Glaucmodma patients demonstrate faulty autoregulation of ocular blood flow during posture change

David W Evans, Alon Harris, Melanie Garrett, Hak Sung Chung, Larry Kagemann

Abstract
Background/aims—Autoregulation of blood flow during posture change is important to ensure consistent organ circulation. The purpose of this study was to compare the change in retinal artery blood flow in glaucoma patients with normal subjects during supine and upright posture.

Methods—20 open angle glaucoma patients and 20 normal subjects, similar in age and sex distribution, were evaluated.

Results—When changing from the upright to supine posture, normal subjects demonstrated a significant increase in OA EDV (p = 0.016) and significant decrease in OA RI (p = 0.0006) and CRA RI (p = 0.016). Glaucma patients demonstrated similar changes in OA measures of EDV (p = 0.02) and RI (p = 0.04), but no change in CRA measures.

Conclusion—Glaucma patients exhibit faulty autoregulation of central retinal artery blood flow during posture change.

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Regulation of blood flow during posture change is important to maintain proper circulatory status in many organs. When in the upright posture, gravity pulls blood away from organs above the heart and towards organs below the heart. To ensure appropriate blood flow when changing from supine to upright posture, vessels below the heart constrict to block hyperaemia and oedema, while vessels above the heart dilate to offset falling perfusion pressure.

An abnormal change in blood flow during postural variation is an indication of vascular irregularity. For example, in the normal foot, postural variation is an indication of vascular dysfuction, however, exhibit wide variation in cerebral blood flow during posture change. In these patients middle cerebral artery blood velocity falls by more than 25% when changing from a supine to upright posture.

Numerous recent studies suggest that dysfunctional ocular circulation contributes to the pathogenesis of glaucoma. Few data are available concerning the autoregulatory response of ocular blood flow to posture change in glaucoma patients. Analysis of ocular blood flow during various body positions may provide insight into the circulatory irregularity of glaucoma patients. The purpose of this study was to measure and compare the ophthalmic and central artery haemodynamics in glaucoma patients and normal subjects in both the seated and supine positions.

Subjects and methods
Paid volunteers, comprising 20 glaucoma patients and 20 normal subjects, participated in this study. This study was approved by the Indiana University institutional review board and all participants reviewed and signed informed consent statements before entering the study. Subjects and patients were examined by members of the Indiana University Medical Center Department of Ophthalmology Glaucoma Service. Both groups were free of diabetes, cardiovascular or respiratory disease, and were taking no medications for systemic hypotension. All patients had glaucomatous type optic disc appearance and/or visual field defects. The patient’s cup/disc ratios were all greater than 0.6 and the loss in visual field sensitivity (as determined by mean defect) ranged from −5.0 to −20.0 dB. No limitation was placed on the minimum level of patient intraocular pressure for study inclusion. The control group was selected to be similar for age, sex distribution, blood pressure, and heart rate to the patient group (Table 1). Normal subjects had no history of ophthalmic disorders and results of an ophthalmic examination were normal. If a patient was on a regimen of ocular hypotensive therapy for glaucoma, he or she ceased taking medication 4 weeks before the start of the experiment.

Methods
This study was performed as part of a larger study in which participants were admitted to the General Clinic Research Center (GCRC) of the Indiana University Hospital for over-
Table 2 Results for glaucoma patients and normal subjects in sitting and supine positions (mean (SD))

<table>
<thead>
<tr>
<th></th>
<th>Glaucoma</th>
<th>Normal</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56 (12)</td>
<td>58 (11)</td>
<td>NS</td>
</tr>
<tr>
<td>Sex</td>
<td>13M/7F</td>
<td>10M/10F</td>
<td>NS</td>
</tr>
<tr>
<td>BP sys (mm Hg)</td>
<td>132 (20)</td>
<td>131 (21)</td>
<td>NS</td>
</tr>
<tr>
<td>BP dias (mm Hg)</td>
<td>76 (10)</td>
<td>76 (12)</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>76 (14)</td>
<td>74 (10)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 1 Age, sex distribution, heart rate, systolic blood pressure, and diastolic blood pressure (mean (SD)) for the glaucoma patients and normal subjects

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<td>Heart rate (beats/min)</td>
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<td>74 (10)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Statistically significantly different between sitting and supine position. #Statistically significant difference between glaucoma patients and normal subjects.

Table 2 Results for glaucoma patients and normal subjects in sitting and supine positions (mean (SD))

<table>
<thead>
<tr>
<th></th>
<th>Sit</th>
<th>Supine</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>76 (14)*</td>
<td>70 (11)*</td>
<td>0.0001*</td>
</tr>
<tr>
<td>BP sys</td>
<td>132 (20)</td>
<td>131 (21)</td>
<td>NS</td>
</tr>
<tr>
<td>BP dias</td>
<td>76 (10)*</td>
<td>73 (9)*</td>
<td>0.028*</td>
</tr>
<tr>
<td>IOP</td>
<td>18.4 (4)#</td>
<td>17.9 (3)#</td>
<td>0.0004#</td>
</tr>
</tbody>
</table>

Results

Glaucoma patients and normal subjects were similar for heart rate, systolic blood pressure, and diastolic blood pressure in both body position.
Glaucoma patients demonstrate faulty autoregulation of ocular blood flow during posture change

During posture change, both groups showed a significant change in heart rate (glaucoma p = 0.0001; normal p = 0.0001) and diastolic blood pressure (glaucoma p = 0.028; normal p = 0.002). Neither group demonstrated any change for systolic blood pressure or intraocular pressure (Table 2).

Glaucoma patients and normal subjects were similar for measures of retrobulbar haemodynamics while sitting. During supination, glaucoma patients displayed significantly lower central retinal artery (CRA) end diastolic velocity (EDV) (p = 0.013) than normal subjects. When changing from a seated to supine body position, both groups exhibited an increase in ophthalmic artery (OA) EDV (glaucoma p = 0.02; normal subjects p = 0.04) and a significant decrease in OA resistance index (RI) (glaucoma p = 0.04; normal subjects p = 0.0006) (Fig 1). Neither group showed a change in central retinal artery PSV or EDV, while only normal subjects showed a change in CRA RI (p = 0.016) (Fig 2).

Discussion

Glaucoma patients and normal subjects demonstrate similar changes in heart rate, IOP, diastolic blood pressure, and ophthalmic artery haemodynamics during posture change. The CRA RI response to posture variation is significantly different between groups; it falls significantly in normal subjects when changing from a seated to supine position, but shows no change in glaucoma patients.

Constant intraocular pressure during posture change is contrary to the findings of many previous studies (for review see Kothe10). Intraocular pressure has a well established circadian rhythm and is known to peak in the morning and fall during the day, reaching its lowest point in early evening before sleep.11 12 Whereas previous studies were conducted much earlier in the day, during a time period close to the IOP peak, our study was conducted between 6 and 7 pm, a time when IOP is known to be near its diurnal trough. The factors which control the circadian rhythm of IOP remain poorly understood. We speculate that the differences noted between the results of this study and previous studies may be related to factors that control IOP circadian rhythm. Further posture studies at different times of the day could potentially elucidate these differential diurnal IOP postural responses, if they exist.

Measures of CDI blood flow velocity and vascular resistance, as obtained in our study, cannot be used to quantitatively assess volumetric blood flow. Both vessel diameter and velocity are needed for this purpose. No technique is currently available to accurately and non-invasively measure retrobulbar vessel diameter. Nevertheless, data do indicate that changes in CDI velocity measures are highly predictive of changes in volumetric flow both in vitro13 14 and in vivo, in cerebral vessels.15

Further, considerable evidence points to a close correlation between higher resistance...
index and increased vascular resistance downstream from the point of CDI measurement. Consequently, our data suggest that distal vascular resistance falls in the ophthalmic artery of both normal subjects and glaucoma patients during supination. In the CRA, only normal subjects demonstrate such a change.

The internal carotid artery supplies the orbit and over 80% of the cerebrum. Anatomically, the ophthalmic artery exits the internal carotid artery behind the orbit and immediately bifurcates into the middle cerebral and anterior cerebral arteries. Data from the middle cerebral artery demonstrate a small non-significant change in blood flow velocity during posture change. This result is unlike our ophthalmic artery data, which demonstrate a significant increase in velocity during supination. It appears from these data that the major feeding vessel of the brain (that is, middle cerebral artery) is more tightly autoregulated than the major feeding vessel of the eye (that is, ophthalmic artery), even though these arteries are in very close anatomical proximity. Results from other studies support this conclusion. Data show that middle cerebral artery blood velocity remains constant as blood pressure rises during isometric exercise. On the contrary, ophthalmic artery blood velocity increases significantly during similar conditions. Further, mild hypercapnia induces significant elevation of middle cerebral artery blood flow velocity, while elevated end tidal carbon dioxide appears to have no effect on the ophthalmic artery blood flow. If the autoregulation of the ophthalmic artery is less stringent than that of cerebral vessels, then this suggests that the eye may be more susceptible to vascular insult than the brain during periods of circulatory stress.

The CRA directly feeds and is the only source of blood supply for the retinal arteries. These distal vessels nourish the retinal ganglion cells and the confluence of unmyelinated nerve fibres anterior to the lamina cribrosa. Glaucoma is a disease known to cause the death of retinal ganglion cells and erosion of the optic nerve head. Numerous studies indicate that glaucoma patients have altered retinal circulation. Extensive morphological studies describe endothelial proliferations in the retinal vessels of glaucoma patients. Further, widespread angiographic circulatory defects appear in the retinal vasculature of open angle glaucoma patients and these patients demonstrate significantly increased arteriovenous passage time. Such defects could potentially increase vascular resistance in the retinal vessels and, in turn, limit the autoregulatory response to posture change in retinobular vessels of these patients. Our data here, taken in conjunction with these previous studies, suggest that the failure to properly regulate CRA blood flow during posture change may be related to dysfunctional retinal circulation in glaucoma patients.

A number of previous studies have demonstrated that ocular pulsatility falls during supination in normal subjects and in patients with chronic open angle glaucoma, ocular hypertensive, and normal tension glaucoma. Ocular pulsatility is related to arterial pressure and reflects the influx of blood into the eye with each heart beat; the greater the pulse amplitude, the greater the bolus of blood entering the eye. Previous pulsatility findings have been interpreted to suggest that during supination, ocular perfusion falls, increasing the potential for tissue hypoxia. This interpretation is contrary to the implications of our results. A fall in distal vascular resistance in the retinobular vessels, when changing from seated to supine posture, suggests an increase (or minimally no change), not a decrease in ocular perfusion during supination.

One limitation of the pulsatility measurement is that it evaluates only the pulse wave in the eye (systole) and is virtually insensitive to the steady state non-pulsatile component (diastole) of blood flow. Accordingly, pulsatile blood flow and volumetric blood flow do not always move in concordance. Shifts in blood flow from the systolic to diastolic component of the cardiac cycle can alter pulsatile flow without changing volumetric flow, or vice versa. For example, when perfusion pressure is reduced in cerebral vessels due to increased intracranial pressure, pulsatile blood flow increases in the major feeding vessel (that is, internal carotid artery), while volumetric blood flow falls in this vessel. Further, during hypoxic hypercapnia, cerebral volumetric blood flow increases substantially (>50%) with no corresponding change in pulsatile blood flow. If overall ocular vascular resistance is falling during supination, as suggested by the CDI data here, then the reduction in ocular pulsatility during supination shown in previous studies may reflect not a reduction in overall ocular perfusion but simply a shift in the blood flow away from systole to diastole.

In summary, unlike the middle cerebral artery, Doppler measures of blood flow velocity in the ophthalmic artery change significantly during posture variation. This is true for both glaucoma patients and normal subjects. While the ophthalmic artery response is similar between groups, differences in measures of central retinal artery resistance index are not. These data indicate that posture change exposes a vascular autoregulatory deficit in glaucoma patients, which appears to be most prominent in the vessels distal to the central retinal artery.

Glucoma patients demonstrate faulty autoregulation of ocular blood flow during posture change


