

## EXTENDED REPORT

## Effect of a nifedipine induced reduction in blood pressure on the association between ocular pulse amplitude and ocular fundus pulsation amplitude in systemic hypertension

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**Background:** The ocular pressure/volume relation, which is described by the Friedenwald equation, forms the basis of intraocular pressure (IOP) measurement with Schiøtz tonometry and measurement of pulsatile ocular blood flow (POBF) with pneumotonometry. Changes in intraocular volume during the cardiac cycle are caused by arterial inflow and venous outflow and are accompanied by changes in IOP. The relation between volume and pressure changes is dependent on the elastic properties of the eye coats as described by the ocular rigidity coefficient. Previous studies indicate that there is a vascular contribution to ocular rigidity and that the volume/pressure relationship may depend on the mean arterial pressure.

**Methods:** The effect of a nifedipine induced reduction in systemic blood pressure on pulse amplitude (PA) as assessed with pneumotonometry and fundus pulsation amplitude (FPA), as measured with laser interferometry was investigated in 16 untreated patients with moderate to severe systemic hypertension (mean arterial pressure 123 (SD 12) mm Hg).

**Results:** The ratio between PA and FPA was taken as a measure of the ocular rigidity coefficient. Nifedipine reduced mean arterial pressure by 17.3% and increased pulse rate by 11.0% ( $p < 0.001$  each). Whereas PA was significantly reduced after administration of nifedipine ( $-15.6%$ ;  $p < 0.001$ ), FPA remained unchanged. Accordingly, the ratio of PA/FPA was reduced from 0.86 mm Hg/ $\mu\text{m}$  to 0.73 mm Hg/ $\mu\text{m}$  after administration of nifedipine.

**Conclusion:** These data are in keeping with previous animal experiments indicating a blood pressure dependent vascular component to the rigidity of the eye coats in vivo. This needs to be taken into account for measurement of IOP with Schiøtz tonometry and POBF with pneumotonometry.

Increased mean arterial pressure will increase pressure in the arterial tree. This may cause an increased blood volume within the choroid, which is assumed to alter the mechanical properties of the eye.<sup>1</sup> In turn the ocular pressure-volume relation may depend on arterial blood pressure according to the Friedenwald equation<sup>2</sup>:

$$E = (\log IOP1 - \log IOP2) / (V1 - V2)$$

In this equation E is the ocular rigidity,  $\Delta IOP = IOP1 - IOP2$  is a change in intraocular pressure (IOP) and  $\Delta V = V1 - V2$  is a change in intraocular volume. This equation, assuming that E is a constant, is used practically as a basis for tonometry,<sup>2</sup> tonography,<sup>3</sup> and measurements of pulsatile ocular blood flow (POBF) using pneumotonometry.<sup>4,5</sup> For small changes in  $\Delta IOP$ , which occur, for instance, during the heart cycle the Friedenwald equation may be simplified to:

$$E = \Delta IOP / \Delta V$$

Several studies indicate that E may depend on choroidal blood volume and that vascular rigidity within the choroid may contribute as a factor in scleral rigidity.<sup>6-9</sup> More recently a systematic investigation in rabbits has provided evidence that there is a linear dependence of E with mean arterial pressure (MAP).<sup>1</sup> Based on measurements of choroidal blood flow and choroidal blood volume with laser Doppler flowmetry during changes in MAP and IOP Kiel showed that E was 0.0094 at a MAP of 40 mm Hg and as much as 0.0184 at a MAP of 100 mm Hg. This indicates that the vascular factor has an important role in the ocular pressure-volume relation and that an increase in MAP of 60 mm Hg almost doubles E.

Investigations of such phenomena in humans is obviously difficult because neither MAP nor IOP can be altered mechanically. In an effort to gain insight into this phenomenon ocular pulse amplitude (PA) and POBF were measured with pneumotonometry<sup>4,5,10</sup> and fundus pulsation amplitude (FPA) was measured with laser interferometry.<sup>11-13</sup> This was done in a group of patients with moderate to severe systemic hypertension before and after administration of the calcium channel blocker nifedipine.

## SUBJECTS AND METHODS

## Subjects

The study protocol was approved by the ethics committee of the Vienna University School of Medicine. The investigation conforms to the principles outlined in the Declaration of Helsinki and was conducted according to the good clinical practice guidelines of the European Union. The nature of the study was explained and all subjects gave written consent to participate. Sixteen male and female subjects (age 59.9 (SD 6.5) years) with moderate to severe hypertension, and a MAP  $> 105$  mm Hg were enrolled. Furthermore, an ophthalmic examination, including slit lamp biomicroscopy and indirect funduscopy was performed in each subject before the study. Inclusion criteria were normal ophthalmic findings and a refractive error of less than 3 dioptres. Exclusion criteria were history of hypersensitivity to oxybuprocaine or nifedipine and history of ocular surgery or relevant ocular disease.

**Abbreviations:** DBP, diastolic blood pressure; FPA, fundus pulsation amplitude; IOP, intraocular pressure; MAP, mean arterial pressure; OPP, ocular perfusion pressure; PA, pulse amplitude; POBF, pulsatile ocular blood flow; SBP, systolic blood pressure

### Study protocol

Studies were performed between 8 am and 11 am at the Department of Clinical Pharmacology, Division of Ophthalmology, Allgemeines Krankenhaus, Vienna, Austria.

After a 20 minute resting period in a dark and quiet room one drop of oxybuprocaine hydrochloride (Benoxinat, Alcon Couvreur, Puurs, Belgium) was instilled in the right eye of each patient for topical anaesthesia and the baseline measurements with the Langham pneumotonometer and the applanation tonometer were undertaken. Thereafter, fundus pulsation amplitudes were assessed with the laser interferometer. Pulse rate and blood pressure were recorded every 5 minutes throughout the study with an automatic oscillometric device. Thereafter, nifedipine 10 mg (Buconif, Nycomed, Vienna, Austria) was applied sublingually. After a decrease of MAP of at least 10 mm Hg had occurred measurement of ocular haemodynamics and intraocular pressure were repeated. Then patients were monitored until stable haemodynamic conditions were reached. All patients were then enrolled in standard hypertension programmes for further treatment.

### Blood pressure and pulse rate

Systolic, diastolic, and mean blood pressures (SBP, DBP, MAP) were measured on the upper arm by an automated oscillometric device (HP-CMS patient monitor, Hewlett Packard, Palo Alto, CA, USA). Pulse rate was automatically recorded from a finger pulse oxymetric device (HP-CMS patient monitor). This system has been previously evaluated.<sup>14</sup>

### Intraocular pressure and ocular perfusions pressure

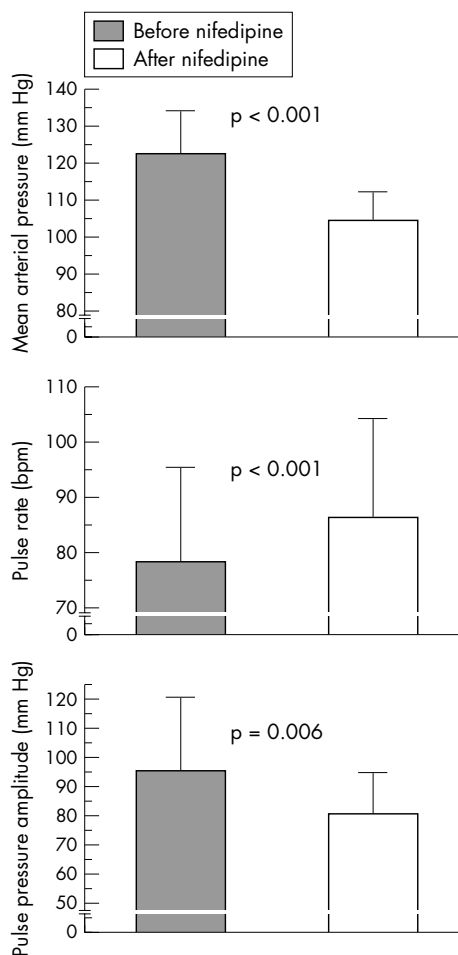
Intraocular pressure was measured with a Goldman applanation tonometer. Ocular perfusion pressure was calculated as  $OPP = MAP - IOP$ .

### Fundus pulsation

Pulse synchronous pulsations of the eye fundus were assessed by laser interferometry on the subject's right eye. The method is described in detail by Schmetterer *et al.*<sup>12-15</sup> Briefly, the eye is illuminated by the beam of a single mode laser diode with a wavelength ( $\lambda$ ) of 783 nm. The light is reflected at both the surface of the cornea and the retina. The two re-emitted waves produce interference fringes from which the distance changes between cornea and retina during a cardiac cycle can be calculated. Distance changes between cornea and retina lead to a corresponding variation of the interference order ( $\Delta N(t)$ ). This change in interference order can be evaluated by counting the fringes moving inwards and outwards during the cardiac cycle. Changes in optical distance ( $\Delta L(t)$ ), corresponding to the cornea-retina distance changes, can then be calculated by  $\Delta L(t) = \Delta N(t) \cdot \lambda / 2$ . The maximum distance change is called the fundus pulsation amplitude (FPA) and estimates the local pulsatile blood flow.<sup>15-16</sup> FPA was calculated as the mean of at least five cardiac cycles. The short term and day to day variability of the method is small.<sup>13</sup> To obtain information on the choroidal blood flow, the macula, where the retina lacks vasculature, was chosen for measurements.

### Pneumotometric measurement of pulsatile ocular blood flow

Pulsatile ocular blood flow was determined with a commercially available blood flow measurement system (OBF System 3000, OBF Labs, Malmesbury UK).<sup>5</sup> The system assesses changes in IOP, which are caused by the rhythmic filling of the intraocular vessels, with a pneumatic applanation tonometer. The maximum IOP change during the cardiac cycle is called pulse amplitude (PA). Based on a theoretical model eye, the POBF is calculated from the IOP variation over



**Figure 1** Effects of nifedipine on mean arterial pressure, pulse rate, and pulse pressure amplitude in patients with systemic hypertension (n = 16). Data are presented as means (SD). p Values are calculated from paired *t* tests comparing baseline data with data after administration of nifedipine.

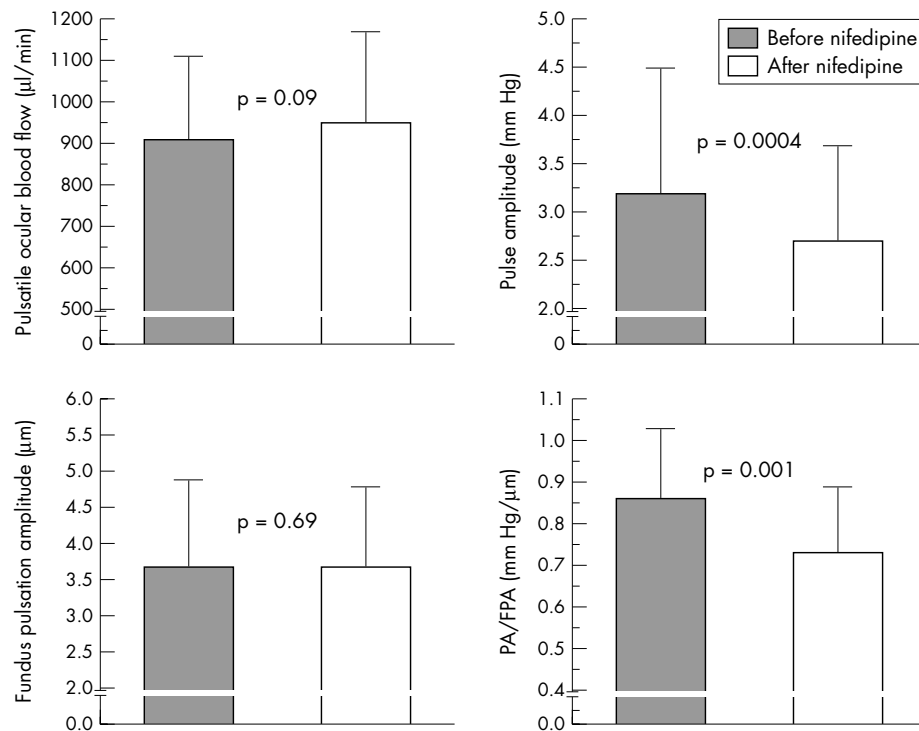
time. This hydrodynamic model is based on the assumption that venous outflow from the eye is non-pulsatile. Moreover, the ocular rigidity, which is used to derive ocular volume changes from changes in IOP, is assumed to be equal for all subjects. The calculation of POBF is automatically derived from the five pulses that are closest to each other in IOP beat to beat variation.

### Data analysis

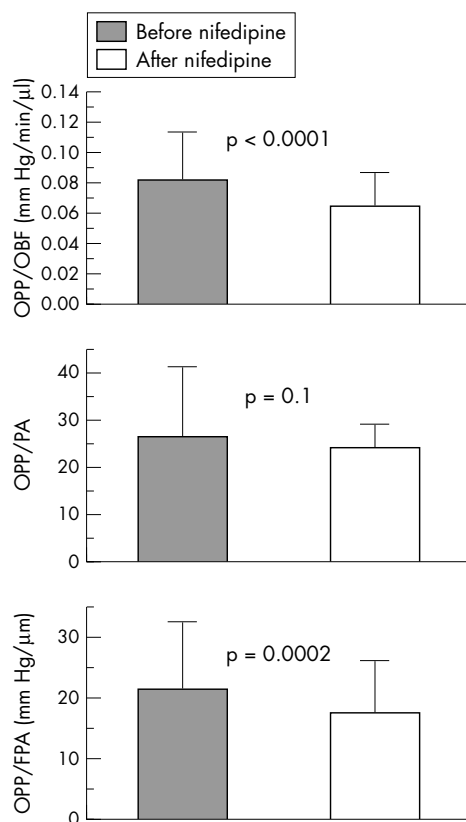
Assuming that FPA is proportional to the change in  $\Delta V$  during the cardiac cycle a factor  $E1 = PA/FPA$  was calculated as a measure of the mechanical properties of the eyeball. This factor was calculated in the hypertensive group before and after intervention with nifedipine. In addition, three factors were calculated as  $RF = OPP/FPA$ ,  $RPA = OPP/PA$ , and  $RPO = OPP/POBF$  in analogy to the choroidal vascular resistance, which is given by  $R = OPP/\text{choroidal blood flow}$ . All outcome parameters are given as means (SD). The paired *t* test was used to assess significant effects of nifedipine administration on the outcome parameters. Linear correlation analysis was used to investigate the association between FPA and the outcome parameters of pneumotometry.

### RESULTS

Nifedipine reduced MAP by 17.3%, an effect which was highly significant ( $p < 0.001$ , fig 1) versus baseline. This



**Figure 2** Effects of nifedipine on pulsatile ocular blood flow, pulse amplitude, fundus pulsation amplitude, and the ratio of pulse amplitude/fundus pulsation amplitude (PA/FPA) in patients with systemic hypertension (n = 16). PA/FPA was calculated as a measure of ocular rigidity. Data are presented as means (SD). p Values are calculated from paired *t* tests comparing baseline data with data after administration of nifedipine.



**Figure 3** Effects of nifedipine on the ratios of ocular perfusion pressure/pulsatile ocular blood flow ocular perfusion pressure (OPP/OBF), ocular perfusion pulse and amplitude pressure (OPP/PA), and ocular perfusions pressure and fundus pulsation amplitude (OPP/FPA) (n = 16). These data were calculated in analogy to vascular resistance data. Data are presented as means (SD). p Values are calculated from paired *t* tests comparing baseline data with data after administration of nifedipine.

decrease in MAP was accompanied by a significant reduction in pulse pressure amplitude (PPA). As expected from the pharmacodynamic profile of the drug, nifedipine increased pulse rate by 11.0% ( $p < 0.001$ ). IOP was not changed by administration of nifedipine (baseline: 13.9 (2.8) mmHg; after nifedipine: 13.7 (2.6) mmHg).

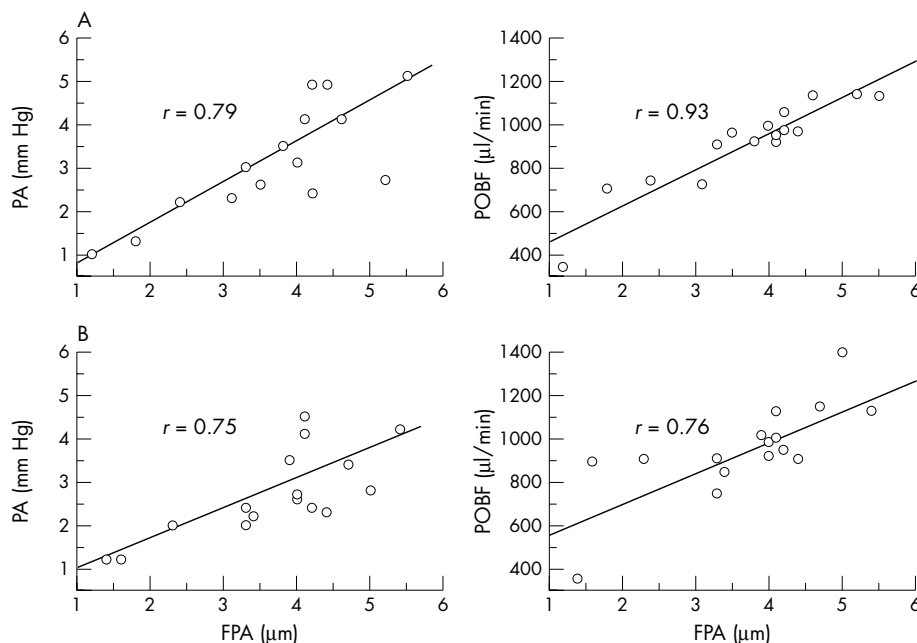
Ocular haemodynamic variables are depicted in figure 2. Administration of nifedipine tended to increase POBF by 4.6%, but the effect did not reach the level of significance ( $p = 0.09$ ). FPA also remained constant after administration of nifedipine. By contrast, PA was significantly lowered by administration of nifedipine ( $-15.6%$ ;  $p < 0.001$ ). Since MAP was reduced after administration of nifedipine without any concomitant change in POBF or FPA, RF and RPO decreased significantly (fig 3). This effect was in the same order for RF ( $-17.8%$ ;  $p < 0.001$ ) and RPO ( $-21.9%$ ;  $p < 0.001$ ). By contrast, RPA was not changed after administration of nifedipine.

Since FPA remained unchanged after administration of nifedipine and PA was significantly reduced E1 was also reduced as shown in figure 2. Accordingly, a decrease in MAP of 17.3% resulted in a decrease in E1 of 15.1%. This decrease in E1 after administration was highly significant ( $p = 0.001$ ). The ratio PA/FPA decreased in 14 of the 16 included subjects.

The association between FPA and the parameters of pneumotometry is depicted in figure 4. Correlation coefficients between FPA and POBF and FPA and PA were highly significant before and after administration of nifedipine. The slope of the regression line between FPA and POBF and between FPA and PA was less steep after administration of nifedipine than under baseline conditions.

## DISCUSSION

This study shows that reduction of systemic blood pressure in patients with systemic hypertension alters E1, indicating vascular contributions to the elastic properties of the eye. Obviously, this conclusion is critically dependent on the assumption that FPA is an adequate measure of  $\Delta V$ . There are several lines of evidence that this is the case. On the one hand



**Figure 4** Linear correlation analysis between fundus pulsation amplitude (FPA) as assessed with laser interferometry and pulsatile ocular blood flow (POBF) as assessed with pneumotonometry (right panel) and FPA and pulse amplitude (PA) as assessed with pneumotonometry (left panel) before (A) and after (B) nifedipine in 16 patients with systemic hypertension.

there is a high degree of association between FPA and PA in healthy subjects.<sup>15,17</sup> Furthermore, we have previously shown that based on a theoretical model FPA measurements provide reasonable estimates of POBF.<sup>18</sup> Finally, the present study design ensures that it is not required that FPA and  $\Delta V$  are perfectly correlated between subjects, but only that the nifedipine induced changes in FPA adequately represent the change in  $\Delta V$ .

The results of this study are in keeping with previous studies indicating that the ocular pressure-volume relation is MAP dependent. Extensive work has been done in a rabbit model in which the MAP can be varied mechanically by use of aortic and caval occluders.<sup>1</sup> Using laser Doppler flowmetry the concentration of moving blood cells was used as an index of ocular blood volume and the blood cell flux (calculated as concentration of moving blood cells  $\times$  velocity of blood cells) was used as an index of choroidal blood flow. Accordingly, a linear relation was found between the ocular rigidity coefficient and MAP in the range between 40 mm Hg and 100 mm Hg. Considering the slope of the reported regression line a 10 mm Hg increase in MAP at 100 mm Hg resulted in an approximately 7.3% increase in the rigidity coefficient. This is in good agreement with the results of the present study indicating an 8.3% increase in E1 with a 10 mm Hg change in MAP. Comparing the results of the present study to the data obtained in healthy volunteers ( $E1 = 0.73 (0.14) \text{ mm Hg}/\mu\text{m}$ )<sup>15</sup> it is clear that administration of nifedipine normalised the ratio of PA/FPA. This indicates that increased E1 is not a consequence of long term hypertension induced structural changes in scleral rigidity, but rather a consequence of increased choroidal blood volume.

Evidence for MAP dependence of the ocular rigidity coefficient also arises from earlier studies investigating the ocular volume-pressure relation in the eye. Most importantly Eisenlohr and Langham<sup>7</sup> have shown that there is a difference between the volume-pressure relation in the living and the dead eye. This difference could be abolished by reducing MAP to a level beyond the IOP. Later the same group showed that during an injection of a fluid the discrepancy between the living and the dead eye increased as the IOP was increased towards MAP, but was abolished

when IOP exceeded MAP.<sup>6</sup> Based on these experiments the authors concluded that an increase in IOP forces blood from the eye dependent on the ratio of IOP and MAP.

The results of the present study may have implications for measurement of IOP using Schiøtz tonometry in patients with systemic hypertension as discussed in detail by Kiel.<sup>1</sup> Since Schiøtz tonometry is becoming less important in clinical routine the significance for POBF measurements using pneumotonometry may be more important. According to the present data pneumotonometric readings among subjects may not be comparable when they have different levels of blood pressure.

In the present study neither POBF nor FPA were altered after administration of nifedipine. This may either be related to a change in choroidal vascular resistance as also evidenced from the decrease in RPO and RF in the present study or a change in flow pulsatility. The latter seems unlikely because PPA, which is the driving force of pulsatile blood flow, was also reduced after nifedipine administration. We can, however, not determine whether the decrease in RPO is due to an autoregulatory response of the choroid in response to the decrease in ocular perfusion pressure as reported previously in rabbits<sup>19,20</sup> and humans.<sup>21</sup> Alternatively, direct vasodilation of the calcium channel blocker may be responsible for the observed results, which has been observed in some but not in all previous studies. In previous studies nifedipine was shown to increase PA exclusively in vaso-spastic patients with normal tension glaucoma,<sup>22</sup> but not in controls. This is compatible with the results of a study from our group, where nifedipine did not alter FPA in healthy subjects, but partially reversed endothelin induced vasoconstrictor effects.<sup>23</sup> A small, but significant increase in peak systolic flow velocity after administration nifedipine was reported in one study,<sup>24</sup> whereas other studies reported no effect on colour Doppler imaging parameters.<sup>25,26</sup>

In conclusion, the present study indicates that the ocular pressure-volume relation is altered during a nifedipine induced reduction in systemic blood pressure in hypertensive patients. This may have clinical implications for the interpretation of IOP data as assessed with Schiøtz tonometry and POBF data as assessed with pneumotonometry.

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