available at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres

BRAIN RESEARCH

Research Report

Carbogen inhalation increases oxygen transport to hypoperfused brain tissue in patients with occlusive carotid artery disease: Increased oxygen transport to hypoperfused brain

Mahmoud Ashkanian[a,*], *Albert Gjedde*[a,b], *Kim Mouridsen*[a], *Manouchehr Vafaee*[b], *Kim Vang Hansen*[b], *Leif Østergaard*[a], *Grethe Andersen*[c]

[a]*Center of Functionally Integrative Neuroscience (CFIN), Aarhus University Hospital, Norrebrogade 44, Bygn. 30, 8000 Aarhus C, Denmark*
[b]*PET Center, Aarhus University Hospital, Denmark*
[c]*Department of Neurology, Aarhus University Hospital, Denmark*

ARTICLE INFO

Article history:
Accepted 18 September 2009
Available online 25 September 2009

Keywords:
Carbogen
Oxygen
Cerebral hypoperfusion
Internal carotid artery disease
CBF
PET

ABSTRACT

Hyperoxic therapy for cerebral ischemia reduces cerebral blood flow (CBF) principally from the vasoconstrictive effect of oxygen on cerebral arterioles. Based on a recent study in normal volunteers, we now claim that the vasodilatory effect of carbon dioxide predominates when 5% CO_2 is added to inhaled oxygen (the mixture known as carbogen). In the present study, we measured CBF by positron emission tomography (PET) during inhalation of test gases (O_2, carbogen, and atmospheric air) in healthy volunteers ($n=10$) and in patients with occlusive carotid artery disease ($n=6$). Statistical comparisons by an additive ANOVA model showed that carbogen significantly increased CBF by 7.51±1.62 ml/100 g/min while oxygen tended to reduce it by –3.22±1.62 ml/100 g/min. A separate analysis of the hemisphere contralateral to the hypoperfused hemisphere showed that carbogen significantly increased CBF by 8.90±2.81 ml/100 g/min whereas oxygen inhalation produced no reliable change in CBF (–1.15±2.81 ml/100 g/min). In both patients and controls, carbogen was as efficient as oxygen in increasing Sa_{O2} or PaO_2 values. The study demonstrates that concomitant increases of CBF and Sa_{O2} are readily obtained with carbogen, while oxygen increases only Sa_{O2}. Thus, carbogen improves oxygen transport to brain tissue more efficiently than oxygen alone. Further studies with more subjects are, however, needed to investigate the applicability of carbogen for long-term inhalation and to assess its therapeutic benefits in acute stroke patients.

1. Introduction

Hyperoxic therapy (>21% oxygen) is widely used in medical practice, such as short-term administration in emergency medicine and chronic treatment of obstructive pulmonary disease. Trials have tested the applicability of normobaric (Flynn and Auer, 2002; Singhal et al., 2002; Kim et al., 2005; Singhal, 2007; Flynn and Auer, 2002) and hyperbaric (Schabitz

* *Corresponding author*. Fax: +0045 8949 4400.
E-mail address: mahmoud@pet.auh.dk (M. Ashkanian).

0006-8993/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.brainres.2009.09.076

et al., 2004; Lou et al., 2004; Badr et al., 2001) oxygen therapy in salvaging ischemic brain tissue. Conflicting results reported by these studies have, however, called into question the efficacy of oxygen treatment in patients with cerebral ischemia. Importantly, some studies have shown that pure oxygen inhalation lowers cerebral blood flow (CBF) (Rostrup et al., 1995; Watson et al., 2000).

Tissue oxygenation depends not only on the oxygen content of the blood (Sa_{O2}) but also on blood flow to the tissue. Previous studies have shown that the gas mixture of 5% CO_2 and 95% O_2 (i.e., carbogen) raises blood flow to normal brain tissue (Macey et al., 2007) and tumors (Kaanders et al., 1998; Siemann, 1998). Recently, we showed that carbogen differs from oxygen by causing concomitant improvement of CBF and Sa_{O2} in healthy adults (Ashkanian et al., 2008). The purpose of the present study was to determine whether carbogen improves tissue oxygenation also in hemodynamically impaired brain tissue. CBF of normal gray matter (GM) is approximately 60 ml/100 g/min. Whereas ischemia refers to a restriction in blood supply with resultant neuronal damage or dysfunction, hypoperfusion is used in the literature as a general term covering a wide spectrum of graded reduction of CBF. The most sensitive early sign of hypoperfusion is protein synthesis, which is inhibited by 50% at cortical CBF around 55 ml/100 g/min, corresponding to a CBF reduction by 8%. In our study, tissue hypoperfusion is defined as CBF at least 10% below the average baseline CBF for GM in the control group. Protein synthesis is completely suppressed at blood flows below 35 ml/100 g/min. At lower flow rates, glucose utilization transiently increases before it sharply declines at CBF below 25 ml/100 g/min (Hossmann, 2006). Here, we use positron emission tomography (PET) to measure CBF changes and Sa_{O2} levels in patients with occlusive carotid artery disease as well as in control subjects during inhalation of three different gases, namely, carbogen, oxygen, and atmospheric air (baseline).

2. Results

As expected, inhalation of oxygen caused CBF in GM to decline in patients as well as control subjects, while inhalation of carbogen caused CBF to increase from baseline. Fig. 1 illustrates the CBF changes that occurred in both hemispheres (ipsilateral and contralateral to the hypoperfused side) in response to each of the three different gases in one patient compared to average changes in the control group (n= 10).

Average CBF values of the hypoperfused regions (patients) are shown in Fig. 2, with the average CBF values of the healthy controls shown for comparison. No significant interactions were found between group and condition (P=0.25), implying similar effects of oxygen and carbogen in the two groups. Comparisons in the additive ANOVA model showed that carbogen significantly increased CBF (7.51±1.62 ml/100 g/min; P<0.01), while CBF tended to decline following oxygen inhalation (–3.22±1.62 ml/100 g/min; P= 0.06).

We found that carbogen raised average CBF in all patients relative to baseline, whereas oxygen caused CBF to decrease in 4 of 6 patients. In the control group, carbogen increased CBF in 9 of 10 subjects, whereas oxygen decreased CBF in 9 of 10 of them.

Separate analysis of the hemisphere contralateral to the hypoperfused hemisphere showed that CBF rose by 8.90± 2.81 ml/100 g/min (P= 0.01) in the carbogen condition compared to no reliable change in the oxygen condition (–1.15± 2.81 ml/100 g/min). As with the ipsilateral hemisphere, carbogen increased average CBF in all cases relative to baseline, while oxygen caused CBF to decrease in 4 of 6 cases.

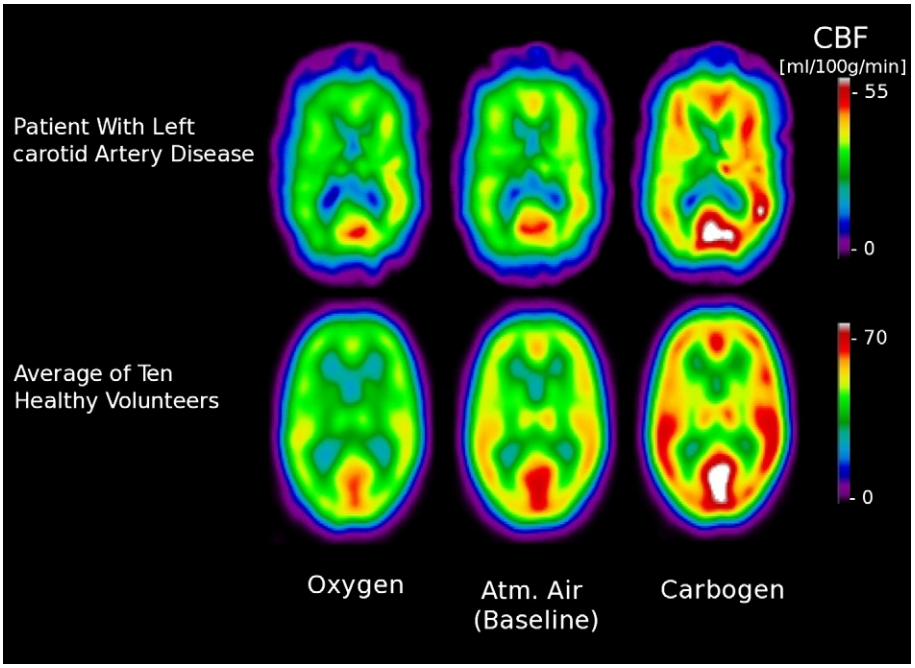

Fig. 1 – CBF changes in one patient with occlusive carotid artery disease compared to averaged CBF changes in ten healthy controls.