Hypercapnia invokes an acute loss of contrast sensitivity in untreated glaucoma patients

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Abstract

Background/aim—It is widely accepted that hypercapnia results in increased retinal, choroidal, and retrobulbar blood flow. Reports of a visual response to hypercapnia appear mixed, with normal subjects exhibiting reduced temporal contrast sensitivity in some studies, while glaucoma patients demonstrate mid-peripheral visual field improvements in others. This suggests that under hypercapnic conditions a balance exists between the beneficial effects of improved ocular blood flow and some other factor such as induced metabolic stress; the outcome may be influenced by the disease process. The aim of this study was to evaluate the contrast sensitivity response of untreated glaucoma patients and normal subjects during mild hypercapnia.

Methods—Ten previously untreated glaucoma patients and 10 control subjects were evaluated for contrast sensitivity and intraocular pressure while breathing room air and then again during mild hypercapnia.

Results—During room air breathing, compared with normal subjects, glaucoma patients had higher IOP (p = 0.0003) and lower contrast sensitivity at 3 cycles/degree (cpd) (p = 0.001). Mild hypercapnia caused a significant fall in contrast sensitivity at 6, 12, and 18 cpd (p < 0.05), only in the glaucoma group.

Conclusion—Glaucoma patients with early disease exhibit central vision deficits as shown by contrast sensitivity testing at 3 cpd. Hypercapnia induces further contrast loss through a range of spatial frequencies (6–18 cpd) which may be predictive of further neuronal damage due to glaucoma.

Glascoma is a disease of the optic nerve resulting in characteristic progressive visual field loss1 and is believed to be of multifactorial origin.2 Compromised ocular haemodynamics have been implicated as a major factor in the aetiology of disease.2–4

Visual function recovery has been reported following glaucoma therapy. For example, central contrast sensitivity improvement has been demonstrated in primary open angle glaucoma patients (POAG) following IOP reduction via β blocker therapy5 6 or trabeculectomy,7–9 and in patients with normal tension glaucoma (NTG) following treatment with a systemic calcium channel blocking agent10 or topical treatment with dorzolamide.11

In addition, it has previously been demonstrated that hypercapnia, when induced by carbogen breathing, results in increased visual field sensitivity in glaucoma patients.12 The precise mechanism of visual function improvement remains unknown. Increased blood levels of carbon dioxide are known to increase both retinal and choroidal blood flow in animals and humans,12–14 with several authors having noted a tight link between ocular blood flow and contrast sensitivity in both POAG15 16 and NTG patients.12 It is likely that a population of neurons that is neither fully functioning nor dead, but compromised as a result of the disease, respond positively to the improved circulation.

In animal eyes hypercapnia is also known to result in acidosis with resulting changes in metabolism and consequent compromise in visual function.19 20 Sponsel et al21 showed that young normal subjects exhibit decreased temporal contrast sensitivity in response to hypercapnia, a finding that would be at odds with a simple hypothesis supporting improved visual mechanisms resulting from improved blood flow in hypercapnia. Similarly, while hyperoxia is known to reduce ocular blood flow22–25 central vision improvements have been demonstrated in patients with early diabetic retinopathy.26 These findings indicate that the extent of vasodilatation and consequent ocular blood flow improvement alone are not sufficient to dictate the visual function outcome during gas perturbations. It would seem that in hypercapnia at least, a complex balance exists between the positive effects of improved circulation and some other negative effect, perhaps because of induced metabolic stress. This balance may shift between central compared with peripheral retina or in the diseased state.

The purpose of this study was to determine the effect of hypercapnia on the central vision, measured by contrast sensitivity, of patients diagnosed with glaucoma. Our hypothesis is that the balance between positive circulatory effects and negative metabolic effects due to hypercapnia shifts in central retina, the latter being more sensitive to metabolic compromise and consequent central vision loss in the diseased state.

Materials and methods

Ten previously untreated glaucoma patients and 10 control subjects were recruited for this study. For contrast sensitivity measures, previous data have shown that the test-retest standard deviation for contrast sensitivity measured...
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alternative forced choice procedure. Sub-
18 cycles per degree (cpd), using a quasi two
mined at four spatial frequencies, 3, 6, 12 and

ton, OH, USA). Contrast sensitivity was deter-
sensitivity were assessed in this manner using
the CSV-1000 instrument (VectorVision, Day-
s held the occluder during vision testing. Best
lens prescription was placed in a lens holder
corrected visual acuity. Each patient’s spectacle
bject practised each test before baseline meas-
function measurements were then taken with-
out the presence of any breathing apparatus.
To assess the room air and hypercapnia con-
ditions, subjects wore a face mask that was
connected to a non-rebreathing valve. The
condition. Bonferroni’s correction was
applied when multiple t tests were performed
using a single data set. Pearson product
moment correlation analysis was used to ascer-
tain any significant association between vari-
able. A p value of <0.05 was considered statisti-
cally significant.

Results
Glaucoma patients and normal subjects were
similar for age, sex distribution, blood pres-
sure, heart rate, and ETDRS acuity at baseline
(Table 1). Intraocular pressure was significant-
ly higher in glaucoma patients (21.03 (SD 3.92) mm Hg) compared with normal subjects
(15.08 (2.35) mm Hg), (p = 0.0003, Table 1). Contrast sensitivity was significantly lower in
glaucoma patients than in normal subjects at 3
cpd, both at baseline (p = 0.001) and in room

Table 1 Baseline characteristics of the normal and
glaucoma groups

<table>
<thead>
<tr>
<th>Glaucoma</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>54.8 (9.48)</td>
</tr>
<tr>
<td>Sex</td>
<td>4F/6 M</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>103.1 (5.27)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>80.9 (13.8)</td>
</tr>
<tr>
<td>ETDRS visual acuity (logMAR)</td>
<td>0.06 (0.13)</td>
</tr>
<tr>
<td>IOP (mm Hg)</td>
<td>21.03 (3.92)*</td>
</tr>
</tbody>
</table>

* Differences between groups at baseline.

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Contrast sensitivity outcomes measured at 3, 6, 12, and 18 cycles per degree (cpd) for glaucoma patients and normal subjects. Measurements were taken at baseline (BL), in room air through a breathing mask (RA), and while breathing carbon dioxide (CO2). Significant differences between groups are noted by the plus symbol, and differences due to conditions are noted by an asterisk.

During hypercapnia, end tidal carbon dioxide increased from 37.1 (2.6) to 43.5 (1.3) mm Hg in normal subjects (p < 0.0001) and from 36.2 (3.1) to 42.8 (4.1) mm Hg in glaucoma patients (p < 0.0001) (Fig 2). This increase in blood levels of carbon dioxide was associated with an increase in blood oxygen saturation, changing from 95.4% (1.6%) to 96.5% (1.1%) for the normal subjects (p = 0.025) and from 95.8% (0.78%) to 96.8% (0.6%) for the glaucoma patients (p = 0.001) (Fig 3). As shown in Figure 1, hypercapnia caused a significant reduction in the contrast sensitivity of glaucoma patients at 6 (p = 0.015), 12 (p = 0.045) and 18 (p = 0.022) cpd. Also, glaucoma patients displayed significantly lower contrast sensitivity than normal subjects at 3 (p = 0.027), 6 (p = 0.016), and 12 (p = 0.05) cpd during hypercapnia. No changes in blood pressure, heart rate, or IOP were noted for either group when comparing room air with the hypercapnic condition.

**Discussion**

Our results indicate that during room air breathing conditions, previously untreated glaucoma patients have significantly reduced contrast sensitivity compared with normal subjects at 3 cpd, but not at 6, 12, or 18 cpd. During hypercapnia, glaucoma patients exhibit a further significant reduction in contrast sensitivity, while normal subjects show no change. Our findings are important in two respects. Firstly, the level of hypercapnia achieved was sufficient to differentiate the responses of normal subjects from those of untreated glaucoma patients; secondly, the finding that central visual field deficit or change in contrast sensitivity with hypercapnia.

An important concern in any study of this type is whether the order of testing or the breathing apparatus could influence the contrast sensitivity findings. A small practice effect for contrast sensitivity, which asymptotes by the second testing session, has been previously reported. To potentially offset this effect, all patients conducted a full contrast sensitivity trial on both eyes before baseline measurements were captured. Although the variability of contrast sensitivity testing increases with age, the study groups were matched for age, and the test environment, including room illumination and refractive correction, was carefully controlled. No significant changes were found between the baseline and room air conditions for either group. Also, for the normal subjects, no significant changes were noted between any of the test conditions—baseline, room air, or hypercapnia. These data strongly
suggest that the acute vision loss demonstrated by the glaucoma patients was not a result of any systematic bias induced by testing order, the breathing face mask, or some other experimental artefact.

Hypercapnia was achieved by mixing 100% carbon dioxide with intake air in a closed breathing system. It is important in such studies to ensure that the appropriate level of hypercapnia is reached, without replacing too much of the intake air with carbon dioxide, leading to hypoxia. Several aspects of our data suggest that this was accomplished in our study. Firstly, the end tidal measurements show a significant increase in blood levels of carbon dioxide of 43.5 and 42.8 mm Hg for the normal subjects and glaucoma patients, respectively. While clearly facilitating a hypercapnic state, these levels did not appear to be excessive. They were similar to end tidal carbon dioxide levels noted during typical late stage sleep (approximately 41 mm Hg) and were well below those attained during general anaesthesia (approximately 50 mm Hg). Also, blood oxygen saturation increased significantly for both groups. Increased blood oxygen saturation is a well known consequence of mild hypercapnia. The elevated blood levels of carbon dioxide reduce the affinity of haemoglobin for oxygen, causing the release of oxygen into the blood stream (Bohr effect). These results, taken together, indicate that hypercapnia was attained without inducing hypoxia.

Despite broad agreement that hypercapnia induces vasodilatation while hyperoxia causes vasoconstriction, the visual outcome remains unpredictable. Simplistically, one might anticipate that improved circulation leads to improved visual function, while reduced circulation compromises it. This hypothesis is not supported by Sponsel's finding that young normal subjects exhibit reduced temporal contrast acuity during hypercapnia. It may be that for young healthy tissue at least, other changes such as metabolic stress, possibly from the induced acidosis in hypercapnia, result in compromised neuronal activity, while the beneficial effects of increased blood flow have only a marginal effect on performance. It may be the case that the responsiveness of tissue to the gas state is greater in disease compromised tissue. In diabetic patients, in whom localised tissue hypoxia underlies the disease, induced systemic hyperoxia improves central visual function despite compromised circulation. It would seem that for the diabetics at least, the balance of outcome is shifted in favour of improved visual function due to metabolic improvements rather than a compromised one due to diminished circulation. These findings may be the result of underlying differences in the disease mechanism, or a shift in balance from circulatory to metabolic factors influencing central compared with mid-peripheral vision. In our study, one normal subject and one glaucoma patient was a diagnosed diabetic without ocular involvement. In these cases, the visual response to hypercapnia did not significantly differ from those of the non-diabetic patients and subjects in the study.

Sponsel and colleagues previously demonstrated that young normal subjects decrease temporal contrast sensitivity during hypocapnia and hypercapnia and that the loss during hypercapnia can be blocked by pretreatment with dorzolamide. These results differ from our data in that we found no change in the normal subjects during elevated carbon dioxide. Several differences in the study designs are important to note. In the previous study, subjects breathed 5% carbon dioxide from a premixed tank. They were required to breathe this mixture for 15 minutes after reaching an end tidal level 15% above baseline. In our study, the carbon dioxide levels were tightly controlled using a gas mixing chamber and the end tidal level 15% above baseline had to be reached for only 3 minutes before testing began. Our design most certainly induced less hypercapnia, possibly providing an insufficient change in physiology to provoke a loss in contrast sensitivity of normal subjects. It is of importance that in our study the normal subjects did show similar trends to the glaucoma patients—that is, falling in contrast sensitivity for 6 and 18 cpd, but these changes did not reach statistical significance. Further, unlike the temporal contrast sensitivity tested at 1 and 4 cpd in the previous experiment, our study evaluated a range of static high spatial frequencies. This difference may be meaningful since the significant changes in contrast sensitivity were noted in our study only for the higher spatial frequencies—that is, 6, 12, and 18 cpd. Irrespective of these differences, it is clear that for the levels of hypercapnia used in our study, untreated glaucoma patients, but not normal subjects, experience a significant fall in contrast sensitivity across a wide range of spatial frequencies.

A further possibility is that the vision loss is caused by a “steal” phenomenon. Studies clearly demonstrate that elevated blood levels of carbon dioxide cause vasodilatation in cerebral and ocular vessels. In glaucoma patients, who may lack ocular vascular autoregulation, this generalised vasodilatation could potentially redirect blood flow away from the optic nerve head (ONH) or other critical tissues in the eye. In normal subjects, who possess functional vascular autoregulation, the ONH and other ocular vessels would be capable of sufficient vasodilatation to offset the potential loss of blood flow and contrast sensitivity; this at least is true for the levels of vasodilatation and hypercapnia used in this study.

In summary, glaucoma patients showed a dramatic loss in central vision function, as measured by static high spatial frequency contrast sensitivity, during hypercapnia that was not exhibited by normal subjects under similar conditions. It appears from these data that elevated blood levels of carbon dioxide, either through excessive vasodilatation or some other unknown mechanism, react with the glaucomatous eye to exacerbate the disease related
vision deficit. A potential role for this effect as a diagnostic tool in the evaluation of risk of neuronal damage due to glaucoma, or in determining therapies for glaucoma is yet to be determined.


