A New System to Supply Carbon Dioxide Safely to Glaucoma Patients

Yoshiaki Niwa,* Alon Harris,† Larry Kagemann,† Tetsuya Yamamoto,* Masayuki Matsubara,* Daisuke Takahashi* and Yoshiaki Kitazawa*

*Department of Ophthalmology, Gifu University School of Medicine, Gifu, Japan; †Departments of Ophthalmology, and Physiology and Biophysics, Indiana University School of Medicine, Indianapolis, IN, USA

Purpose: To develop a new system for safely supplying carbon dioxide (CO₂) to open-angle glaucoma patients.

Methods: The orbital hemodynamics of 7 glaucoma patients were determined by color Doppler imaging under baseline conditions and during CO₂ supplementation sufficient to increase the end-tidal CO₂ partial pressure by 10%. Systemic conditions, including oxygen saturation and blood pressure, were monitored throughout the CO₂ inhalation.

Results: Our results demonstrate that this new system enables us to supply CO₂ in a safe, controlled manner to glaucoma patients.

Conclusions: This new system will be useful for investigating the effects of vasodilation by CO₂ on orbital blood flow.


Key Words: Carbon dioxide, glaucoma, color Doppler imaging.

Introduction

The pathogenesis of glaucomatous optic neuropathy remains unknown. Although increased intraocular pressure is an evident risk factor, glaucomatous optic nerve damage can develop even with only a minimal increase in the intraocular pressure, suggesting that factors other than intraocular pressure may be involved in the development of glaucoma.† Recently, interest has increased in a possible vascular etiology for the glaucomatous changes. In glaucoma patients, evidence supporting a vascular mechanism can be found in the occurrence of optic disc hemorrhage, fluorescein angiographic findings, pulsatile ocular blood flow measurements, digital blood flow measurements, the associations with migraine or immune-related diseases, and nocturnal blood pressure drops in ambulatory blood pressure monitoring.2–8

Assuming a vascular pathogenesis for glaucomatous optic neuropathy, several researchers have advocated the improvement of optic nerve head circulation in addition to the reduction of intraocular pressure as treatment for open-angle glaucoma.9–12 To effect vasodilation in the optic nerve head, breathing carbon dioxide (CO₂) has been tried.6,13 It has been shown that CO₂ affects each part of the central nervous system differently.6,13

We have developed a new system of supplying CO₂ safely to glaucoma patients in order to investigate the effect of vasodilation by CO₂ on orbital blood flow. We report on this new system.

Materials and Methods

Outline of New System to Supply CO₂

The system to supply CO₂ and to monitor the patient is shown in Figures 1 and 2. The patient is kept supine and his pulse rate (PR) and blood pressure (BP) are monitored with an automatic apparatus (Omron HEM-705 CP, Matsuzaka). The nostrils are closed with a nose piece, and a low resistance mouthpiece with a T-style valve is applied (Figure 3). The
end-tidal pressure of CO$_2$ (PCO$_2$ expressed as a percentage), and the respiratory rate are monitored by a combined rapid-response gas analyzer and pulse oximeter (Poette Plus®, Criticare Systems, Waukesha, WI, USA) that samples gas from the mouthpiece. In addition, the device monitors oxygen saturation (SpO$_2$%) and PR. A physician other than the color Doppler imaging (CDI) examiner manages the patient’s systemic condition during the testing.

PCO$_2$ is manually increased by approximately 10% by adding 100% CO$_2$ to the inspired air. The oxygen saturation level is maintained throughout the CO$_2$ inhalation. Before CO$_2$ inhalation, patients are instructed to gesture when an examiner questions them to confirm safety.

**Evaluation of Safety of System**

Of the 7 patients, 5 had normal-tension glaucoma and 2 had primary open-angle glaucoma. None had any cardiovascular or respiratory disease. The patient ages ranged from 32–80 years, averaging $60.9 \pm 16.4$ years. Three were men and 4 were women (Table 1).

Each patient had been resting for 10 minutes when his PR and BP were first measured. End-tidal CO$_2$% was recorded on each breath for 3 minutes. Then the baseline CDI measurements of the ophthalmic artery (OA) and the central retinal artery (CRA) were taken. Once the baseline conditions had been established, CO$_2$ was supplied slowly to increase the end-tidal CO$_2$% by 10% under careful monitoring by the physician. After CO$_2$ had been supplied for 10 minutes, the PR and BP were measured again and end-tidal CO$_2$% was recorded on each breath for 3 minutes. Then CDI was performed on the OA and the CRA under the increased PCO$_2$ condition. When all measurements were completed, the CO$_2$ supply was terminated and the end-tidal CO$_2$% was monitored until it returned to the baseline value.

Statistical analysis was done using Wilcoxon’s signed rank sum test to compare CDI parameters at the baseline and during the CO$_2$ supply.

The study protocol was approved by the Ethical Review Committee of Gifu University, and informed written consent was obtained from each patient.

**Results**

Carbon dioxide inhalation did not change the patient’s SpO$_2$%, which remained between 98 and 99%. The fluctuation of the end-tidal CO$_2$% was approximately 5%, and end-tidal CO$_2$% returned to the baseline level approximately 30 seconds after the CO$_2$ supply was terminated. Carbon dioxide inhalation did not change PR and BP significantly. No patient complained of discomfort or shortness of breath during the CO$_2$ inhalation.
Discussion

We have developed a new system of supplying CO₂ to glaucoma patients to investigate the vasodilatory effect of this gas on orbital blood flow. The system enables us to supply CO₂ safely because it provides close monitoring of the end-tidal CO₂% and delivers sufficient oxygen. Although the number of cases in this preliminary report was small, all patients tolerated the intervention well.

Physicians who support the theory of a vascular etiology in glaucoma prescribe vasoactive agents, such as calcium channel blockers, these agents are reported to have a favorable effect on the glaucomatous visual field. Recently, CO₂ inhalation has been suggested as a new glaucoma treatment, to vasodilate the vessels in the optic nerve head. Our system facilities this treatment, as we were successful in keeping the PCO₂ level within a narrow, safe range by supplying the minimum volume of CO₂ necessary and by closely monitoring the end-tidal CO₂%. In a previous study, the effects of a predetermined concentration of CO₂ were investigated. Maintaining CO₂ at a fixed level can create problems because the same concentration of CO₂ can alter PCO₂ levels differently in different individuals. We successfully increased and maintained the CO₂ level approximately 10% higher than the determined baseline end-tidal CO₂%, so that we could study the effect of breathing CO₂ under a uniformly increased PCO₂ condition.

In vitro studies in the 1930s confirmed that CO₂ produces cerebral vasodilation. In 1948, Kety and Schmidt demonstrated by the nitrous oxide method that CO₂ inhalation increased cerebral blood flow. Now it is known that increased arterial PCO₂ causes the change in cerebral blood flow. Carbon dioxide does not directly affect the cerebral vessels, but accelerates the cerebral blood flow by lowering the extracellular fluid pH of the brain. Patterson et al. investigated the cerebral blood flow of normal volunteers and reported that inhalation of 2.5% CO₂ did not increase cerebral blood flow, but that 3.5% CO₂ inhalation increased it by approximately 10%. They speculated that PCO₂ had a threshold above which CO₂ increased cerebral blood flow.

In conclusion, the new system enables us to supply CO₂ to glaucoma patients in a safe and controlled manner. A prospective study is ongoing in an attempt to determine the response of orbital blood vessels to CO₂ inhalation in normal tension glaucoma patients and the results will be reported shortly.

References


Table 1. Background of Subjects

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Systemic Disease</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>67</td>
<td>—</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>Female</td>
<td>34</td>
<td>—</td>
<td>1% carteolol hydrochoride, b.i.d. (OU)</td>
</tr>
<tr>
<td>3</td>
<td>Female</td>
<td>62</td>
<td>—</td>
<td>Brovincamine fumarate, 20 mg, t.i.d.</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>46</td>
<td>—</td>
<td>Nilvadipine, 2 mg, b.i.d.</td>
</tr>
<tr>
<td>5</td>
<td>Female</td>
<td>67</td>
<td>—</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>Female</td>
<td>85</td>
<td>DM</td>
<td>Nilvadipine, 2 mg, b.i.d.</td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>65</td>
<td>DM</td>
<td>0.5% betaxolol hydrochoride, b.i.d. (OU)</td>
</tr>
</tbody>
</table>

DM: diabetes mellitus; OU: Oculus uterque (both eyes).


