The effect of simulated obstructive apnoea on intraocular pressure and pulsatile ocular blood flow in healthy young adults

P O Lundmark, G E Trope, J G Flanagan

Aim: To investigate the effect of negative inspiratory effort, as generated by the Mueller manoeuvre, on intraocular pressure (IOP) and pulsatile ocular blood flow (POBF) in healthy young adults.

Methods: Seven volunteers with no history of systemic or ocular disease were recruited (mean age 30.7 years, range 25–40 years, M/F: 4/3). After initial instruction and practice of the Mueller manoeuvre, baseline measurements of IOP and POBF were obtained for both eyes after 10 and 15 minutes of rest, respectively, in the supine position. Thereafter, the Mueller manoeuvre was performed creating a mouthpiece pressure of –20 cm H₂O, for at least 15 seconds followed by a 5 minute rest. The manoeuvre was repeated with a mouthpiece pressure of –40 cm H₂O. IOP and POBF were measured 5–15 seconds into the manoeuvre for both –20 cm H₂O (M2A) and –40 cm H₂O (M4A) and directly upon recovery (after two respiratory cycles) from each manoeuvre (M2B, M4B). Baseline measurements were compared using paired t-test, whereas manoeuvre induced changes in IOP and POBF were analysed individually using repeated measures ANOVA with Student-Newman Keuls post hoc analyses. Linear regression analysis was used to investigate a dose-response effect.

Results: No significant differences were found between baseline measurements so they were subsequently pooled. There was a significant decrease in IOP for M2B (9.2%, p = 0.039), M4A (13.8%, p = 0.05), and M4B (15.6%, p < 0.05), relative to baseline. A dose-response relation was found for the effect of mouthpiece pressure on measurements 5–10 seconds into the manoeuvre (M2A and M4A, r² = 0.54, p = 0.045). There was a trend of increased POBF relative to baseline for all measurements; however, significance was reached for M4B only (p = 0.039).

Conclusion: It was shown that forced inspiratory efforts as generated by the Mueller manoeuvre are associated with a dose dependent decrease in IOP and a concomitant increase in pulsatile ocular blood flow.

Recent research has indicated that OSA may have neuro-ophthalmological consequences. Mojon and coworkers found a high prevalence of primary open angle glaucoma among patients with sleep apnoea, and Hayreh described a high prevalence of sleep apnoea among patients with anterior ischaemic optic neuropathy. Other neuro-ocular manifestations reported in case series/reports have included visual field defects and swelling of the optic disc.

Despite the suggested risk of OSA on ocular structures, little is known about the immediate consequences of inspiratory efforts on IOP and ocular haemodynamics. Therefore, in this study we investigated the acute effect of negative intrathoracic pressure, as generated by forced inspiratory effort (Mueller manoeuvre), on IOP and pulsatile ocular blood flow (POBF) in healthy young adults.
in a supine position and after instillation of a topical anaesthetic (one drop of oxybuprocaine (proparacaine) HCl, 0.5%, Diopitic Lab). The OBf tonograph works on the pressure-volume relation described by Langham et al., where the amplitude and the shape of the IOP pulse together with the heart rate form the basis for calculation of the pulsatile component of ocular blood flow. As the major part of the total ocular circulation is accounted for by the choroid, it is thought that POBF reflects the pulsatile component of the total ocular blood flow. Although the exact proportion of the total blood flow that is pulsatile is currently unknown, estimates indicate it to be between 50% and 80%.

The OBf instrument samples IOP at 200 Hz over a time interval of 5–20 seconds using a sterile disposable probe. A built-in processor analyses different characteristics of the IOP pulse waves and selects the five most representative pulses for the calculation of POBF (µl/min). Other output parameters include IOP (mean, maximum, minimum), pulse amplitude, pulse volume, and a number of flow related measures. In this study, only average IOP and POBF were included in the analyses. Measurements obtained with the OBf tonograph have been reported to have acceptable accuracy and reproducibility.

Forced inspiratory efforts were generated by performed Mueller manoeuvres. A Mueller manoeuvre represents the opposite of a Valsalva manoeuvre by forced inspiration against occluded upper airways. The Mueller manoeuvre is associated with a reduction in arterial blood pressure, stroke volume, and cardiac output caused by several mechanisms with different time constants. Several studies have used the Mueller manoeuvre to simulate the acute haemodynamic effects of negative intrathoracic pressure during obstructive sleep apnoea.

To control the Mueller manoeuvre, the subject breathed through a mouthpiece with a ventilatory hole that could be blocked with one finger at the end of expiration. The mouthpiece was connected to a manometer and a pressure transducer via a system of tubing (Fig 1), and the signal from the pressure transducer was amplified (Validyne) and sampled at 100 Hz by a multichannel acquisition software (Windaq/100, Dataq Instruments, OH, USA). Mouth pressure changes have been shown to closely reflect changes in the intra-alveolar pressure. Before measurements the system was calibrated against a water column. To ensure that the inspiratory effort was maintained at a constant level during the manoeuvre a custom made audiofeedback system was used where the subject matched two audible tones by adjusting the mouthpiece pressure (Fig 1).

Brachial blood pressure (BP) was recorded from the subject’s right arm in the supine position and after 5 minutes, rest using an automatic oscillometric blood pressure monitor (Lifestat 200, Physio-Control, Redmond, WA, USA). Average values were calculated from three recordings, separated by 1 minute intervals.

In addition to brachial BP, beat to beat finger arterial BP was measured from index or middle finger of the left hand using the Finapres 2300 device (Ohmeda, Madison, WI, USA). Analogue outputs of blood pressure and heart beat were recorded at 100 Hz, in parallel with the mouthpiece pressure. Finger arterial BP was not included in the final analysis.

**Protocol**

After initial instruction and a satisfactory practice of the Mueller manoeuvre, baseline measurements of IOP and POBF were obtained from one eye after 10 minutes’ and 15 minutes’ rest in the supine position (Fig 2). Thereafter the Mueller manoeuvre was performed at the end of a normal expiration, creating a mouthpiece pressure of approximately −20 cm H₂O for at least 15 seconds, followed by 5 minutes of rest. The Mueller manoeuvre was then repeated creating a mouthpiece pressure of −40 cm H₂O for at least 15 seconds.

We chose these two levels of inspiratory effort based on reported measurements of oesophageal pressure in subjects with sleep apnoea where the inspiratory effort has been shown to vary between −19 cm H₂O and −48 cm H₂O depending on age and sleep stage. The mouthpiece was not provided with an air leak; however, subjects were asked to avoid using cheeks or the tongue to maintain the negative pressure during the manoeuvre.

Measurements of IOP and POBF were obtained 5–10 seconds into the manoeuvre for both −20 cm H₂O (M2A) and −40 cm H₂O (M4A) and directly upon recovery from each manoeuvre—that is, within two respiratory cycles (M2B and M4B). These measurements were performed directly after the manoeuvre to investigate the effects of simulated apnoea termination when profound increases in systemic blood pressure and intracranial pressure are known to occur.

**Figure 2** An outline of intervention and measurements included in the study. Scales are not proportional. Each Mueller manoeuvre was at least 1.5 seconds. The two Mueller manoeuvres were separated by 5 minutes’ recovery. IOP/POBF measurements are marked with arrows. B1 and B2. Baseline measures performed after 10 and 15 minutes of rest respectively. M1 and M3. IOP/POBF measurements performed 5–10 seconds into the Mueller manoeuvre. M2 and M4. IOP/POBF measurements performed 1–2 respiratory cycles after completed Mueller manoeuvre.

**Figure 1** (Left) Equipment used for the Mueller manoeuvre: mouthpiece, manometer, pressure transducer, and amplifier (Validyne). Output was calibrated against a water column. (Right) Audiofeedback system built to help the subject keep a constant inspiratory effort during the Mueller manoeuvre.
Statistical analyses
Baseline measurements were compared on an individual basis, using paired t tests. The effects of the Mueller manoeuvres on IOP and POBF were analysed as changes relative to baseline, using repeated measure analysis of variance (ANOVA) and Student-Newman Keul tests for pairwise comparisons. These analyses were performed individually and for the group as a whole. Associations between respiratory effort and change in IOP and POBF were tested for by linear regression analyses. Spread of data is expressed in standard deviation (SD) for individuals and in standard error of the mean (SEM) for the group of subjects. Statistical significance was set at p<0.05 (two tailed test). All statistical analyses were conducted using the SAS (8.2) statistical package.

RESULTS
A sample from one subject of the recorded mouthpiece pressure, beat to beat finger arterial BP, and pulse rate during a Mueller manoeuvre of −40 cm H2O is shown in Figure 3.

At the beginning of the manoeuvre there was a parallel decline in BP and pulse rate. For the shortest manoeuvres—that is, around 15 seconds, this decline would last the whole manoeuvre, or almost the whole manoeuvre. In subjects with manoeuvres longer than 15 seconds, pulse rate started to increase before the end of the manoeuvre. Immediately after a completed manoeuvre there was a marked increase in both BP and pulse rate, followed by a gradual decline to pre-manoeuvre levels.

Demographics of the subjects are presented in Table 1. There were no statistical differences between baseline measurements of the IOP and POBF. As a result, measurements at B1 and B2 were pooled and an average baseline value was used for comparison with measurements during the two Mueller manoeuvres.

Results from the two Mueller manoeuvres are shown in Tables 2 and 3, and average results for all individual mean outcomes (n = 7) are illustrated in Figures 4 and 5.

Negative mouthpiece pressure was associated with a lowering in IOP (Table 2). This effect was most marked for the greater negative pressure (−40 cm H2O) where the decrease in IOP varied between −4.3% and −33.0% and reached significance for all subjects and the group as a whole. The lesser negative pressure manoeuvre (−20 cm H2O) was associated with smaller magnitudes of change of IOP and with greater interindividual variability of the direction of the early responses in particular. Whereas average decrease in IOP for the whole group reached significance both during and after the Mueller manoeuvre at −40 cm H2O (M4A: −13.8%, M4B: −15.6%, p = 0.004), only the period after the manoeuvre, or almost the whole manoeuvre. Immediately after a completed manoeuvre there was a marked increase in both BP and pulse rate, followed by a gradual decline to pre-manoeuvre levels.

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Table 1 | Demographic and pooled baseline measurements of BP, IOP, and POBF

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Eye</th>
<th>Age (years)</th>
<th>SBP/DBP (mm Hg)</th>
<th>Baseline IOP (mm Hg)</th>
<th>Baseline POBF (μl/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>R</td>
<td>28</td>
<td>101.7/65.7</td>
<td>19.6</td>
<td>664.2</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>L</td>
<td>25</td>
<td>101.0/62.3</td>
<td>23.7</td>
<td>506.7</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>L</td>
<td>40</td>
<td>105.7/68.3</td>
<td>18.1</td>
<td>645.8</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>L</td>
<td>24</td>
<td>112.0/64.0</td>
<td>18.6</td>
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<tr>
<td>5</td>
<td>M</td>
<td>L</td>
<td>35</td>
<td>103.3/62.0</td>
<td>10.6</td>
<td>589.4</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>L</td>
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<td>114.7/64.0</td>
<td>15.6</td>
<td>536.4</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>R</td>
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<tr>
<td>All</td>
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<td>30.7</td>
<td>107.3/65.2</td>
<td>17.6</td>
<td>578.7</td>
</tr>
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</table>

*Average of B1 and B2.
Inspiratory effort varied both in duration and in created pressure among the subjects (Tables 2 and 3). Mean inspiratory pressures deviated slightly from the two target pressures (range: 0.5–5.8 cm H2O difference), and most subjects (five out of seven) overshot or undershot in the same direction during both Mueller manoeuvres. In general, duration of the manoeuvres exceeded the minimum time of 15 seconds. Subjects 2, 3, and 4 completed the first manoeuvre within 1 second of the minimum time, whereas in all other cases duration of the manoeuvres exceeded the minimum time by between 6.4 and 27.7 seconds. On average, female subjects undershot pressure by 0.9 cm H2O and exceeded the minimum manoeuvre time by 8.0 seconds, whereas male subjects overshot pressure by 0.6 cm H2O and exceeded the minimum manoeuvre time by 16.8 seconds. However, because of the small sample size neither pressure nor duration was significantly different between the sexes.

**DISCUSSION**

In this study we have demonstrated a significant association between inspiratory effort, as measured by negative mouth pressures, and an acute decline in IOP. In addition, by recording the change in IOP at two different levels of inspiratory effort we were able to show that a dose-response relation exists between the inspiratory effort and the magnitude of change in IOP. To the best of our knowledge this is the first time the effect of graded negative respiratory effort on IOP has been reported. However, the results are not surprising if we consider the intracranial fluid dynamics of the Valsalva manoeuvre. Several studies have shown that IOP may increase by up to 56% during the straining phase of the Valsalva manoeuvre—that is, phase II of the manoeuvre when the subject is maintaining a predetermined pressure (usually 40 mm Hg).48–47 Most of this response is believed to be attributed to a mechanical effect of elevated intrathoracic pressure during the manoeuvre on venous return from the head, transmitted to the ocular venous pressure,49 and finally to the IOP by vascular volume changes within the rigid scleral chamber.49 In the corresponding phase of the Mueller manoeuvre—that is, when the subject is maintaining a constant negative pressure, the venous return to the heart is known to increase.51 As the venous return from the head is likely to increase by the same mechanism, associated reduction in episcleral venous pressure will lower outflow resistance leading to a drop in IOP through the same pressure-volume relation that accounts for the increase in IOP during the Valsalva manoeuvre. The suggested mechanism is supported by a significant positive linear relation that

**Table 2** The effect of Mueller manoeuvres (–20 cm H2O and –40 cm H2O) on IOP relative to baseline measurements

<table>
<thead>
<tr>
<th>Mueller manoeuvre – 20 cm H2O</th>
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<tbody>
<tr>
<td>Inspiratory effort</td>
<td>Change in IOP relative to baseline</td>
</tr>
<tr>
<td>Duration (seconds)</td>
<td>Mean P (cm H2O)</td>
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<tr>
<td>Subject</td>
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<tr>
<td>1</td>
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<td>27.3</td>
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</table>

Analyses include repeated ANOVA and Student-Newman Keuls post hoc tests for each subject separately, and for the group as a whole. Only significant p values are shown.

*Group mean (SEM).

†p<0.05 relative to baseline.

‡p<0.01 relative to baseline.

§p<0.05 relative to early Mueller manoeuvre.

**Table 3** Effect of Mueller manoeuvres (–20 cm H2O and –40 cm H2O) on POBF relative to baseline measurements

<table>
<thead>
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<tbody>
<tr>
<td>Inspiratory effort</td>
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</tr>
<tr>
<td>Duration (seconds)</td>
<td>Mean P (cm H2O)</td>
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was found for the dependence of the decrease in IOP upon the negative mouth pressure in the approximate range from −20 cm H₂O to −40 cm H₂O (p = 0.045). In this dose-response relationship the estimated rate of decline in IOP was found to be 4.9% per 10 cm H₂O of negative intrathoracic pressure. There are no reports available by which this rate can be compared with the effects of positive intrathoracic pressures; however, the existence of a similar dose-response has been reported with graded Valsalva manoeuvres and graded Valsalva-like expiratory efforts.

The mean duration of the two manoeuvres were nearly the same (27.3 and 27.4 seconds respectively), but the difference between early and late measurements reached significance for the lower negative pressure only (M2A v M2B, p<0.05). This indicates that the effect of negative intrathoracic pressures on IOP rapidly reaches its maximum at higher levels of inspiratory efforts whereas at low levels the decline in IOP is less steep.

Pulsatile ocular blood flow measurements were characterised by marked intraindividual and interindividual variability (Table 3). Most likely this can be explained by the effect of the manoeuvre on variables that form the POBF—that is, ocular pulse wave and heart rate. The cardiovascular effects of the Mueller manoeuvre are well described. Negative pleural pressure swings of the manoeuvre are associated with fluctuations in both cardiac stroke volume and heart rate, which in turn will influence the outcome of the mathematically derived POBF. As these cardiovascular responses have been shown to vary considerably between subjects performing the manoeuvre, we could expect greater variability in POBF measurements than during normal breathing. Group averages of POBF, nevertheless, demonstrated a clear trend towards manoeuvre induced increments (Fig 5), and in spite of the small sample size this effect was significant for late measurements at pressures of −40 cm H₂O (p = 0.039). These results are directionally opposite to the effect of the Valsalva manoeuvre on POBF as reported by Schmetterer et al. In their study OBF measurements at the end of Valsalva manoeuvres of 40 mm Hg (corresponding to 53.3 cm H₂O) produced a reduction in POBF of 7%, which was less than the increase of 8.6–19.5% found during the graded Mueller manoeuvres in our study. However, although the respiratory stimuli in both studies were approximately of the same strength and duration, results should be compared with caution for several reasons. Firstly, measurements in the two studies were obtained at different phases of the employed manoeuvres. This means that the recorded vascular response reflects not only the mechanical effect of positive or negative intrathoracic pressures on the cardiovascular system, but also baroreceptor and chemoreceptor activity in response to changes in arterial pressure and blood gases at the time of the measurement. Secondly, it is, therefore, possible that the magnitude of response found in our late measurements can be explained, at least partly, by the fact that these were obtained during the recovery phase of the Mueller manoeuvre when the release of inspiratory strain and a concomitant increase in sympathetic outflow are known to cause marked increases in blood pressure, pulse pressure and heart rate. Secondly, while measurements were obtained in a supine position during the Mueller manoeuvre, subjects were sitting in the study of Schmetterer et al. Recent studies have found that posture influences the cardiovascular responses to the Valsalva and Mueller manoeuvres. The greater decrease in IOP when subjects performed the Valsalva manoeuvre in a supine versus sitting position indicates that this may also hold true for the ocular response. Hence, the magnitude of responses to the Valsalva and Mueller manoeuvres in both studies may have been closer if they had been performed with the same posture.
There are a number of limitations in this study that need to be addressed. One of the major problems is that manoeuvres were not randomly ordered. Although IOP measurements with the OBF have shown acceptable accuracy\(^{33,35}\) and test-retest reproducibility,\(^{34,36}\) it is well established that repeated applanation tonometry can produce a reduction in IOP through a massaging effect of the eyeball.\(^{41}\) That this effect may hold true also for the OBF machine is indicated in a study by Kergoat and Faucher,\(^{42}\) where repeated measurements significantly reduced IOP, although did not significantly affect POBF measurements.

Another factor that may have affected our results is the negative relation that has been shown to exist between ocular axial length and POBF.\(^{43,44}\) The effect that this is expected to have on interindividual variability was compensated for by the experimental design whereby subjects served as their own controls. As the effect of a change in the volume of each blood bolus entering the eye will depend on the total volume of the eye, there are reasons to control for axial length in any studies where a stimulus will impose effects on the systemic circulation (for example, respiratory manoeuvres, \(O_2, CO_2\) breathing).

Finally, there is a need to comment on the method that was used to measure ocular blood flow in this study. Although pneumotonography and the IOP waveform based calculation of pulsatile ocular blood flow has become a widely accepted technique through the availability of the Langham and OBF systems, the question remains unanswered as to what properties of ocular blood flow this technique truly measures. Calculation of the ocular pulse volume that forms the basis of the algorithmically derived POBF, is based on the assumption that the pressure-volume relation of the eye\(^{40,44,45}\) is constant.\(^{27,28,45}\) However, experimental work on rabbits has shown that the pressure-volume relation is dependent on systemic arterial pressure because of its effect on blood volume and possibly because of myogenic autoregulatory properties of the choroid.\(^{46,47}\) As pointed out by Kiel,\(^{48}\) this may entail a potential source of error when ocular blood flow is measured with the OBF system at different systemic blood pressures. Hence, this method may not be ideal for blood flow quantification during respiratory manoeuvres.

The study presented was inspired by an accumulating number of reports on the possible relation between obstructive sleep-apnoea and neuro-ophthalomological consequences.\(^{21-25,68}\) Because of the inaccessibility of the eye during sleep, we chose to study the acute consequences of obstructive apnoea by graded Mueller manoeuvres. Contrary to the reported haemodynamics of obstructive apnoea and the Mueller manoeuvre,\(^{49,50}\) there was a significant decrease in IOP that lasted into the recovery period of the manoeuvre. These observations are in concordance with the stable IOP after prolonged apnoea events that Mojon and coworkers,\(^{51}\) reported in a case series of three patients with moderate sleep apnoea. Although lowering of IOP may promote perfusion of the ocular structures, as indicated by the increased POBF found in this study, we are not able to tell whether this holds true in an older population or in repeated obstructive sleep apnoea. As the apnoea is related to both acute fluctuations in systemic blood pressure, intracranial pressure and blood gases, and long term adaptations of the autonomic regulatory mechanisms,\(^{52,53}\) there are several mechanisms that may be involved in a possible link between this common sleep disorder and the reported ophthalmological findings. Further research in this field is therefore warranted.

**ACKNOWLEDGEMENTS**

P Lundmark received partial support from the Glaucoma Research Society of Canada. J Flanagan and G Trope are supported by the Canadian Institutes of Health Research.

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