*Acta Oncologica* Vol. 33, No. 7, pp. 807–811, 1994

# CARBOGEN BREATHING IN PATIENTS WITH GLIOBLASTOMA MULTIFORME SUBMITTED TO RADIOTHERAPY

## Assessment of gas exchange parameters

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**It has been reported that carbogen breathing yields a remarkable increase of radiosensitivity in murine tumour models. Hence, application of carbogen might be promising in radiotherapy of human tumours. We describe a method to increase arterial oxygenation and to ensure stability of $O_2$ and $CO_2$ during carbogen breathing in patients with malignant disease. We measured in 6 patients with histologically proven intracranial glioblastoma multiforme arterial blood gases, inspired and expired gas concentrations and vital signs either baseline and during carbogen breathing. The highest values of arterial oxygenation were achieved after 10 min of carbogen breathing and they remained stable up to 15 min. In none of our patients was $N_2$ wash-out from the lungs completed in 15 min of carbogen breathing. In conclusion, carbogen breathing increased arterial oxygenation in patients with intracranial malignant diseases. The system used is reliable and of practical use. Monitoring of expired gas concentrations is highly recommended.**

It has been shown that the degree of response to radiotherapy in metastases of the head and neck region is significantly correlated to the levels of oxygenation within these tumours in humans (1). More recently, it has been reported that the combination of relevant dose–fractionation regimens with both carbogen (a gas mixture of 95% $O_2$ and 5% $CO_2$) and 100% oxygen breathing yields a remarkable increase in radiosensitivity in murine tumour models (2). Moreover, the evidence that a combination of carbogen breathing and nicotinamide further increases radiosensitivity in animal tumours has prompted renewed interest in carbogen breathing for clinical application (3).

Received 1 June 1993.
Accepted 17 April 1994.
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Short reports on the effect of carbogen breathing on oxygenation in man have been recently published (2, 4). In one of these studies (2) the effect of carbogen breathing was evaluated by observing the changes in the saturation of oxyhemoglobin in the limb using near-infrared spectroscopy and/or measuring $pO_2$ in venous blood in five normal volunteers. In another study (4) the effect of carbogen breathing was evaluated in three healthy volunteers by measuring the $O_2$ tension in arterial blood samples obtained from the femoral artery before and after 5 min of carbogen breathing.

Given that the rationale of using carbogen breathing is to elevate arterial $pO_2$ and thereby oxygenation of tumour to increase its radiosensitivity, the crucial point is to assess the highest achievable level of arterial $pO_2$ and to maintain this level for the time required to complete the established dose–fractionation regimen of radiotherapy. For such a purpose, the stability of the gas mixture breathed and of the respiratory and cardiovascular parameters during carbogen breathing play an important role. However, data concerning the behaviour of these parameters during car-

 ISSN 0284-186X

bogen breathing in patients with malignant diseases have not been reported so far.

The aim of the present study was two-fold:

a) to describe a method ensuring the stability of $O_2$ and $CO_2$ levels in the gas breathing mixture to reach the highest achievable $pO_2$ level;

b) to assess the stability of the vital signs in the patients breathing carbogen for the time required to complete radiotherapy.

Data reported here refer to the preliminary phase of our study protocol aimed to evaluate the clinical results of radiotherapy with twice fractionation schedule combined with carbogen breathing and nicotinamide in patients with histologically proven 'glioblastoma multiforme'. This preliminary phase deals with the method used to give an adequate concentration of gas mixture and to evaluate its cardio-pulmonary effects in patients.

## Material and Methods

We studied 6 patients (Table 1) who gave their informed consent to the study. Each patient underwent chest x-ray and electrocardiogram to exclude prior cardio-pulmonary disease. After local anesthesia, in all patients but one (F.A.) a cannula was inserted in the brachial artery to obtain arterial blood samples. Given that in a normal subject breathing 100% oxygen the alveolar nitrogen will normally be reduced to less than 2.5% after 7 min and that the rise of oxygen concentration may be delayed by the ventilation-perfusion maldistribution (5), we decided to take arterial blood samples before and after 10 and 15 min during carbogen breathing. Due to technical problems, in patient F.A. an arterial blood sample was only obtained through direct puncture of the brachial artery at 15 min of carbogen breathing (Table 2). In two patients (B.R. and M.E. (Table 2)) an arterial sample was also obtained at 5 min of carbogen breathing to check the accuracy of gas mixture administration.

Before starting the procedure, samples of gas mixture coming from the tank provided by the company were analyzed by means of mass spectrometer (Air Spec 2000 Chest, U.K.) to check the concentration of $O_2$ and $CO_2$ to be administered. These samples were obtained from the tank placed both in the vertical and horizontal positions after adequate shaking. Despite certification provided by the company, the $CO_2$ percentage found in the tank at mass spectrometer ranged between 3 and 11% instead of the 5% requested. Hence, to administer the right concentration of gas mixture (95% $O_2$ and 5% $CO_2$) we used a gas mixing device (KM 100-3 M Sol, Italy) connected to two separate tanks containing 100% $O_2$ and 10% $CO_2$ respectively. The mixing device was located in the treatment room, while the tanks equipped with their proper gas lines outside the room. The inspiratory gas mixture composition was checked with a gas spectometer before starting the procedure. Each patient was then connected to the properly humidified inhalation system through a mouthpiece equipped with a two-way low dead space non rebreathing valve (Hans-Rudolph). A nose clip was also employed to avoid accidental air inhalation during carbogen administration. In all patients pH, $paO_2$, $paCO_2$ were measured as well as oxygen saturation using IL 1231 and CODX 238 (Instrumentation Laboratory, U.S.A.) respectively. Expiratory gas concentrations before and during carbogen breathing were also monitored in all patients (Table 3) as well as breathing rate, tidal volume, minute ventilation, blood pressure and heart rate (Table 4).

**Table 1**

*Patients characteristics*

| Age (years) | Name | Sex | Karnofsky index | Site of tumour |
|---|---|---|---|---|
| 24 | B.R. | Female | 90 | Left parietal lobe |
| 64 | M.E. | Male | 90 | Right frontal lobe |
| 53 | F.A. | Male | 90 | Right temporal lobe |
| 56 | F.E. | Male | 90 | Left parietal lobe |
| 63 | C.E. | Female | 90 | Right frontal lobe |
| 70 | S.I. | Female | 80 | Left parietal lobe |

**Table 2**

*Gas exchange parameters before (basal) and during carbogen breathing*

| Name | Time min | pH | $paO_2$ mmHg | $paCO_2$ mmHg | Sat. % |
|---|---|---|---|---|---|
| B.R.* | Basal | 7.417 | 94 | 37.1 | 95.5 |
| | 5 | 7.406 | 467 | 37.3 | 97.6 |
| | 10 | 7.416 | 448 | 36.0 | 97.7 |
| | 15 | 7.417 | 441 | 35.9 | 97.7 |
| M.E.* | Basal | 7.442 | 79 | 35.0 | 96.0 |
| | 5 | 7.416 | 442 | 37.0 | 98.3 |
| | 10 | 7.422 | 483 | 36.4 | 99.0 |
| | 15 | 7.433 | 476 | 34.8 | 99.0 |
| F.A. | Basal | – | – | – | – |
| | 10 | – | – | – | – |
| | 15 | 7.407 | 469 | 36.2 | 98.6 |
| F.E. | Basal | 7.410 | 92 | 34.5 | 97.0 |
| | 10 | 7.415 | 416 | 36.7 | 99.0 |
| | 15 | 7.417 | 420 | 36.9 | 99.0 |
| C.E. | Basal | 7.584 | 122 | 24.8 | 97.0 |
| | 10 | 7.490 | 407 | 31.6 | 98.0 |
| | 15 | 7.471 | 418 | 33.4 | 98.2 |
| S.I. | Basal | 7.444 | 114 | 30.5 | 96.3 |
| | 10 | 7.439 | 375 | 31.4 | 97.2 |
| | 15 | 7.448 | 409 | 30.1 | 97.7 |

* Arterial blood samples were also obtained at 5 min (see text).

**Table 3**

*Values of expiratory gas concentrations (FE) before (basal) and during carbogen breathing*

| Name | Time min | $FEO_2$ % | $FECO_2$ % | $FEN_2$ % |
|---|---|---|---|---|
| B.R. | Basal | 17.4 | 3.3 | 79.0 |
| | 10 | – | – | – |
| | 15 | 87.4 | 8.4 | 3.5 |
| M.E. | Basal | 17.8 | 2.9 | 78.3 |
| | 10 | 85.4 | 8.3 | 5.6 |
| | 15 | – | – | – |
| F.A. | Basal | 17.4 | 3.0 | 78.7 |
| | 10 | 84.3 | 7.7 | 7.1 |
| | 15 | – | – | – |
| F.E. | Basal | 17.6 | 3.3 | 78.3 |
| | 10 | – | – | – |
| | 15 | 84.5 | 5.8 | 9.55 |
| C.E. | Basal | 17.3 | 2.1 | 80.1 |
| | 10 | 87.6 | 6.7 | 4.9 |
| | 15 | – | – | – |
| S.I. | Basal | 17.8 | 2.8 | 78.6 |
| | 10 | 86.9 | 5.3 | 7.3 |
| | 15 | 82.7 | 4.7 | 12.0 |

## Results

Changes of baseline arterial blood gas values in patients breathing carbogen are reported in Table 2. Baseline values were normal in 5 patients except one (C.E.) in whom baseline hyperventilation (VE 12.6 l/min, Table 4) accounts for a marked increase of both pH and $paO_2$ as well as for a marked reduction of $paCO_2$ baseline values. In one patient (F.A.) in whom cannulation of brachial artery was unsuccessful, an arterial blood sample was obtained only at 15 min of carbogen breathing through direct puncture of brachial artery. In 5 patients $paO_2$ values at 10 min of carbogen breathing were lower than those expected in normal subject breathing 100% $O_2$ for adequate period of time (5). No significant changes in $paO_2$ up to 15 min of carbogen breathing were observed in these 5 patients. In patient F.A. the $paO_2$ value available only at 15 min was as high as that observed in the remaining patients (Table 2). In two patients (B.R. and M.E.) arterial blood gas analysis was also performed at 5 min and it showed $O_2$ saturation values lower than those observed in these two patients at 15 min (Table 2). No changes of $paCO_2$ were observed in all patients at any stage of our study.

In Table 3 the values of expiratory gas fractions are reported. This table shows that in 4 out of 6 patients the analysis performed on the expiratory gas collected in a

**Table 4**

*Cardiac and respiratory parameters before (basal) and during carbogen breathing*

| Name | Time min | BP mmHg | HR cycles/min | RR breaths/min | VE l/min | TV ml/min |
|---|---|---|---|---|---|---|
| B.R. | Basal | 125/75 | 70 | 21 | 6.9 | 320 |
| | 10 | 95/65 | 72 | 28 | 17.7 | 630 |
| | 15 | 95/65 | 80 | 26 | 16.8 | 640 |
| M.E. | Basal | 200/120 | 118 | 21 | 10.8 | 510 |
| | 10 | 225/125 | 118 | 22 | 16.0 | 720 |
| | 15 | 235/140 | 120 | 23 | 17.0 | 730 |
| F.A. | Basal | 120/70 | 96 | 9 | 12.2 | 1350 |
| | 10 | 115/80 | 96 | 20 | 17.8 | 890 |
| | 15 | 115/80 | 90 | – | – | – |
| f.e. | Basal | 160/85 | 98 | 13 | 7.8 | 600 |
| | 10 | 155/90 | 100 | 15 | 17.0 | 1130 |
| | 15 | 155/85 | 98 | 16 | 17.8 | 1110 |
| C.E. | Basal | 120/80 | 80 | 21 | 12.6 | 600 |
| | 10 | 140/85 | 78 | 21 | 22.2 | 1050 |
| | 15 | 140/80 | 78 | 23 | 28.5 | 1230 |
| S.I. | Basal | 130/75 | 80 | 16 | 9.7 | 600 |
| | 10 | 155/90 | 80 | 13 | 29.1 | 2230 |
| | 15 | 145/90 | 80 | 17 | 22.3 | 1310 |

Abbreviations: BP = arterial blood pressure; HR = heart rate; RR = respiratory rate; VE = minute ventilation; TV = tidal volume

Douglas bag gave $CO_2$ concentrations ranging between 4.6 and 5.1%. In two patients (F.E. and S.I.) the baseline expired $CO_2$ concentration increased only up to 2.5% in both cases during carbogen breathing suggesting that accidental inhalation of room air during breathing test occurred in these two patients. This is confirmed by the high values of $N_2$ concentration found in the expired gas at 15 min (9.55 and 12.0% respectively).

In Table 4 cardiac and respiratory parameters before and during carbogen breathing are reported. In patient M.E. the baseline values of both the blood pressure and heart rate were elevated and a further increase of these values during carbogen breathing was observed. In patient F.A., a baseline low respiratory rate (RR) with a high minute ventilation (VE) as well as with an increase of tidal volume (TV) was observed. In patient C.E., the high baseline respiratory rate accounts for the elevated value of VE and hence for the observed pattern of respiratory alkalosis (Table 2). During carbogen breathing, while no patient showed a significant change in cardiovascular parameters, a marked increase of both the VE and TV was observed in all patients but one (F.A.). In this latter patient, in whom baseline values of VE and TV were abnormally elevated, carbogen breathing determined a marked rise in both RR and VE coupled with a slight decrease of TV.

## Discussion

Following the observation that carbogen enhances blood flow in mice tumour and increases the partial pressure of oxygen within tumours (6, 7), it has been suggested that carbogen should remarkably increase tumour radiosensibility (8). As a consequence, the clinical application of carbogen might be promising in radiotherapy of human tumours. The inhalation of carbogen seems to be a reliable method to elevate arterial $pO_2$ in healthy volunteers (2, 4). As a matter of fact, carbogen breathing increases arterial oxygenation in humans even through the stimulation of the respiratory system elicited by $CO_2$ (5). No information is available so far on the effect of carbogen breathing in patients with malignant diseases. This point may be crucial when dealing with patients affected by intracranial tumours, given that the biochemical changes induced by carbon dioxide may cause a variation of intracranial pressure in these patients (5, 9). On the other hand, the purpose of the carbogen breathing test is to increase arterial oxygenation and the results of the present study are consistent with this effect in our patients (Table 2). We could emphasize that, as expected (5), to obtain a significant and sustained increase of arterial oxygenation, a period of carbogen breathing longer than 5 min is needed. In fact, in two patients (B.R. and M.E.) in whom arterial blood samples were obtained at 5 min of carbogen breathing (Table 2), the resultant $O_2$ saturation was lower than that achieved after 15 min of carbogen inhalation. Moreover, the use of a mixing gas device enables us to ensure the stability of $O_2$ and $CO_2$ concentrations during the test of carbogen breathing in patients with malignant cerebral disease to be submitted to radiotherapy. In addition, the measure of the expired gas concentrations, which provides a feature of the intrapulmonary gas exchange during carbogen breathing, allows us to follow the $N_2$ wash-out from the lungs. This information may help to establish the actual time in which the highest achievable value of oxygenation is reached. Our data show that in none of our patients the $N_2$ wash-out was completed after 15 min of carbogen breathing. Moreover, in two of our patients (F.E. and S.I.) the high concentration of $N_2$ found in the expired gas was likely due to accidental inhalation of room air during carbogen breathing. The $N_2$ wash-out from the lungs shows at least two gas exchange components: the earlier component has a short wash-out time, while the wash-out time of the second component is longer. It is reasonable, therefore, to start the radiotherapy when the short time gas exchange component has been completed, i.e. after approximately 7 min of hyperoxic gas mixture administration (5). In fact at this time our data show that the gas concentrations in the lungs become stable and the arterial oxygenation has reached the highest achievable value, provided that the patients have performed the test correctly (as did 4 patients out of 6).

In our study we have experimental evidence that the carbogen breathing increased arterial blood oxygenation in these 6 patients, but we cannot give any information on the oxygenation of the tumour or on its radiosensitivity. In the patients of the present study the postulated rise of systemic blood pressure during the carbogen breathing (6) was not achieved (Table 4). In fact, we observed only slight fluctuations of systemic blood pressure from baseline conditions during the following 15 min of carbogen breathing. Hence, the increment of the systemic blood pressure following carbogen administration reported in an experimental study (6) has not been confirmed in this study in man. This may be accounted for the $CO_2$ concentration used in this study.

In conclusion, our data demonstrate that carbogen breathing may increase arterial oxygenation in patients with intracranial malignant diseases. The system used to ensure the appropriate gas mixture concentrations appears to be reliable and of practical use. Monitoring of expired gas concentrations is highly recommended.

## ACKNOWLEDGEMENTS

The authors would like to thank Professor Juliana Denekamp, Gray Laboratory (CRC), Northwood, for useful suggestions and Edo Fornai, B.S., for his invaluable technical assistance.

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