or cardiovascular disease, were excluded.

Tumour thickness was measured with a B scan and axial eye length with an A scan. As POBF values can vary with axial length,<sup>18</sup> control subjects with asymmetrical (>3 mm) axial lengths were also excluded. POBF was measured using the OBF Tonograph (ver10.0, OBF Labs UK, Cleverton, Wiltshire, UK), which is based on the original Langham OBF system. It consists of a floating tip pneumotonometer, which ensures a constant appraising force for recording the ocular pulse, and a tonograph unit linked to a computer for automatic selection and analysis of consecutive pulses to derive measurements of the various ocular pulse characteristics, including pulse amplitude (PA) and POBF. POBF determined in this way reflects only the pulsatile component of blood flow to all the intra-ocular structures and does not specifically distinguish the component distributed to the tumour. However, it is non-invasive, easy to measure and is also free from observer error as pulse selection and analysis are computerised and based on consistent criteria.

Following instillation of oxybuprocaine 0.4% and fluorescein drops, intraocular pressures were measured using Goldmann applanation tonometry before commencement of tonography. Tonographic measurements were taken with the patient rested and seated at a slit lamp using the same OBF Tonograph throughout by a single examiner (Y.C.Y.), who was masked to the laterality of the affected eye. Tonography was repeated three times in each eye, with the first eye chosen at random and alternating between eyes in quick succession to eliminate the effects of first exposure and any variation in ocular blood flow caused by physiological cardiovascular changes.<sup>19,20</sup> To counter any effects of diurnal variation,<sup>21</sup> all tonographic measurements were taken in mid-afternoon.

Mean values of PA in mmHg and POBF in  $\mu\text{l min}^{-1}$  were calculated for each subject. The correlation coefficients of tumour thickness with both absolute mean POBF and the difference in mean POBF were calculated. To assess the repeatability of POBF measurements, the coefficients of variation (CV) of three successive measurements in affected and unaffected eyes were calculated. The paired *t*-test was used for statistical hypothesis testing.

## RESULTS

The mean age of patients with choroidal melanoma was 55 years (SD 10.9 years). The tumour affected the right eye in 6 patients and the left eye in 11. All tumours were melanotic and had not broken through Bruch's membrane and the retinal pigment epithelium. The tumour thicknesses ranged from 1.92 mm to 8.51 mm (mean 4.7 mm).

In the control group there was no significant inter-ocular difference in any of the parameters. Patients with choroidal melanoma had a significantly higher POBF in affected eyes ( $p = 0.003$ ) but no difference in IOP or PA between eyes (Table I).

Mean coefficient of variation of three readings was 7.76% in unaffected eyes and 8.97% in affected eyes. This difference was not statistically significant ( $p = 0.33$ ). No correlation was found between tumour thickness and absolute POBF ( $r = -0.24$ ) or between tumour thickness and inter-ocular difference in POBF between affected and unaffected eyes ( $r = -0.17$ ).

## DISCUSSION

In the healthy eye, over 90% of ocular blood flow is distributed to the choroid.<sup>22,23</sup> The physiological ocular pulse which results from the pulsatile nature of blood flow in intra-ocular vessels has been shown to arise from the choroidal vessels.<sup>24</sup> POBF values which are derived from recordings of the ocular pulse therefore reflect the pulsatile component of blood flow in the choroid.<sup>13</sup>

In this study, we succeeded in our aim of determining whether choroidal melanomas cause a

**Table I.** Summary of results for the melanoma group and the control group

Parameter	Affected eye/right eye <sup>a</sup> (SD)	Unaffected eye/left eye <sup>a</sup> (SD)	<i>p</i> value
<i>Melanoma group (n = 17)</i>			
Mean IOP (mmHg)	15.05 (2.29)	15.89 (2.11)	0.12
Mean PA (mmHg)	2.48 (0.76)	2.33 (0.74)	0.21
Mean POBF ( $\mu\text{l min}^{-1}$ )	1040.81 (366.58)	876.37 (296.71)	0.003
Mean axial length (mm)	22.13	22.28	0.31
<i>Control group (n = 22)</i>			
Mean IOP (mmHg)	15.2	15.5	0.72
Mean PA (mmHg)	2.63 (1.00)	2.70 (0.70)	0.60
Mean POBF ( $\mu\text{l min}^{-1}$ )	816.73 (238.98)	825.45 (181.06)	0.81

IOP, intraocular pressure; PA, pulse amplitude; POBF, pulsatile ocular blood flow.

<sup>a</sup>In the melanoma group the affected eye was compared with the unaffected eye; in the control group the right eye was compared with the left eye.

measurable change in POBF. The higher POBF values observed in eyes with choroidal melanoma indicate that the pulsatile component of choroidal blood flow was increased. Assuming that the blood flow in the healthy choroid remained unaltered, this finding implies that the increase in choroidal blood flow is due to the tumour circulation. It is well established from theoretical analysis and histological morphometric studies on malignant melanomas that an increase in vascularity within a tumour is associated with increased vascular space, blood volume and flow.<sup>1</sup> In cutaneous melanoma, clinical measurements of blood flow using colour Doppler imaging have been found to correspond to vascular morphology on histological studies.<sup>25</sup> In uveal melanoma using colour Doppler imaging, Lieb *et al.*<sup>9</sup> and Wolff-Kormann *et al.*<sup>10</sup> both found increased blood flow parameters in untreated tumours and reduced blood flow in irradiated tumours. In one patient with a treated tumour, Wolff-Kormann reported a recurrence of high blood flow parameters coinciding with tumour recurrence detectable clinically. These findings and those of our study further support a role for ocular blood flow measurement in the assessment of choroidal melanoma.

Although follow-up measurements were not performed in this study we were able to calculate the coefficient of variation of POBF readings repeated in quick succession as an index of reproducibility. The mean coefficient of variation of three repeated readings was below 9% (2.3–18%), which is clinically acceptable. Bosem *et al.*<sup>26</sup> also reported a low coefficient of variation of repeated POBF readings (CV 7.5%) in eyes with glaucoma. There was, however, a wide inter-individual variation in the POBF in eyes with melanomas (SD 366.58), such that there was a considerable overlap of POBF values between the affected eyes and controls. This is due to the inherent inter-individual variability of this parameter, which is also present in healthy eyes.<sup>27</sup> This emphasises the importance of demonstrating an inter-ocular difference in POBF or changes in POBF over time within an individual's eye when comparing POBF values. Although the mean POBF value in eyes with melanoma is higher than that found in other studies in eyes with other conditions,<sup>28–31</sup> a direct comparison of POBF measurements made in small groups of patients with different diseases should be avoided due to the high inter-individual variation of this parameter.

In this study, no correlation was found between tumour thickness and the absolute POBF or the magnitude of the POBF rise in affected eyes. As the whole tumour circulation contributes to the POBF, it would be more appropriate to correlate tumour volume with POBF. However, due to the irregularity

of the tumour shapes, their volumes could not be accurately determined from our recordings of maximal basal dimensions and thicknesses alone. Wolff-Kormann *et al.*<sup>10</sup> also reported no correlation between tumour blood flow and thickness with colour Doppler imaging, but in contrast Srivastava *et al.*<sup>32</sup> found unrecordable blood flow in thin cutaneous melanomas but higher blood flow in thicker tumours and postulated a relationship between tumour thickness and blood flow.

As the ocular pulse is a pressure pulse due to an afferent bolus of blood to the eye, the pulse amplitude is greater when the globe is less distensible or when the perfusion pressure is increased. The latter is apparent following carotid endarterectomy, which causes an increase in pulse amplitude and POBF by an increase in the perfusion pressure.<sup>33</sup> Although carotid studies were not performed, the inter-ocular difference in POBF found in the melanoma patients is unlikely to be due to carotid disease as none of the patients had a history of cardiovascular disease or symptoms and signs of carotid occlusion. When ocular rigidity is reduced and the globe is more distensible, the pulse amplitude is reduced as the pressure pulse is converted to a volume pulse. This is seen in high myopia, corneal thinning, staphyloma<sup>34</sup> and after trabeculectomy.<sup>35</sup> In such situations when the ocular rigidity has been significantly altered by a pathological process or surgical procedure, POBF measurements are actually invalid as the volume/pressure relationship values for normal globes used in the derivation of POBF are no longer applicable.<sup>36</sup> The absence of a significant inter-ocular difference in pulse amplitude between affected and unaffected eyes suggests that the ocular rigidity in these patients was not affected by the tumour.

To the best of our knowledge, this is the first study to investigate POBF in choroidal melanoma. Although POBF has been found to be reduced in certain conditions including glaucoma, cataract and diabetic retinopathy,<sup>28–31</sup> the significance of such findings is uncertain. Fundamental studies to validate the theoretically derived POBF values and clinical studies to determine reference ranges and variation in health and diseases are required before any meaningful interpretation of this parameter can be made.

In conclusion, this study provides further evidence that tumour blood flow can be quantified indirectly by a non-invasive technique. As it is not possible to verify these techniques with direct, invasive methods, such data must, at present, be interpreted with caution. It is essential at this stage to evaluate not only the applicability of new techniques but also the validity and repeatability of their measurements. With regard to these considerations the measure-

ment of global pulsatile blood flow changes using the OBF Tonograph may prove to be of value in the assessment of eyes with choroidal melanoma.

Key words: Ocular, Blood flow, Pulsatile, Choroidal, Melanoma.

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