Hyperoxia improves contrast sensitivity in early diabetic retinopathy

Alon Harris, Oliver Arend, Ronald P Danis, David Evans, Sebastian Wolf, Bruce J Martin

Abstract

Aim—The cause of vascular and visual pathology in diabetic retinopathy remains unknown. If retinal hypoxia plays a role, then early in the course of diabetes 100% oxygen breathing should normalise both contrast sensitivity and retinal blood flow.

Methods—This hypothesis was tested in 12 diabetic patients with minimal retinopathy who, none the less, exhibited reduced contrast sensitivity (p=0.003 versus 12 age and sex-matched controls) and prolonged retinal arteriovenous dye transit (p=0.0001 versus controls).

Results—Isocapnic hypoxia failed to alter contrast sensitivity in controls, while it significantly improved contrast sensitivity in patients (at 12 cpd; p=0.042) to levels indistinguishable from normal. Individual improvement in contrast sensitivity correlated positively with the severity of the initial defect (r=0.84, p=0.0008). Hypoxia also had haemodynamic effects: it slowed retinal arteriovenous passage of fluorescein dye in controls, but did not further slow this transit time in patients.

Conclusions—These results demonstrate the reversibility of early contrast sensitivity deficits in diabetes mellitus, and support the hypothesis that factors linked to tissue hypoxia initiate both visual and vascular dysfunction in diabetic retinopathy.

(Dr J Ophthalmol 1996; 80: 209–213)
SCANNING LASER OPHTHALMOSCOPY
To assess retinal arteriovenous passage time nine diabetic subjects and 11 control subjects underwent scanning laser video fluorescein angiography during normal conditions and then during isocapnic hyperoxia created by breathing 100% oxygen. The two conditions were randomised and the subjects and technical staff masked to this order. Carbon dioxide was added during hyperoxic exposure to render control and high oxygen conditions isocapnic. Subjects breathed from a mouthpiece connected to a low resistance, two way breathing valve. On the inspired side, 100% oxygen was added to a mixing chamber, to which small amounts of carbon dioxide were added for isocapnia. This protocol raises end tidal partial pressure of oxygen (P02) to 600–700 mm Hg while leaving end tidal partial pressure of carbon dioxide (PCO2) constant at 35–40 mm Hg. Both of the end tidal gases were monitored by rapid response specific gas analysers placed in the initial portion of the expired air stream. Hyperoxia (or normoxia) was maintained for 15 minutes before fluorescein angiography and contrast sensitivity measurements were carried out. Arteriovenous passage time was measured by computer from digitised angiograms by calculating the time between the dye appearance (defined as attainment of 10% maximum dye intensity) on the temporal superior artery and the corresponding temporal vein.

CONTRAST SENSITIVITY
Contrast sensitivity was assessed in all 20 subjects during normal conditions and during isocapnic hyperoxia created by breathing 100% oxygen. The two conditions were randomised and the subjects were masked to their order.

STATISTICAL ANALYSIS
Unpaired t tests were used to compare baseline or hyperoxic measurements in normal versus diabetic people. Paired t tests were used to assess changes in each group as induced by hyperoxia; Bonferroni's correction was applied when multiple t tests were performed using a single data set. A p value of <0.05 was regarded as statistically significant; all t tests were two tailed.

Results
The insulin dependent diabetic patients and the normal controls were similar in mean age (23 (SD 8) years for patients; 26 (7) years for controls; p=NS), and in sex distribution (seven male, five female controls; six male, six female patients). Two hours before the study, blood glucose in the diabetic patients (n=9) averaged 202 (34) mg/dl.

ROOM AIR
While breathing room air, diabetics displayed reduced contrast sensitivity at 12 and 18 cpd compared with controls (Fig 1; p=0.003 at 12 cpd, p=0.006 at 18 cpd). Diabetic patients also demonstrated slowed arteriovenous passage time through the retina while breathing room air (Fig 6; p=0.0001).

HYPEROXIA
During the imposition of isocapnic hyperoxia, normal subjects showed no alterations in contrast sensitivity (Fig 2) while arteriovenous passage time was substantially slowed in these subjects (Fig 6; p=0.0001). In contrast,
Hyperoxia significantly improved contrast sensitivity in diabetic patients at 12 cpd (Fig 3; p=0.042), without substantially altering arteriovenous passage time (Fig 6). Further, the improvement in contrast sensitivity at 12 cpd in diabetic patients during hyperoxia eliminated the differences in contrast sensitivity between the two groups; no significant differences in contrast sensitivity were found between normals and diabetic patients in hyperoxia (Fig 4). Similarly, hyperoxia eliminated the differences between normals and diabetic patients in arteriovenous passage time seen during room air breathing (Fig 6).

The improvement in contrast sensitivity at 12 cpd with hyperoxia in diabetic patients was proportional to the initial decrement in contrast sensitivity (Fig 5; r = +0.84; p = 0.0008). Impairment was determined relative to the mean sensitivity at 12 cpd as measured in the present control group.

**Discussion**

In this study we confirmed that insulin dependent diabetic patients with minimal retinopathy exhibit both visual (reduced contrast sensitivity) and retinovascular (slowed arteriovenous dye passage) abnormalities. When hyperoxia was imposed upon these patients, contrast sensitivity significantly improved at 12 cpd to levels indistinguishable from normal, even as arteriovenous passage time was unchanged. This result in patients contrasts with that found in healthy people, in whom hyperoxia did not alter contrast sensitivity even as it substantially slowed arteriovenous passage time.

The retinal vascular and visual defects caused by diabetes have been hypothesised to result from either localised tissue hypoxia or from hyperglycaemic pseudohypoxia. According to the latter hypothesis, cytosolic NADH/NAD + ratios, elevated in true hypoxia, are also elevated when hyperglycaemia results in excess reduction of glucose to sorbitol (via aldose reductase) and the subsequent excessive oxidation of sorbitol to fructose. The resulting redox imbalance mimics that caused directly by low PO2. If either theory is correct, then delivering more oxygen to a hyperglycaemic tissue should correct either low tissue PO2 or the redox imbalance and improve tissue function.

We found both that hyperoxia improved mean contrast sensitivity in a group of diabetic patients, and that the improvement in sensitivity was proportional to the initial impairment. This result suggests that, at least in diabetic patients with minimal retinopathy, some aspects of diminished visual function remain acutely reversible. That these changes were seen at 12 cpd, and not more clearly, at 18 cpd, probably results from the smaller variance of repeated measures obtained at 12 cpd. The result also suggests that some factor linked to retinal tissue hypoxia (or pseudohypoxia) causes the contrast sensitivity decline seen early in the course of insulin dependent diabetes. Earlier studies using the pattern electroretinogram hypothesised that diabetes mellitus may affect the larger retinal ganglion cells most severely, although more generalised effects at every retinal neurosensory cell could not be ruled out. The mechanism linking diabetes to retinal neurosensory cell dysfunction is
arthrovenous passage time is only partly dependent on bulk retinal blood flow: many factors, both blood flow and non-blood flow dependent, affect its value. Consequently, the slower arthoovenous passage time exhibited by diabetic patients could be created entirely by variables independent of flow, such as tissue blood volume or vascular permeability.

When healthy tissue is perfused with blood with increased oxygen content, blood flow decreases to allow total oxygen delivery to remain constant. This response, seen in the healthy retina, probably slowed arthoovenous dye passage in hyperoxia in this study in healthy individuals. These hyperoxia induced changes in retinal haemodynamics in healthy eyes left contrast sensitivity unchanged. On the other hand, earlier work suggests that diabetes blunts or abolishes hyperoxia induced vasoconstriction in affected tissues: retinal blood flow diminishes less than normal, or not at all, in diabetic patients breathing 100% oxygen. Our finding that there was no change in retinal arthoovenous passage time in diabetic patients given 100% oxygen to breathe may indicate a blunted vasocostrictor or autoregulatory capacity in that tissue. However, as before, the indirect nature of the measurement makes it impossible to determine whether blood flow, or tissue oedema or permeability factors, are altered by hyperoxia in diabetes. What our data do indicate is that the haemodynamic response to an autoregulatory challenge is abnormal in diabetic patients with minimal retinopathy, providing further evidence that vascular abnormalities are present early in disease.

In conclusion, we have demonstrated reversibility (via 100% oxygen breathing) of the contrast sensitivity defects seen early in the course of diabetic retinopathy, and the association of these defects with retinal haemodynamic abnormalities. That an increase in arterial oxygen content can restore visual function in these people testifies both to the potential reversibility of early visual deficits in diabetes, and to the role of hypoxia (or hyperglycaemic pseudohypoxia) in their initiation. Supported by NIH grant EY 10180-01 and an unrestricted grant from Research to Prevent Blindness, Inc. AH is a recipient of the William and Mary Greave Award from Research to Prevent Blindness.

Hyperoxia improves contrast sensitivity in early diabetic retinopathy


