EXPIRED CARBON MONOXIDE AS A MARKER OF CO POISONING AND ITS APPLICATION IN DETERMINING TREATMENT END-POINTS

By

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A thesis submitted in fulfilment of the requirements for the degree of

Doctor of Medicine

University of Tasmania, 27 August 2005
DECLARATION OF ORIGINALITY

This thesis contains no material that has been accepted for the award of any other degree or diploma in any tertiary institution and to the best of my knowledge and belief, the thesis contains no material previously published or written by another person, except where this is referenced in the text.

I am responsible for the initiation and presentation of this thesis. The full extent to which others have contributed to the data contained herein is detailed in the acknowledgments.

David R. Smart

Date 27th August 2005
STATEMENT OF AUTHORITY OF ACCESS

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Date 27th August 2005
ACKNOWLEDGEMENTS

This thesis is exclusively my own work, however I am extremely grateful for assistance with data collection and care of patients, provided by my colleagues Dr Harry Oxer, Dr Paul Mark, Dr Neil Banham, Professor George Jelinek and Mr Jack Hodge. Mr Tom Nalpon provided valuable advice and technical assistance with the offgassing apparatus and its connection for sampling from patients receiving hyperbaric oxygen. Mr Nalpon made modifications to the hyperbaric chambers to permit sampling of patients’ exhaled breath from outside the chamber. He also assisted with photography of equipment for the thesis. Advice was received on screening cognitive function tests from the Selby Neurosciences Centre (WA) staff; Dr Linda Hayward, Ms Susan Scott, and Ms Carmella Mazella. Cognitive function screening for poisoned patients was undertaken by hyperbaric specialist nurses, Ms Sharon Keetley and Ms Sue Thurston. Secretarial assistance was received from Mrs Margaret Beattie. Carboxyhaemoglobin and arterial blood gas measurements were undertaken by the Department of Clinical Chemistry, Fremantle Hospital under the direction of Mr Simon Langston. I have received significant advice during preparation of the manuscript from Associate Professor Janet Vial and Associate Professor David Johns, Department of Medicine, University of Tasmania. I am also grateful for the advice and assistance from Mrs Dace Shugg, in the structuring and layout of this thesis, and Associate Professor John Williamson, Department of Anaesthesia, University of Adelaide, for his constructive critical commentary. The discussion and conclusions drawn in this thesis are my own personal interpretation of the data.

Clinical data for controls and poisoned patients were collected at the Departments of Emergency Medicine and Hyperbaric Medicine at Fremantle Hospital, Western Australia, in 1992 and 1993 when I was working at Fremantle Hospital in Perth, Western Australia. The thesis has been prepared over 1994 to 2004 after I returned to Royal Hobart Hospital in February 1994.

Some control data for smokers and non-smokers was collected at the Rockingham-Kwinana Hospital Health expo, held in November 1993. The project was completed with the last poisoned patients receiving three-month follow-up in January 1994. The research was undertaken while I was employed as Senior Registrar in Hyperbaric Medicine and Emergency Medicine at the Fremantle Hospital and Rockingham-Kwinana District Hospital, Western Australia.

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## SUMMARY OF ABBREVIATIONS USED IN THIS THESIS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ATA</td>
<td>Atmospheres absolute = the pressure relative to a vacuum (1 ATA = 101.3 kilopascals)</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval (statistical)</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>CO offgassing</td>
<td>Process of carbon monoxide being excreted in the breath as it is eliminated from the body</td>
</tr>
<tr>
<td>CO</td>
<td>Carbon monoxide</td>
</tr>
<tr>
<td>COHb</td>
<td>Carboxyhaemoglobin</td>
</tr>
<tr>
<td>COHb%</td>
<td>Carboxyhaemoglobin percent = the amount of carbon monoxide bound to haemoglobin, expressed as a percentage of total haemoglobin</td>
</tr>
<tr>
<td>CONSB</td>
<td>Carbon monoxide neuropsychiatric screening battery. A series of psychometric tests to measure cognitive function.</td>
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<tr>
<td>DCI</td>
<td>Decompression illness = a syndrome caused by the formation of nitrogen bubbles in the body of a diver after decompression from exposure to compressed air</td>
</tr>
<tr>
<td>DNS</td>
<td>Delayed neurological syndrome = a syndrome of delayed deterioration in neurological or cognitive function occurring 3–40 days after apparent recovery with acute treatment</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram = measurement of the electrical activity of the heart using skin electrodes</td>
</tr>
<tr>
<td>ED</td>
<td>Emergency department</td>
</tr>
<tr>
<td>ECO</td>
<td>Mean expired carbon monoxide concentration, expressed in parts per million</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>-------------</td>
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<tr>
<td>FrO2</td>
<td>Fraction of concentration of inspired oxygen, expressed as decimal 0 - 1.0, indicating of the relative amount of oxygen in the total inspired gas</td>
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<tr>
<td>FSQ</td>
<td>Functional status questionnaire</td>
</tr>
<tr>
<td>GCS</td>
<td>Glasgow coma score (scale 3-15) = description of conscious state Detailed in appendix 18.2.1</td>
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<tr>
<td>GHQ-12</td>
<td>General health questionnaire (12 questions)</td>
</tr>
<tr>
<td>Hb</td>
<td>Haemoglobin</td>
</tr>
<tr>
<td>HBO</td>
<td>Hyperbaric oxygen</td>
</tr>
<tr>
<td>HBOT</td>
<td>Hyperbaric oxygen treatment or hyperbaric oxygen therapy</td>
</tr>
<tr>
<td>HMF</td>
<td>Higher mental function</td>
</tr>
<tr>
<td>LOC</td>
<td>Loss of consciousness</td>
</tr>
<tr>
<td>LPG</td>
<td>Liquid propane gas</td>
</tr>
<tr>
<td>Min</td>
<td>Minute</td>
</tr>
<tr>
<td>MMSE</td>
<td>Mini-Mental State Examination. A cognitive function test with a score from 0 to 30. Detailed in appendix 18.2.2.</td>
</tr>
<tr>
<td>NBO</td>
<td>Normobaric oxygen = 100% oxygen breathed at ambient atmospheric pressure (Usually 101.3 kPa)</td>
</tr>
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<td>NNT</td>
<td>Number needed to treat. The number needed to treat using a therapeutic modality to gain one extra good outcome</td>
</tr>
<tr>
<td>O2</td>
<td>Oxygen</td>
</tr>
<tr>
<td>P</td>
<td>Pressure</td>
</tr>
<tr>
<td>PaO2</td>
<td>Alveolar oxygen partial pressure</td>
</tr>
<tr>
<td>PaO2</td>
<td>Arterial oxygen pressure</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>PtO₂</td>
<td>Pressure of inspired oxygen = the partial pressure of the inspired oxygen</td>
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<tr>
<td>PNS</td>
<td>Persistent neurological sequelae = persistent neurological or cognitive deficits after treatment for acute CO poisoning</td>
</tr>
<tr>
<td>ppm</td>
<td>Parts per million</td>
</tr>
<tr>
<td>PSig</td>
<td>Pounds per square inch gauge pressure = the measured pressure in PSI, which is above ambient pressure</td>
</tr>
<tr>
<td>RMV</td>
<td>Respiratory minute volume = the amount of breath exhaled in one minute (litres)</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation (statistical)</td>
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2. THESIS ABSTRACT

Carbon monoxide (CO) is a colourless, odourless toxic gas that is able to substitute for oxygen at many levels in the oxygen cascade. CO poisoning is responsible for nearly a quarter of suicide deaths in Australia, and hundreds of individuals sustain non-fatal poisoning every year. Up to two thirds of individuals who survive CO poisoning have long-term neurological or cognitive impairment. Despite years of study by medical researchers, a reliable marker of acute CO poisoning severity that correlates with outcome has not been identified. Oxygen is known to be an antidote to CO poisoning, yet there is significant debate regarding the dose required, and the treatment duration. The end-point of CO excretion from the body is the lungs. Measurement of expired CO has been documented since the 1980’s, however there has been limited study of ECO in poisoned patients.

In this research ECO was investigated as marker of CO poisoning, and its application in determining treatment end-point. A low cost, portable and non-invasive apparatus was successfully developed for measurement of ECO, oxygen concentration and minute volume. The apparatus was then evaluated in a variety of settings, for adults and children, and to establish baseline ranges for non-smokers, smokers and poisoned individuals, breathing air, NBO and HBO. The technique of measuring ECO was further investigated to determine the relationship between ECO and COHb, and for the diagnosis of CO poisoning. The apparatus was evaluated in the clinical setting to determine pulmonary CO elimination kinetics. A prospective series of CO poisoned patients was enrolled to determine if acute ECO levels correlated with clinical outcomes and to assess whether unrecordable ECO was a suitable marker of treatment end-point. In this research, expired oxygen concentration was also monitored, to ensure that all individuals received the stated dose of oxygen.

Baseline levels of ECO were found to be very low in healthy non-smoking volunteers, and in non-smoking divers treated for decompression illness, consistent with the observation that most CO derives from exogenous sources. Smokers had higher baseline ECO than non-smokers, and smoker ECO levels correlated positively with the number of cigarettes smoked per day, and negatively with the time since last cigarette.

Breathing air and NBO, a strong positive linear relationship between the ECO and COHb was observed for non-poisoned smokers, poisoned individuals and pooled data. Expired CO concentration increased in proportion with increasing FIO2, for 0.21 (air) to 1.0 (NBO). While breathing 100% oxygen,
increasing ambient pressure from 1 ATA to 2.8ATA did not alter the ECO concentration (ppm) in each breath. However, elimination of CO was greatly enhanced due to the increased density of gas at higher pressures. Each tidal volume at 2.8ATA actually contains 2.8 times as many molecules of CO compared with the same tidal volume at 1ATA ambient pressure. When poisoned subjects breathed NBO and HBO, significant amounts of ECO were detectable when the COHb was unrecordable using the biochemical method. This suggested that ECO more accurately reflected remaining CO in body stores than COHb, however this might have resulted from the limits of the biochemical method for detecting low levels of COHb (< 2%). Concurrent measurement of expired oxygen provided useful confirmation that the intended 100% oxygen dose was delivered to all treated individuals.

ECO was a useful non-invasive test to diagnose acute (< 6 hours) CO poisoning, when ECO values were > 40 ppm. For ECO values of 7 ppm to 40 ppm, clinical information would be needed to separate mildly poisoned individuals from smokers. Expired CO and COHb were equally effective in identifying acutely poisoned individuals, from smokers and non-smokers. Critical values of ECO >40 ppm or COHb > 7% were shown to be highly specific for CO poisoning.

Expired CO demonstrated single stage exponential elimination kinetics in both NBO and HBO treatment environments. CO elimination in HBO was significantly faster than NBO. There was a seven to ten-fold variation in CO elimination between individuals in either treatment (NBO or HBO). Based on these findings, current empirical regimens may over-treat some individuals and under-treat others. The half-lives determined for ECO elimination were longer than those determined for COHb. This suggests that elimination of CO via the breath may be slower than elimination from Hb. If unrecordable ECO proved useful as a treatment endpoint, this would allow treatment to be tailored to the individual’s acute CO load.

In the clinical series of 66 acutely poisoned patients, there were a high number of males sustaining CO poisoning from deliberate self-harm. These individuals had longer exposures, greater neurological toxicity, and were more likely to have LOC than accidental exposures. The greater toxic effect and higher CO body load was most likely due to breathing leaded petrol exhaust containing high CO levels to attempt suicide. In keeping with their greater neurological toxicity, there was a positive correlation between ECO, COHb levels, and the severity of poisoning. The ECO measurement breathing oxygen correlated significantly with the severity of neurological impairment in the ED. This provided support for ECO levels as useful guide to acute clinical poisoning severity. However, acute ECO and COHb
levels measured in the ED were not predictive of outcome at 3 months. This may have been affected by significant delays in transferring patients for HBO treatment.

Just over 28% of patients had poor outcomes at 3 months, using unrecordable ECO as a treatment endpoint. At this point, patients who had abnormal neurological or cognitive function remained abnormal at 3 months. Unfortunately the treatment endpoint using ECO did not prevent cases of DNS, or the need to provide follow-up for CO poisoned patients. The occurrence of DNS after all CO had been removed suggests that DNS may result from mechanisms other than direct CO toxicity.

Poor outcomes were associated with delays to study entry, suicide attempts, motor vehicle exhaust as a source of CO and acidosis measured in the ED. Individuals with LOC did not have a significantly worse outcome than those remaining conscious during their CO exposure. HBO and NBO treated patients had similar levels of PNS, however the HBO group had a lower incidence of DNS – an unexpected finding. Because the study was not randomized, it was not possible to conclude this is a definite treatment effect. Compared with NBO, HBO treatment led to faster removal of CO, and shorter treatments.

Measurement of ECO constitutes a novel non-invasive method of monitoring of acute CO poisoning. It has potential to compliment existing methods of monitoring acute CO poisoning, and may be useful as a non-invasive test to diagnose CO poisoning. Clinical outcomes in this series compared favourably with other series of similar severity poisoning in the literature. However, further research using a randomized controlled trial is required to determine if unrecordable ECO is a useful guide to treatment endpoint.