Rebreathing into a bag increases human retinal macular blood velocity

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Abstract

Aims—The effect of rebreathing into a bag (RB) on retinal macular blood velocity was evaluated in healthy volunteers.

Methods—Ten normal volunteers, whose ages ranged from 17 to 34 years, performed RB over 135 to 260 seconds (mean (SD) 193 (38) seconds) while retinal macular blood velocity was determined non-invasively using the blue field simulation technique.

Results—Leucocyte velocity significantly increased (p<0·05) at 2 minutes and at the end of RB by 53% (42%) and 92% (65%), respectively (95% confidence interval of the mean (CIM)). All subjects observed an increase in the density of leucocytes. At the end of RB, mean systolic brachial arterial pressure and heart rate were significantly increased by 24% (11%) and 37% (15%) respectively (p<0·01). At 2 minutes, end tidal oxygen concentration in the exhaled air was 47% (8%) (95% CIM) below and carbon dioxide was 41% (16%) above baseline (p<0·001). The RB produces a large increase in macular leucocyte velocity, suggesting an increase in blood flow.

Conclusion—Although RB has some systemic risk due to hypoxia and hypercapnia, RB for a short period of 1 or 2 minutes might be of help in the treatment of retinal arterial obstructive diseases in young patients without cardiovascular disorders if other treatments do not show any beneficial effects.

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Retinal arterial occlusion (RAO) or ophthalmic artery obstructive disease usually results in severe visual loss and treatment is seldom beneficial. A procedure that would induce a dilatation of retinal vessels and an increase in retinal blood flow could perhaps move a fresh embolism downstream into a smaller arteriole and thus decrease the extent of the ischaemic lesion. Reports in the literature have shown evidence that emboli can move downstream into smaller vessels or can completely disappear in the course of RAO.[1] [2]

The simple task of rebreathing into a bag (RB) produces both hypercapnia, which is known to increase retinal blood flow,[3] [4] and hypoxia, which causes vasodilatation.[5] In addition, both hypercapnia and hypoxia can also increase cardiac output and raise systemic arterial blood pressure,[6] which, in turn, increase ocular perfusion pressure.

The RB procedure has been applied to treat hyperventilation syndrome.[7–9] The efficacy of this method for the treatment of RAO or amaurosis fugax,[10] however, has not yet been demonstrated in animal or clinical studies.[11] As a first step, the aim of this study was to evaluate, non-invasively, the effect of RB on retinal macular blood velocity in healthy volunteers using the blue field simulation technique.

Materials and methods

Ten healthy non-smoking volunteers (10 eyes) with a normal ophthalmic examination, except for mild refractive error, participated in this study. Their ages ranged from 17 to 34 (mean 25·8 (SD 6·3) years). All were naive with regard to retinal and respiratory physiology as well as the blue field simulation technique (BFS)[12] and rebreathing procedure. Subjects refrained from caffeine consumption for at least 5 hours before the experiment since caffeine has some effect on the human macular circulation.[13] This research followed the tenets of the declaration of Helsinki. Informed consent was obtained after the nature, possible consequences, and risks of this study were fully explained.

Retinal macular blood velocity was measured using the BFS technique,[12] which allows the determination of leucocyte velocity (Vleuco) in the macular capillaries. In this technique, subjects can adjust the velocity and density of simulated leucocytes displayed on a computer monitor to match those of their own entoptically observed leucocytes.

In the macular microcirculation, where capillaries are 7–10 μm in diameter, the Vleuco is equal (within a few per cent) to the mean velocity of whole blood.[14] This velocity can be assumed to represent flow because
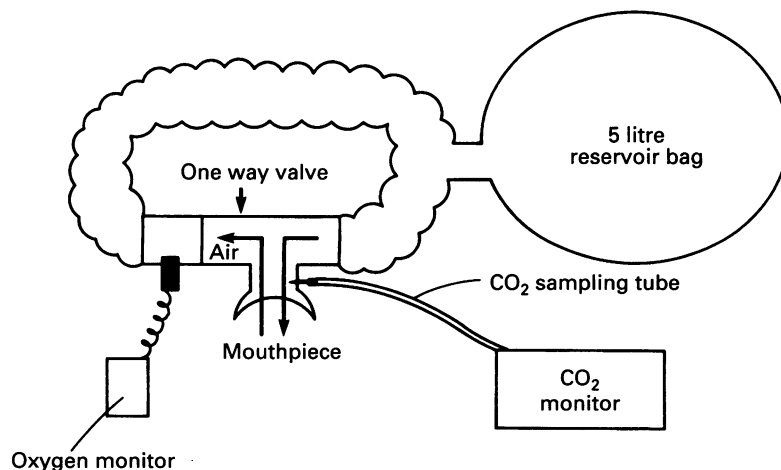
Figure 1 Schematic diagram of the rebreathing system. Total volume=5660 ml.

One way valve

Air

Mouthpiece

5 litre reservoir bag

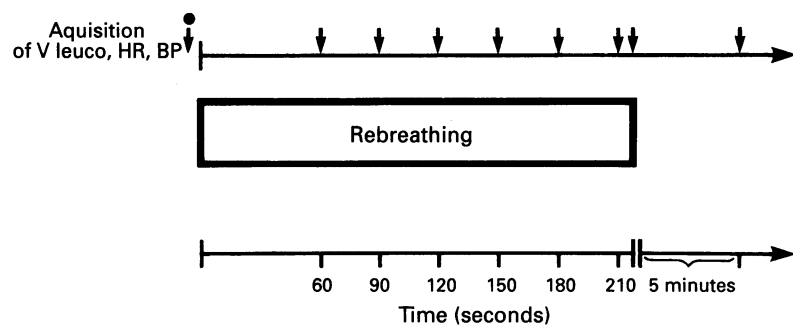CO_2 sampling tube

CO_2 monitor

Oxygen monitor

Figure 2 Time sequence of measurements of heart rate (HR), systemic blood pressure (BP), and macular leucocyte velocity (Vleuco) during rebreathing (RB). (●) =Baseline.

these capillaries probably have a constant diameter.[15-17]

EXPERIMENTAL PROCEDURE

For RB, a closed system with a 5 litre reservoir bag was used (Fig 1). The total volume in this system was 5660 ml. End tidal carbon dioxide and oxygen levels in exhaled air were measured continuously using a carbon dioxide monitor (Datex 223) and oxygen monitor (Cole-Palmer 095506). During the experiment, the brachial arterial pressure was measured at 30 second intervals with a standard digital sphygmomanometer cuff. The heart rate was monitored continuously by an earlobe transducer. Breathing rate was determined from end tidal carbon dioxide tension in the exhaled air.

The blue field entoptic phenomenon and the computer simulation were viewed alternately with the dominant eye. Firstly, subjects practised five matching trials comparing two simulated fields. Then, a practice session of 10
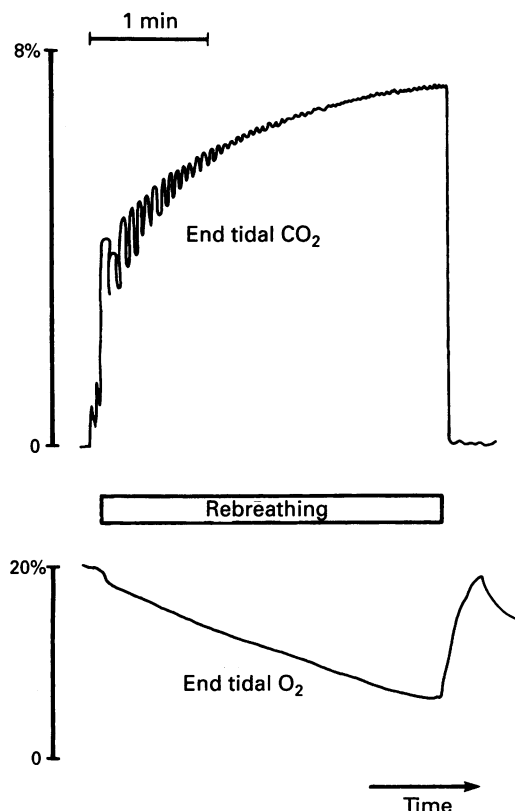
matching trials comparing the blue field entopic phenomenon to the computer simulation was conducted in each subject. The coefficient of intrasubject Vleuco variability was mean 19·0% (SD 7·5%) (range 9–31%) for these trials.

A practice session of RB was also performed to familiarise subjects with the actual experimental procedure of rebreathing. Volunteers were asked to maintain RB for as long as possible. Baseline measurements of leucocyte velocity as well as density and pulsatility were obtained by one matching trial before actual RB. To facilitate the measurement procedure during RB, only the velocity of the simulated particles was adjusted while density and pulsatility of leucocytes were kept constant at baseline values. Data were acquired every 30 seconds starting at 1 minute after the beginning of RB, at the end of RB, and at 5 minutes after the end of RB (Fig 2).

Percentage increases in Vleuco at 2 minutes of RB and at the end of RB were calculated and averaged. Statistical analysis (paired t test) was performed with the results obtained at baseline, at 2 minutes of RB, and at the end of RB.

Results

Typical end tidal carbon dioxide and oxygen concentrations during RB are shown in Figure 3. RB was performed for 135 to 260 seconds (mean 193 (SD 38) seconds). During RB, subjects experienced some suffocation and tiredness. Two of them had a light headache for a few hours. There were no serious complications.

For each subject, the Vleuco over the course of RB is plotted in Figure 4. Percentage change in Vleuco, systemic blood pressure, heart rate, and end tidal carbon dioxide and oxygen concentration are summarised in Table 1. The Vleuco increased significantly above baseline at 2 minutes and at the end of RB by 53% (42%) and 92% (65%) (95% CIM), respectively. These increases were statistically significant ($p=0·018$ and $0·019$, respectively). Nine out of 10 subjects observed an increase in Vleuco during RB; only one subject who had a very high velocity at baseline showed a decrease in Vleuco. All subjects reported a subjective increase in the density of leucocytes within the field of observation after approximately 1 minute of RB. This increase was not measured quantitatively during the experiment. Following the end of RB, Vleuco returned towards baseline and at 5 minutes Vleuco was higher by 15% (24%) (95% CIM, $n=9$). This difference from baseline, however, was not statistically significant.

There was no significant correlation between the percentage changes in Vleuco and the end tidal carbon dioxide or oxygen levels both at 2 minutes and at the end point. Moreover, no significant correlation was found between Vleuco and the duration of RB.

Figure 3 Typical end tidal carbon dioxide and oxygen responses during rebreathing.
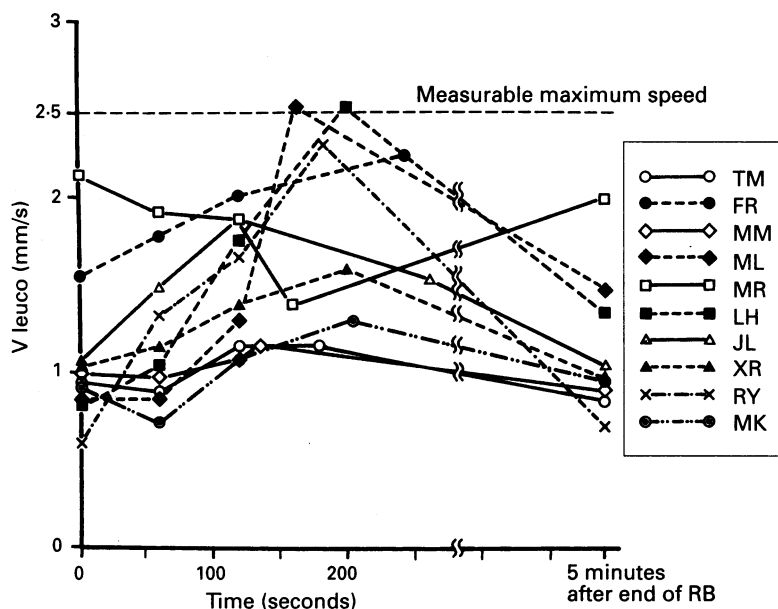
Discussion

Nine out of 10 volunteers demonstrated an

Figure 4 Macular leucocyte velocity, Vleuco at 2 minutes, end of rebreathing (RB), and 5 minutes after the end of RB for each of the 10 subjects.

increase in Vleuco. For the group, there was a significant average increase of 53% at 2 minutes and an even larger average increase of 92% at the end of RB.

The rather small variability in end tidal oxygen concentration at the end of RB suggests that a decrease in end tidal oxygen of approximately 64% (4%) (95% CIM) is the factor that forces a subject to terminate the experiment. This is confirmed by previous studies showing that during breath holding attempts the drop in partial pressure of oxygen in terminating the procedure is more important than the rise in partial pressure of carbon dioxide.[18]

The large variability in the increase in Vleuco cannot be explained by the variability of the systemic response,[14] as measured by the end tidal carbon dioxide and oxygen concentration, since there were no significant correlations between Vleuco and those variables. Tsacopoulos[3] showed that mean retinal circulation time, measured by fluorescein angiogram and densitometry, decreased significantly with increases in arterial partial pressure of carbon dioxide. Therefore, the variability in the response in Vleuco could be due to the variability of arterial carbon dioxide among individuals.

Many studies have been performed to investigate the change in retinal haemodynamics under the conditions of either hypoxia, hypercapnia, or both.[3 19–22] Using BFS and measurement of retinal vessel diameter, Fallon *et al*[19] reported a 36% increase in macular blood flow at 10 to 12 minutes of isocapnic hypoxia (10·5% oxygen

breathing). Sponsel *et al*,[22] using the same BFS technique, found a 23% increase in Vleuco during the breathing mixture of 16% oxygen, 5% carbon dioxide, and 79% nitrogen, a mixture that is similar to that occurring during RB. Some of the differences between our study and those mentioned above could be due to the fact that a closed rebreathing system produces continuous alterations in concentrations of inhaled gas, whereas in the other study the concentrations of the gases used were kept constant throughout the experiment. The continuous alterations in exhaled gas produced in the present study showed a larger effect on Vleuco than the constant one. Moreover, this large increase in Vleuco is not surprising since RB produces a large drop to 7% in oxygen level and to 8% in carbon dioxide in exhaled air at the end of RB. Even at 2 minutes of RB, end tidal oxygen concentration was 5–9% and carbon dioxide was 6·4–8·6%. The end tidal carbon dioxide concentration can be considered to be close to the concentration in arterial blood since the lungs and the reservoir bag constitute a closed system.[23]

The RB procedure has the inherent disadvantage that for a short period of time there is a decrease in inspired oxygen which could be harmful to the ischaemic retina. This hypoxia, however, is very short lived and if it results in the dislodging of an embolus, it would provide an obvious advantage outweighing transient hypoxia.

Complete vascular occlusion causes severe ischaemia accompanied by the release of chemical mediators such as adenosine which produces marked vessel dilatation.[24–26] It is possible that under conditions of long standing complete retinal artery occlusion RB may not result in any further dilatation. Thus, RB may be beneficial only if administered quickly.

A different situation in which RB may be more useful could be in cases of amaurosis fugax which is thought to be caused by partial occlusion, spasms of the ophthalmic artery or emboli of a vessel. RB, which within 2 minutes produced a significant increase in Vleuco, could help dislodge the emboli and reopen the partially occluded vessels.

The current study shows that 2 minutes of RB results in a significant increase in Vleuco in young normal subjects. The long term goal of our efforts is to determine the efficacy of RB in preventing permanent visual loss following amaurosis fugax and impending RAO. This condition usually occurs in older people with risk factors such as atherosclerosis, hypertension, and cardiovascular disorder.[27] Hypercapnia and hypoxia produced by RB could produce some systemic risk.[28] Further studies need to be carefully done in these types of patients to assess the overall clinical usefulness of RB. It has been reported, however, that either branch or complete RAO can occur in relatively young patients in the third or fourth decade although this is rare.[10 29–32] The RB may be applicable for the treatment in an acute stage of such a devastating disease only in those young patients who are proved not to have systemic cardiovascular problems.

Table 1 Percentage change (SD) in leucocyte velocity in the macular capillaries (Vleuco), systemic blood pressure (BP), heart rate (HR), and end tidal O_2 and CO_2 concentration

	Vleuco	BP	HR	O_2	CO_2
2 Minutes of RB	53 (42)*	17 (12)**	23 (18)**	46·6 (10·5)***	38·6 (19·2)***
End of RB	92 (65)*	26 (13)**	37 (20)**	63·6 (6·1)***	51·2 (26·0)***

Numbers are expressed as 95% confidence interval of the mean.
RB=rebreathing procedure.
*p<0·05; **p<0·01; ***p<0·001.

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