Acute Oxygen Therapy and
Cognitive and Driving Performance
in Hypoxaemic COPD.

Jeffrey John Pretto
Bachelor of Applied Science
Graduate Diploma in Biomedical Instrumentation
Certified Respiratory Function Scientist

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1. Certificate of Authorship

I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person nor material which to a substantial extent has been accepted for the award of any other degree or diploma at Charles Sturt University or any other educational institution, except where due acknowledgment is made in the exegesis. Any contribution made to the research by colleagues with whom I have worked at Charles Sturt University or elsewhere during my candidature is fully acknowledged.

I agree that this thesis be accessible for the purpose of study and research in accordance with the normal conditions established by the Executive Director, Library Services or nominee, for the care, loan and reproduction of theses.

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Jeffrey J. Pretto
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3. **Abstract**

Chronic obstructive pulmonary disease (COPD) is a debilitating chronic disease affecting nearly one in five Australians over the age of forty. In its advanced form, COPD causes low blood oxygen levels (hypoxaemia) which are known to adversely affect cognitive and neuropsychological function. Consequently, current Australian guidelines for assessing fitness to drive recommend that individuals requiring long-term oxygen therapy for the treatment of this disease should probably utilise oxygen therapy whilst driving. There is however no satisfactory documented evidence to support this recommendation, and furthermore, providing this therapy for all eligible drivers has significant safety and economic implications.

The aim of this study was to investigate whether acute oxygen therapy improves cognitive and/or driving performance in patients with hypoxaemic COPD, with the primary purpose being to enable evidence-based recommendations to be made on the use of this therapy whilst driving a motor vehicle.

I have investigated the effects of short-term oxygen therapy in a group of thirty hypoxaemic subjects with COPD who held a current driving licence. Driving performance was assessed using a computer-based driving simulation task, and neurocognitive performance was assessed by measuring reaction times using the psychomotor vigilance task (PVT). Testing was performed whilst the patient received intranasal oxygen or intranasal air delivered in a double-blinded, randomized crossover manner to enable appropriate study control and minimize bias.

I was unable to demonstrate any differences between any of the driving performance measurements, nor or in any of the neurocognitive (PVT) measurements indicating that acute oxygen therapy provides no measurable benefit over breathing medical air. Furthermore, no relationships could be found between driving or neurocognitive performance and baseline characteristics. This implies that it is not possible to predict those individuals likely to benefit most from oxygen therapy from a neurocognitive perspective.

The conclusions from these findings are that acute oxygen therapy does not improve simulated driving performance or neurocognition in hypoxaemic COPD.
These data do not support the recommendation that oxygen should be used whilst driving in this patient group and the recommendations should be altered to reflect these findings.
4. Publications and Presentations Arising From This Research

Publication in peer-reviewed journal (see appendix)

- Jeffrey J. Pretto and Christine F. McDonald. Acute oxygen therapy does not improve cognitive and driving performance in hypoxaemic COPD. Respirology, 2008, 13: 1039-44

Published abstracts (see appendix)

- Jeffrey J. Pretto and Christine F. McDonald. The acute effects of oxygen therapy on cognitive and driving performance in hypoxaemic COPD. Respirology, 2006, 11 (suppl. 2), A3.

- Jeffrey J. Pretto and Christine F. McDonald. The acute effects of oxygen therapy on cognitive and driving performance in hypoxaemic COPD. Respirology, 2006, 11 (suppl. 5), A151.

Presentations (see appendices for abstracts)

- Jeffrey J. Pretto and Christine F. McDonald. The acute effects of oxygen therapy on cognitive and driving performance in hypoxaemic COPD. Annual Scientific Meeting, Australian & New Zealand Society of Respiratory Science, Canberra, ACT, 2006. (Received Best Oral Presentation Award).

- Jeffrey J Pretto and Christine F McDonald. The acute effects of oxygen therapy on cognitive and driving performance in hypoxaemic COPD. International Traffic Medicine Association 20th World Congress, Melbourne, Victoria, 2006.

- Jeffrey J. Pretto and Christine F. McDonald. The acute effects of oxygen therapy on cognitive and driving performance in hypoxaemic COPD. Asian Pacific Society of Respirology (APSR) – 11th Congress. Kyoto, Japan, 2006. (Awarded the inaugural APSR Pharmaxis Travel Award).

- Jeffrey J. Pretto and Christine F. McDonald. The acute effects of oxygen therapy on cognitive and driving performance in hypoxaemic COPD. TSANZ Annual Scientific Meeting (Victorian Branch), Melbourne, 2007 (Received Best Oral Presentation in Clinical Research Award).

- Jeffrey J. Pretto. The acute effects of oxygen therapy on cognitive and driving performance in hypoxaemic COPD. Faculty of Science Postgraduate Seminar Day, Charles Sturt University, Wagga Wagga, NSW, 2008.
5. **Other Contemporaneous Publications during this Research**


6. Background and Literature Review

6.1. Australian Driver Medical Standards

Austroads is the association of Australian and New Zealand road transport and traffic authorities and its purpose is to contribute to the achievement of improved Australian and New Zealand transport related outcomes. They regularly publish and distribute their Assessing Fitness to Drive document the latest version of which was published in 2006 (Austroads, 2006). The purpose of this document is to provide clear medical standards for licensing of drivers whilst also outlining general guidelines to assist health professionals in managing and advising patients about driving. This document includes information relating to driving and licensing issues for a range of specific diseases. It represents current medical knowledge and its application to the transport environment in Australia and New Zealand.

Section 19 of this publication deals specifically with respiratory disease, and on the issue of hypoxaemia states:

*Individuals requiring long-term oxygen therapy should probably use their oxygen while driving due to improved performance while receiving oxygen (LOE I, II).*

This statement is referenced to two studies (Crockett et al., 2000, Hjalmarsen et al., 1999). Crockett’s study is a Cochrane review of the clinical utility of domiciliary oxygen therapy in COPD (Crockett et al., 2000), and there is no specific mention made within this review about the use of supplemental oxygen therapy whilst driving. Hjalmarsen’s study (Hjalmarsen et al., 1999) specifically investigated the acute effects of oxygen therapy on cognitive function in COPD, however no mention was made of effects on driving performance.

Given that neither of the studies specifically addressed the use of oxygen whilst driving, the Austroads statement regarding ‘improved performance’ likely refers to improved *cognitive* performance rather than improved *driving* performance. The level of evidence (LOE) of I and II quoted in the Austroads statement refers to the hypothesis that supplemental oxygen leads to improved cognitive performance – there is no such body of evidence in the literature indicating that oxygen therapy causes improved driving performance (addressed in section 4.10 of this review).
6.2. Hypoxaemia

The term hypoxaemia refers to low blood oxygen levels and is strictly defined as a low arterial oxygen content. Arterial oxygen content can be reduced with a normal oxygen partial pressure purely by a reduced oxygen carrying capacity. This is seen in dyshaemoglobininaemias such as anaemia (where the total haemoglobin level is reduced), and carbon monoxide poisoning (where oxygen carrying capacity is compromised). Whilst these conditions certainly reduce the oxygen carrying capability of arterial blood, the term hypoxaemia is generally used to indicate that the arterial oxygen partial pressure is reduced.

There are 5 physiological causes of reduced arterial oxygen partial pressure (West, 1978):

1. reduced inspired oxygen partial pressure
2. pulmonary ventilation-perfusion mismatch
3. diffusion limitation at the alveolar – capillary membrane
4. pulmonary shunting
5. alveolar hypoventilation

Except at high altitude, the first cause is not commonly encountered in the clinical setting. However all other causes are potentially possible in the presence of lung disease.

6.3. Quantifying Hypoxaemia

Arterial oxygenation is most accurately measured by directly sampling arterial blood and analysing the partial pressure of oxygen using a blood gas analyser. This provides the PaO₂ where the lower-case ‘a’ represents ‘arterial’. Whilst oxygen does not strictly exert a ‘gaseous pressure’ in the blood since it is either dissolved in the plasma or combined with haemoglobin, the PaO₂ represents the effective gaseous pressure that would result if a gas is allowed to equilibrate with the arterial blood. PaO₂ allows us to conveniently consider oxygen to be acting as a gas in the
blood when, for example, we are considering driving pressures across tissue and/or pulmonary capillary membranes.

An alternative method for quantifying blood oxygen levels is to estimate the oxygen saturation of the arterial blood (SaO$_2$). SaO$_2$ is the ratio of oxygenated haemoglobin to total haemoglobin and is most accurately measured using a haemoximeter to analyse arterial blood. This device is essentially a spectrophotometer which uses multiple wavelengths to measure the individual haemoglobin levels in the blood sample and to then calculate SaO$_2$ (Ruppel, 2009).

Given the relationship between oxygen saturation and oxygen partial pressure as described by the oxygen dissociation curve, it is theoretically possible to determine oxygen partial pressure from oxygen saturation (SO$_2$) and vice versa. However the precise relationship between PO$_2$ and SO$_2$ is dependent on multiple other factors (including temperature, carbon dioxide levels and pH) such that precise estimation of PO$_2$ from SO$_2$ is not possible. Whilst not providing a direct surrogate for estimating arterial oxygenation, oxygen saturation does provide a clinically useful estimate of oxygen content provided the limitations of the measurement are appropriately considered.

Whilst the measurement of PaO$_2$ or SaO$_2$ requires invasive blood sampling, pulse oximeters allow non-invasive estimation of arterial oxygen saturation. The pulse oximeter is also a spectrophotometer utilising multiple wavelengths, however it is used in vivo and passes the light through living tissue. The resultant measurement, SpO$_2$, provides an estimate of true SaO$_2$ however its major difference is that it measures the ratio of oxygenated haemoglobin to available haemoglobin rather than to total haemoglobin as SaO$_2$ does. Despite this limitation, the pulse oximeter’s major advantages are its ability to non-invasively provide an estimate of arterial oxygen status, and its ability to be used to monitor trends over time.

6.4. Chronic Obstructive Pulmonary Disease

COPD is a common disease in the community and is projected to rank fifth as a worldwide burden of disease by the year 2020 (Pauwels et al., 2001). Its currently estimated prevalence in Australia is over 2.6 million cases (Access Economics,
The disease places an enormous burden on health costs in this country with an average of 1,740 GP visits per day and over 50,000 annual hospital admissions due to COPD (Crockett et al., 2002), which equates to a health system expenditure of $900 million per annum (Access Economics, 2008). COPD affects mainly older people and as the population ages over the coming decades the incidence of the disease is expected to increase. Major COPD symptoms include chronic cough, increased production of mucus, increased shortness of breath and reduced exercise tolerance.

The aetiology of COPD is predominantly directly attributable to tobacco smoking, however there are other less common causes. Chronic airflow obstruction due to asthma can lead to fixed or irreversible airflow obstruction, and the rare alpha-1-antitrypsin deficiency (caused by a genetic abnormality) results in emphysema. Whilst not common within Australia, the burning of biomass within the home environment for heating and cooking purposes is now understood to be a significant contributor to the worldwide incidence of COPD (Mannino and Buist, 2007).

Treatment options for COPD are limited and are detailed in the COPD-X statement on managing this condition (Abramson et al., 2006). Whilst there has been recent interest in pharmaceutical options with the development of specific classes of bronchodilators such as tiotropium, complete reversibility of airflow limitation is generally not achievable and is indeed one of the primary requirements to diagnose this condition. However optimisation of inhaler therapy is considered important (Abramson et al., 2006). Surgical treatment options for COPD such as bullectomy, lung volume reduction surgery or lung transplantation are generally limited to a minority of specific patients. Appropriate treatment of aggravating factors such as sleep apnoea, gastro-oesophageal reflux and minimisation of alcohol and sedative usage is also considered important (Abramson et al., 2006).

Improving function by exercise training and pulmonary rehabilitation programs offers demonstrable improvements in quality of life in this disease, and currently such programs provide a beneficial treatment modality suitable for most COPD patients. The fundamental aim of these programs is to improve overall ‘fitness’ to enable optimal use of the limited capacity of the cardiorespiratory system. A further important management approach for COPD is preventing further deterioration and
smoking cessation provides the most effective strategy for achieving this (Abramson et al., 2006). Preventing infections and exacerbations (by influenza and pneumococcal vaccination for example) is an important management strategy for this disease, as is supplemental oxygen therapy in those identified as likely to benefit (described in detail in section 6.9.)

6.5. COPD and Hypoxaemia

The primary physiological manifestation of COPD is chronic obstruction of the airways which, especially in advanced forms of the disease, can lead to marked maldistribution of ventilation and blood flow throughout the lungs. This ventilation-perfusion mismatching (V/Q mismatch) contributes to inefficiency in the gas exchange capability of the lung, causing decreased oxygenation of arterial blood.

Emphysema, where there is physical destruction of the lung tissue, may also be present in COPD. In addition to the airflow obstruction caused by loss of the parenchymal support to the airways, emphysema is also characterized by a reduction in the total alveolar surface area available for gas exchange. These factors can also result in a worsened gas exchange ability of the lungs, and potentially contributing further to reduced oxygenation of arterial blood.

Not all patients with COPD exhibit resting hypoxaemia. The reason for this is multifactorial, however it is likely to relate to the enormous reserve capacity of the lungs whereby there can be substantial disease or damage present before there is any noticeable effect on arterial gas tensions at rest. Under resting conditions where the metabolic demands on the respiratory system are at their lowest, arterial oxygenation may be perfectly adequate despite significant respiratory disease being present. However, the effects of the pathological disease process of COPD on arterial blood gas tensions become particularly evident during exercise where the metabolic demands of the exercising muscles place additional stresses on the pulmonary gas exchange system. This exercise-induced arterial desaturation is a common, but not universal, observation in COPD.
Another feature of COPD is the occurrence of disease exacerbations which are defined as events in the natural course of the disease characterised by a change in symptoms beyond day-to-day variability, sufficient to warrant a change in management (Celli and MacNee, 2004). Exacerbations in COPD are largely a feature in moderate to severe disease (BTS, 1997) and acute hypoxaemia often results.

However, in advanced COPD the disturbances to the normal physiological gas exchange may become severe enough to result in arterial oxygen desaturation even whilst resting. Ongoing hypoxaemia at rest caused by COPD is the focus of this review and other causes of hypoxaemia, whether acute or chronic, are not specifically addressed.

6.6. Cognitive Function in COPD

As part of the Nocturnal Oxygen Therapy Trial (NOTT) investigating the comparative effectiveness of nocturnal versus continuous oxygen treatment in hypoxaemic COPD (NOTT, 1980), Grant et al presented baseline neuropsychologic findings in 121 COPD patients with arterial oxygen levels less than 55 mmHg (Grant et al., 1980). Although this study did not specifically investigate the effects of hypoxaemia on neuropsychological function, it was the first to document the incidence of brain dysfunction in this patient group. They found that many COPD patients who could still function on an ambulatory basis did have neuropsychologic deficits suggestive of organic brain dysfunction. They found 77% of their patient group to have abnormal neuropsychologic function, with 40% having at least moderate impairment.

They also found a significant correlation between arterial oxygenation and neuropsychologic function indicating worse cognitive function for those most severely hypoxaemic. Interestingly, they found that higher cognitive functions such as reasoning and perceptual-motor integration were most severely affected, whereas memory and verbal skills were relatively well preserved. Of course, this descriptive study could not determine whether these cognitive deficits were attributable to the hypoxaemia or to other manifestations of the COPD disease.
process, however the significant correlation between degree of hypoxaemia and degree of cognitive dysfunction is supportive of the existence of a causative link between the two.

One of the limitations of this study was the lack of an adequately matched control group with which to compare the results. The same researchers presented updated data from a larger group of 203 patients enrolled in the NOTT study, and also included comparative data from an age, sex and education matched group (Grant et al., 1982). Their conclusions were essentially identical to the previous study in that cerebral disturbance is common in hypoxaemic COPD with 77% found to have neuropsychologic deficit suggestive of cerebral dysfunction. They also reasoned that the observed neuropsychologic deficit in hypoxaemic COPD is caused, at least in part, by insufficient oxygenation of brain tissue.

Neuropsychological functioning was assessed in a group of 100 COPD patients with mild hypoxaemia (mean PaO₂ of 66 mmHg) by Prigatano et al (Prigatano et al., 1983). Compared with a normal control group, they found a significant, but modest, impairment in neuropsychological test performance with impairment in abstract reasoning, memory and speed of performance consistently found. Further, after allowing for other confounding factors, they found a correlation between neuropsychological impairment and resting arterial oxygenation. This further supports the notion that hypoxaemia itself is a contributing cause for the neuropsychological deficits observed in this disease.

As part of their battery of psychological testing in this study, Prigatano’s group also assessed other factors which may have affected the overall neuropsychological performance (Prigatano et al., 1983). They also found that factors such as poor motivation, fatigue and depression (all of which are known to be present in the COPD population under study) did not account for the differences observed.

Incalzi and colleagues (Incalzi et al., 1993) subjected a group of 36 severe COPD patients on long-term oxygen therapy (LTOT) to a battery of 19 psychological tests exploring eight cognitive domains in an effort to characterize the neuropsychologic profile of patients with COPD. Their control groups included an age-matched normal group, a more elderly normal group, a Alzheimer-type dementia group, and
a multi-infarct dementia group. Compared with the aged-matched normal subjects, patients with COPD showed a diffuse cognitive deterioration which was less severe on average than the Alzheimer group. Discriminate analysis of cognitive test scores showed that nearly half of the COPD group had a specific pattern of cognitive abnormality characterized by a dramatic impairment in verbal and verbal memory tasks, well-preserved visual attention, and diffuse worsening of other functions. Overall, only 12% of COPD patients were functionally characterized as normal adults of similar age. The data also suggested that disease duration rather than disease severity accounts for cognitive deterioration. This finding supports the notion that long-term or chronic hypoxaemia is particularly important in inducing neurocognitive degeneration.

In a similar study, Incalzi’s group further investigated the mechanisms accounting for verbal memory impairment in severe hypoxaemic COPD (Incalzi et al., 1997). They found a great inter-individual variability in verbal memory pattern in this patient group, but only a fifth of COPD patients were found to have normal verbal memory. They confirmed that cognitive deterioration in general was a common finding in advanced COPD, and interestingly, that both this and depressed memory function were associated with poor medication adherence. This finding has important clinical implications in the management of this disease.

Meek et al (Meek et al., 2001) investigated another aspect of cognitive dysfunction in COPD disease management – that of patients’ ability to recall symptoms. They studied a group of thirty male subjects with severe COPD, only 5 of which required LTOT but with an overall mean PaO₂ of 68 mmHg. They did not find significant errors in recalling symptoms of dyspnoea and fatigue over a two week period, however the applicability of their findings to other COPD patients is difficult since the baseline cognitive evaluation of their patient group did not reveal the cognitive deficits that others had found (Grant et al., 1982, Incalzi et al., 1997). This may have been because of the low incidence of hypoxaemia in Meek’s patient group. Put another way, Meek found that memory for symptoms is good in severe COPD patients who do not have cognitive deficits. This is perhaps an unsurprising result.

In a group of 17 patients with severe COPD but relative normoxaemia (mean PaO₂ of 89 mmHg), Shim et al found global impairment in memory, attention,
visuospatial scanning ability and in motor function (Shim et al., 2001). Various forms of memory impairment were found in 87% of patients. Utilizing proton magnetic resonance spectroscopy (HMRS), this group was also able to demonstrate cerebral metabolic abnormalities in COPD – the first to show functional cerebral abnormalities in COPD. Whilst this important study did not reveal the mechanism for the abnormality nor investigate the clinical significance of their findings, it does provide the first evidence for real, metabolic changes in cerebral function in COPD in spite of an absence of chronic hypoxaemia. In HMRS, it also suggests a potentially powerful tool which may have utility in the investigation of the effects of therapeutic interventions on cerebral metabolism.

Liesker and colleagues focused specifically on non-hypoxaemic COPD in their study of 30 COPD patients with an average PaO₂ of 76 mmHg (Liesker et al., 2004). Comparing a battery of nine psychometric test results with a control group matched for age, education level and intelligence quotient, they found significant impairments in cognitive performance, particularly those aspects involving speed of information processing. They also reported that memory performance was largely unaffected in the COPD group – in contrast to the findings of Shim (Shim et al., 2001) in a group of similarly normoxaemic COPD patients, and to Incalzi’s (Incalzi et al., 1993) findings in a hypoxaemic group.

Although Orth and colleagues did not directly assess neurocognitive impairment, they did compare driving simulator performance in a group of 17 moderately severe COPD patients with an age-matched control group (Orth et al., 2008). They found that accident frequency (but not concentration faults) on the simulator was significantly higher in the COPD group. Whilst their suggestion that impaired driving performance in COPD may have crucial consequences for driving licensing of these patients, they found that driving impairments could not be predicted on the basis of disease severity. Their patient group was relatively mildly hypoxaemic with a mean PaO₂ of 69 mmHg.

To summarize, the literature indicates that cognitive abnormalities are common in COPD, with or without resting hypoxaemia. The types of cognitive deficits include memory, ability in abstract reasoning, speed of performing, and in coordination of simple motor tasks. There appears to be a relationship between degree of
hypoxaemia and degree of cognitive impairment suggesting that hypoxaemia may provide an important causative contributor. However the presence of cognitive abnormality in non-hypoxaemic COPD indicates that hypoxaemia is not the sole cause of these deficits.

6.7. **Supplemental Oxygen Therapy**

All living tissue requires oxygen to survive so a critically important requirement for sustaining life is adequate oxygen delivery. Oxygen delivery to the tissues is fundamentally dependent upon 3 components: adequate oxygen uptake in the lungs, adequate oxygen carrying capacity of the blood, and appropriate blood supply to the tissues. Many disease states can interfere with one or more components in this chain, and can therefore interfere with oxygen delivery. Supplemental oxygen therapy is indicated when oxygen delivery is compromised for any reason and is a routine form of treatment for a variety of clinical situations. Specific examples include dyshaemoglobinemia such as reduced haemoglobin content and carbon monoxide poisoning, compromised lung function such as occurs in premature infants and in severe lung disease, and where cardiac output is compromised such as in atrial septal defects and myocardial infarction.

The fundamental principle behind supplemental oxygen therapy is that supplying an inspired gas with increased oxygen tension will increase the uptake of oxygen at the pulmonary level, improve arterial oxygenation and hence oxygen content, and therefore improve overall oxygen delivery to all body tissues. Oxygen therapy has been used for many years in the treatment of acute, especially life-threatening, illnesses. However it has only been in recent decades when reliable oxygen supplies have become both accessible and affordable that LTOT has become a common treatment modality. Individuals with chronically reduced oxygen delivery capabilities are now prescribed oxygen therapy in an effort to improve overall oxygen delivery.

Methods of supplemental oxygen supply and delivery have changed over recent years as technological developments have enabled better efficiencies and economies. Heavy high-pressure steel gas cylinders have largely been replaced in
the domiciliary setting with oxygen concentrators – electrically powered devices which use a molecular sieve to filter nitrogen from ambient air. This results in the production of gas comprising approximately 95% oxygen. These devices have been used as the primary means of providing LTOT since their introduction into Australia in the late 1970s, however the standard oxygen concentrator is bulky and requires connection to a mains electricity source to continue functioning.

There have also been substantial technological developments in devices for the supply of portable oxygen creating significant changes in the way in which oxygen can be supplied away from the home or hospital setting. Refillable liquid oxygen systems and low-weight, aluminium portable gas cylinders allow much greater portability. Also, electronic oxygen-conserving devices which deliver oxygen only during inhalations extend the life of each cylinder refill and thereby allow greater range for oxygen use. Because of these cost-efficient developments, portable oxygen therapy is now a commonly prescribed treatment which allows patients to continue to receive the beneficial effects of supplemental oxygen whilst away from the healthcare facility or domiciliary setting.

6.8. Problems Associated with Oxygen Therapy and Driving

Over and above the general safety recommendations when using compressed gas cylinders, there are additional issues to be taken into consideration when transporting medical oxygen in cylinders. Whilst oxygen is not classified as a flammable gas, it does support combustion and therefore poses a significant fire risk. In the event of an automobile accident, the combustion-promoting characteristics of a large source of oxygen can turn a small heat or fire source, into a major fire.

Like all compressed gas cylinders, oxygen cylinders should be handled carefully since they can potentially become a dangerous missile in the event of breakage at the cylinder neck. There is an Australian Standard for the transportation of gas cylinders (Standards_Australia, 2002) which describes, albeit very briefly, the conditions under which cylinders should be transported. This standard states that compressed gas cylinders:
- should not be subjected to undue shock
- must be secured whilst being transported
- must be kept away from artificial sources of heat and away from solar radiation
- should, where practicable, be stored and used vertically
- must have the shut-off valve closed during transportation if containing flammable or toxic gases

Compressed medical grade oxygen is not classified as a flammable or toxic gas, so its use during transportation does not specifically contravene this standard. Oxygen cylinders clearly need to be secured within the vehicle and kept away from heaters, and also not in direct sunlight.

Securing oxygen cylinders within the vehicle is also problematic. Patients using oxygen whilst driving are advised by the oxygen supply companies to either place the cylinder securely under a seat, or if not possible, to use the car seat belt to secure the cylinder to the car seat.

Another safety precaution recommended by oxygen supply companies include the need to not permit smoking nor open flames near where oxygen is being used – this clearly precludes smoking within the vehicle whilst oxygen is being used.

### 6.9. Long-Term Oxygen Therapy (LTOT) in COPD

Chronic hypoxaemia due to COPD has been treated with LTOT since the 1960s when it became feasible to supply this therapy in the domiciliary setting. Petty’s early work in this area suggested that continuous oxygen therapy can effect a clinical improvement in this patient group (Petty and Finigan, 1968, Petty et al., 1969, Petty et al., 1971). From a theoretical perspective it was presumed that reversal of hypoxaemia with LTOT would prove beneficial in the overall management of the disease, however it was not until the publication of two landmark studies in the early 1980s that this was categorically shown (MRC, 1981, NOTT, 1980).
The MRC study was specifically designed to answer the question of whether any objective improvements could be demonstrated in using LTOT (MRC, 1981). In this study, 87 hypoxaemic COPD patients were randomised to receive either usual treatment, or usual treatment plus LTOT delivered over 15 hours per day. The fundamental conclusion of this study was that oxygen therapy reduced mortality over 3 years in this patient group.

The NOTT study was designed to investigate whether continuous oxygen therapy provided a benefit over nocturnal oxygen therapy only and studied 203 patients on an average of 18 hours of oxygen therapy per day compared with 12 hours per day (NOTT, 1980). They found that mortality in the continuous oxygen group was half that of the 12-hour group after 26 months of treatment. The conclusions to be drawn from the MRC and NOTT studies is that survival in hypoxaemic COPD is better with oxygen therapy than without, and that use for more hours per day is better than overnight or 12-hour per day use.

The primary indication for LTOT in the treatment of COPD is the ongoing presence of hypoxaemia despite optimal medical management. Whilst many with COPD demonstrate hypoxaemia during acute exacerbations of the disease, it is in those patients who continue to demonstrate hypoxaemia (as defined by a reduction in arterial oxygen pressure to less than 55-60 mmHg) whilst being optimally managed who qualify for LTOT. Guidelines for the provision of LTOT in COPD have been established by the Thoracic Society of Australia and New Zealand and describe indications and recommendations for the provision of LTOT in this country (McDonald et al., 2005).

LTOT requires the provision of a reliable, continuous oxygen supply and oxygen concentrators have been successfully used in Australia for this purpose for almost three decades for supplemental oxygen delivery within the home. Ambulatory oxygen therapy provides additional benefit over usual LTOT since it allows oxygen therapy to be used over a longer period of the day which was shown to be beneficial by the NOTT study (NOTT, 1980). In addition, it allows the patient to undertake exertional activities which may not normally be achievable, and may even encourage more exertion – the overall effect is to achieve additional training.
effects. Other benefits offered by portable oxygen systems include increasing the patient’s sense of independence and improving accessibility to social interactions.

Portable oxygen equipment can also be used whilst driving motor vehicles and it is the widespread use of portable oxygen which raises the question of whether it is necessary for oxygen to be used whilst driving. A key aspect to answering this question requires reviewing the literature on the effects of hypoxaemia and its reversal on cognitive function.

6.10. Effects of Hypoxaemia on Cognitive Function

It has long been recognized that acute hypoxaemia causes a definite impairment in cognitive function. Haldane et al made this conclusion as early as 1919 whilst studying acclimatization to reduced atmospheric pressure (Haldane, 1919).

Developments in air-flight technology and particularly in aviation medicine led to further investigations in the post-second world war period into the effects of hypoxaemia on cognitive function. Determining the oxygen level at which measurable changes in cognitive function occurred is particularly important given that aircraft cabins are not pressurized to sea level pressures, but typically to effective altitudes of 8,000 feet. This corresponds to inspired oxygen tension of approximately 108 mmHg, compared with the normal sea-level value of about 150 mmHg (Crow and Kelman, 1971). Investigations into effects on cognitive function of this reduction in inspired oxygen yielded conflicting results – some suggesting cognitive impairment (Crow and Kelman, 1969, Denison et al., 1966, Gedye, 1964), whilst others indicating no measurable difference compared with sea level oxygen concentration (Crow and Kelman, 1971, Kelman et al., 1969).

One of the important differences between these studies was the choice of instruments used to assess cognitive function. This issue is problematic throughout the neuropsychological literature, and furthermore the term ‘cognitive function’ is a complex one and its assessment can be performed in many varied ways. It is likely that differing aspects of cognitive function (such as short-term memory and reaction time assessments for example) are more susceptible to the effects of
hypoxaemia. As a result, conclusions about the effects of hypoxaemia on ‘cognitive function’ in general may be highly dependant upon the aspect or domain being investigated. To further confuse this complex issue, different instruments used to assess cognitive function may be more or less sensitive at detecting subtle changes than other measurement tools.

As part of an early study investigating the effects of continuous oxygen therapy in COPD, Krop and co-workers provided the first comparison of neuropsychologic function between hypoxic and non-hypoxic COPD (Krop et al., 1973). A group of 10 hypoxic COPD patients (mean $\text{PaO}_2$ of 51 mmHg) scored significantly lower in 5 of 10 neuropsychologic tests compared with 12 non-hypoxic COPD patients (mean $\text{PaO}_2$ of 67 mmHg) with similar degree of airflow obstruction.

In a study investigating the association between chronic hypoxaemia and impaired mental functioning, Huppert (Huppert, 1982) found an association between memory impairment and hypoxaemia. However there was lack of an appropriate control group, low patient numbers and heterogeneity within the subject group (some of which were not clearly hypoxaemic). The validity of the findings in this study are therefore questionable.

In an interestingly different approach to assessing the neuropsychological effects of short-term hypoxaemia, Cohen et al (Cohen et al., 1986) studied 12 patients who had been on LTOT for an average treatment time of 20 months. A battery of neuropsychological tests were performed at ‘usual’ blood oxygen levels whilst on oxygen therapy, and also whilst receiving air via nasal cannulae (randomly allocated and blindly received). Inspired gas levels were maintained for 4 hours prior to performance of the test battery. Mean arterial oxygen levels fell from 86 to 59 mmHg whilst breathing air ($\text{SpO}_2$ from 95% to 90%). No significant differences were found in neuropsychological test scores and the authors concluded that there was no evidence of impairment of intellectual function over a 4 hour period of oxygen withdrawal. This degree of arterial desaturation is of similar magnitude to that observed during commercial air flight travel (Naughton et al., 1995), and this study lends support to findings from other studies showing minimal neuropsychological effects at these blood oxygen levels (Crow and Kelman, 1971, Crow and Kelman, 1969).
The usual immediate response to acute hypoxia is a relative hyperventilation, which manifests as a reduction in arterial carbon dioxide levels. This hypocapnia is known to cause constriction of arterial blood vessels serving the brain (Gotoh et al., 1965). Hypocapnia in its own right has also been shown to cause psychomotor and cognitive deficits (Gibson, 1978, Rahn, 1946). Hypocapnia can clearly therefore have a confounding effect on studies investigating neuropsychological consequences of acute exposure to hypoxia – without adequate control, any measured cognitive changes could be attributable to hypoxia, to hypocapnia, or to the combined effects of both phenomena.

In their well-controlled study, Berry and co-workers (Berry et al., 1989) paid particular attention to this and other potentially confounding variables. Whilst maintaining isocapnic conditions, they found only two motor functioning tests (the Digit Symbol test and the Finger Tapping test) in a battery of eight neuropsychological tools to be affected by hypoxaemia in a group of ten normal subjects. They argued that other studies that had shown oxygen sensitivity to other neuropsychological tests may have resulted from lack of control of the confounding influences that they had identified and controlled. In any event, the maximum level of oxygen desaturation in their study was relatively modest with maximum arterial desaturation to 80% (corresponding to a PaO$_2$ of approximately 50 mmHg).

In response to concerns about levels of hypoxaemia observed during and following routine anaesthesia, Noble and colleagues investigated psychomotor performance and cognition during moderate hypoxaemia in a group of normal subjects (Noble et al., 1993). A battery of psychometric tests were performed in two groups of normal subjects whilst breathing air and hypoxic gas in a double-blinded manner. Despite a substantial decrease in average arterial oxygen saturation from 97% on air to 78%, only small adverse effects on psychometric performance were detected. They concluded that short-term hypoxaemia to a saturation of about 80% has significant but unimportant effects on some cognitive processes in normal subjects. They also highlighted some of the problems associated with learning effects with some of the neurocognitive assessment tools.
Most of the studies investigating the effects of hypoxaemia on cognitive function have assessed the response of normal subjects, with presumably normal blood oxygen levels, to short-term exposure to reduced inspired oxygen concentrations. The situation with patients with chronic lung disease and long-term exposure to reduced blood oxygenation is quite different. Whilst there are certainly some adaptive neuromuscular strategies that such patients exhibit to cope with the reduced capacity of the cardiorespiratory system to supply oxygen, there are also likely to be some neurocognitive adaptations to the hypoxaemia as well. This means that results from studies involving short term hypoxaemia in normal subjects cannot be necessarily applicable to the chronically hypoxic COPD patient. As a consequence when considering what happens in hypoxic COPD, results from other studies in normal subjects should be used as a guide only as to the oxygen level at which cognitive function begins to deteriorate and to what types of deficits can be expected.

6.11. Effects of Hypoxaemia on Driving Performance

Whilst ‘cognitive dysfunction’ in general may be attributable to hypoxaemia, the type of dysfunction caused is clearly important in determining whether hypoxaemia will affect driving performance. Grant et al (Grant et al., 1980) found that complex perceptual integrative abilities and simple motor and attention skills were commonly deficient in hypoxaemic COPD. These cognitive skills are arguably the most important required for driving a motor vehicle, so there is clearly a logical argument that driving ability will be adversely affected by hypoxaemia.

Presumably because of the relatively low risk of being exposed to hypoxic conditions whilst driving a motor vehicle (in contrast to the potentially high risk associated with aircraft travel), very little research has been published investigating the effects of hypoxaemia on driving performance. In fact, a search of the literature reveals only one full publication purportedly investigating this issue (Ramsey, 1970). Ramsey performed simple reaction time measurements in 2 study groups of thirty before and after driving in commuter traffic for 90 minutes. It was argued that exposure to traffic for this period of time would reduce blood oxygen levels by raising carboxyhaemoglobin (COHb) concentration. However neither COHb levels
nor accurate arterial oxygenation were measured – oxygen content of finger capillary blood was the only estimate of oxygenation made. The two groups comprised thirty young, healthy male students and thirty older patients with a variety of respiratory illnesses who were presumed to be hypoxic although no clinical data is presented and no documentation of oxygen status was made. Ramsey found a significant deterioration in reaction time measurements in the groups exposed to traffic, although with the lack of information supplied it is difficult to attribute this change to the effects of hypoxaemia alone (if indeed hypoxaemia was present at all). The lack of information provided, the poorly controlled methodology, the lack of standardization in study design, the poor quality data collection, the simplicity of the measurements made and the apparent lack of appropriate statistical analysis probably negate the findings of this study.

Sung et al studied a group of ten healthy male students (average age of 24 years) using a driving simulator to assess the effects of oxygen concentration on fatigue (Sung et al., 2005). Inspired oxygen concentrations of 18%, 21% and 30% were delivered, however no details regarding the method of delivery were supplied, nor were any measurements of blood oxygen levels performed. They found that subjective fatigue and reaction times whilst driving over a period of two hours was worse on 18% oxygen and best on 30%. However there is a lack of detail provided regarding the statistical analyses performed, and the variance in the data presented suggests that these conclusions might be inappropriate. Given that only young healthy subjects participated, it is unlikely that significant cognitive dysfunction could be expected with the relatively modest reductions in inspired oxygen concentration delivered. This study is more an evaluation of the effects of increased oxygenation rather than of hypoxaemia. Interestingly, apart from the reaction time assessments no data is supplied regarding the actual driving performance on the simulator – the major conclusions of the study were drawn from subjective assessment of fatigue.

There is one further published account of the effects of hypoxia on driving performance, however this is an abstract of a presentation made at the British Thoracic Society scientific meeting (Patel, 2003). A small group of seven hypoxic COPD patients were found to improve steering performance whilst breathing supplemental oxygen as assessed using a steering simulator. Increasing oxygen
saturation from mean SpO₂ values of 85% on air to 96% on oxygen resulted in improved response times, decreased steering errors and fewer off-road events. Worsening of driving performance was found in a separate group of six normoxic COPD patients who were exposed to reduced inspired oxygen concentrations (with saturation falling from 95% at baseline to 88%). The authors concluded that supplemental oxygen is beneficial to steering ability. Being published as an abstract only precludes detailed analysis of this study, however one limitation appears to be that the simulator used evaluated steering performance only and other facets of motor vehicle driving such as speed maintenance, braking performance etc. were not assessed. The small patient numbers are also a limitation of the study.

There is clearly a lack of well-controlled studies investigating the effects of hypoxaemia on driving performance – either in healthy subjects exposed to reduced oxygen environments, or in patients with conditions causing chronic hypoxaemia. Whilst the first of these questions may appear to be of academic interest only, there are certainly situations where a healthy motor vehicle driver may predictably be exposed to hypoxic conditions. Driving in alpine areas where the oxygen pressure of ambient air is reduced significantly from sea level values is one such example.

As mentioned earlier, many studies, particularly in the aviation domain, have demonstrated cognitive deficits evident at altitudes as low as 8,000 feet (Crow and Kelman, 1969, Denison et al., 1966, Gedye, 1964). Whilst driving at this altitude is not possible in Australia where the highest driveable road is approximately 6,000 feet, sealed roads at or above this altitude are more commonplace elsewhere in the world. For example, the city of La Paz in Bolivia at an altitude of approximately 13,000 feet is accessible by bus route. Apart from the usual precautions regarding driving under alpine conditions, there are no specific published recommendations taking hypoxia in consideration when driving at altitude. Whether the types of cognitive decline experienced at driving altitudes translates into increased driving risk remains to be identified.

Hypoxic driving in Australia more frequently occurs when those individuals who are hypoxaemic at sea level are in control of a motor vehicle. The magnitude of the potential risk that these drivers may impose on the country’s roads is difficult to estimate for a number of reasons. Firstly, not all hypoxaemic patients would
necessarily have been identified. One potential mechanism for estimating the number of patients with known hypoxaemia is to examine all those patients registered for use of long-term supplemental oxygen. However this is also problematic since there is no national database (nor is there a Victorian state-wide database) logging all patients receiving domiciliary oxygen. In addition, oxygen supply companies are reluctant to divulge information about numbers of patients that they supply domiciliary oxygen to, presumably for commercial reasons. An Access Economics report in 2008 estimated approximately 15,000 Australians were eligible for provision of LTOT however not all would have been receiving it (Access Economics, 2008). Anecdotally, the proportion of COPD patients receiving LTOT through the Austin Health domiciliary oxygen program who hold current driving licences is estimated to be around 50%. These figures suggest that there are potentially thousands of individuals within Australia for whom driving whilst hypoxaemic would be a common experience.

A further relevant consideration relates to the additional arterial desaturation that occurs with exertion that is commonly observed in severe lung disease. As mentioned in section 4.5 of this review, the metabolic demands that exercising muscles place on a dysfunctional pulmonary gas exchange system may result in exercise-induced arterial desaturation. Whether the exertional demands involved in driving a motor vehicle are heavy enough to cause significant desaturation has never been studied in detail, but could theoretically contribute an additional effect over and above baseline hypoxaemia. The predominant exertional requirements of driving are likely to relate effort involved in steering control, however given the preponderance of current motor vehicles with power steering this is likely to provide only modest increase in workload and hence in exercise-related desaturation. Nevertheless the physical demands of driving on oxygenation in respiratory compromised patients may warrant further investigation.


Early studies investigating the efficacy of continuous oxygen therapy focussed primarily on assessment of clinical symptoms (Petty and Finigan, 1968, Petty et al., 1969, Petty et al., 1971). Other aspects of this treatment modality such as quality of
life assessment, and effects on neurocognitive function would not be performed until later.

Following the work of Jacobs et al (Jacobs et al., 1971) who demonstrated that hypoxic treatment could alleviate some of the neuropsychologic symptoms of senility, Krop and colleagues published the earliest study investigating the neuropsychological effects of continuous oxygen therapy (Krop et al., 1973). They performed a battery of ten neuropsychologic tests on a group of ten hypoxaemic patients (average PaO₂ of 51 mmHg) before and after four weeks of continuous supplemental oxygen treatment. At baseline, they found that neuropsychologic function was worse than in a group of 12 non-hypoxaemic COPD patients with mean PaO₂ of 67 mmHg and almost identical degree of airflow obstruction. However, after four weeks of oxygen therapy there were significant improvements in eight of the ten neuropsychologic tests such that the initial differences between the treatment and the control groups were no longer evident. There was no change in any of the control group neuro-psychometric measurements over the four-week period.

Some limitations in this study include the fact that there was no blinding of the treatments received, and as pointed out by Heaton et al (Heaton et al., 1983), there was no effort made to ensure that the subjects were clinically stable prior to enrolment – the observed improvements may have occurred without oxygen therapy. Furthermore, it is not clear in the study methodology if the post treatment testing was performed whilst breathing room air or whilst on oxygen treatment – this would be expected to have a bearing on the study results. Nevertheless, whilst the strength of the conclusions in this study are somewhat tempered by these limitations, this data was the first to suggest that improvements in neurocognitive function could be achieved by relief of chronic hypoxaemia with the use of continuous oxygen therapy over the short to medium term.

A further early study investigating the physiological, clinical and neuropsychologic effects of LTOT in hypoxaemic COPD was reported by Block and colleagues (Block et al., 1974). This study was similar to that of Krop’s (Krop et al., 1973) in that ten patients were studied over a four-week LTOT period with the baseline PaO₂ being 51 mmHg. The results were also similar with nine of ten tests of
neuropsychologic function improving. However the baseline testing conditions are unclear and it appears that assessment was performed breathing air at baseline, and breathing oxygen for the post LTOT tests. This is an inappropriate comparison to make to investigate the effects of four weeks of LTOT on cognitive function, similarly to the problems noted for Krop’s study (Krop et al., 1973) above. The lack of an appropriate control group, and the lack of treatment blinding once again temper the validity of the conclusions of this study.

Brezinova and colleagues set out to investigate the effect of LTOT on EEG activity in a small group of patients with COPD (Brezinova et al., 1979). Unfortunately the study was very poorly controlled, and the report was very brief with critical information omitted. The study design did not allow the hypothesis to be investigated, and their conclusion that LTOT improves cerebral function was unfounded and is misleading.

The comprehensively performed NOTT trial (NOTT, 1980) investigating efficacy of LTOT included neuropsychologic assessment before and after six months of LTOT treatment in hypoxaemic COPD. Heaton and colleagues reported these results separately (Heaton et al., 1983) and aimed to overcome the limitations identified in Krop and colleagues’ work (Krop et al., 1973). Rigorous entry criteria into the study were applied and included documented stable clinical status and stable hypoxaemia with PaO$_2$ less than 60 mmHg breathing room air. A total of 150 patients completed both baseline and post six months of treatment psychological evaluations. A healthy control group matched for age, sex, education, socioeconomic status and neighbourhood of residence was recruited to document the practice effects on repeated administrations of the psychological tools.

Overall in the oxygen treatment group, there were statistically significant improvements for neuropsychologic global judgement and for the following four individual ability areas: verbal/language functioning, abstraction and flexibility of thinking, simple sensory, and simple motor abilities. It was emphasized however that ‘these improvements were relatively subtle and did not constitute a major reversal of the baseline neuropsychologic impairment in the patients with COPD’ (Heaton et al., 1983). Analysis of more limited data over a 12-month period indicated that continuous oxygen therapy (twenty hours per day) might have some
advantage over nocturnal oxygen therapy (twelve hours per day) in enhancing neuropsychologic function.

It is noteworthy that the improvements observed in this study indicate higher cortical function and motor-sensory abilities – precisely the cognitive domains required for effective motor vehicle driving. It is also important to note that all neuropsychologic testing performed in Heaton and colleagues’ study were performed off supplemental oxygen and therefore, rather than reflecting the short-term acute effects of oxygen supplementation, the improvements noted indicate some carry-over improvement in underlying cognitive operation. The authors suggest that the observed improvements might reflect improved maintenance of neuronal physicochemical integrity, formation of neurotransmitters, or other metabolic tasks (Heaton et al., 1983).

Borak et al measured cognitive and neuropsychologic status in 90 hypoxaemic COPD patients before and after twelve months of LTOT (Borak et al., 1996). They found no change in intelligence quotient nor in visual and spatial memory function, but there were highly significant improvements in speed of work, and in recent verbal memory (P<0.001 for both). They also found improvements in emotional status, depression and anxiety, psychological tension, general mood, self-esteem and attitude toward life and therapy. Whilst these improvements may have resulted from improved long-term oxygenation of the central nervous system, the non-specific effects of the improved mobility and reduced dyspnoea caused by the oxygen therapy may also play a role. In addition, as suggested by Cottrell et al in their evaluation of review of LTOT patients (Cottrell et al., 1995), the psychosocial benefits of the frequent follow-up visits may also have contributed to the observed improvements.

Incalzi and co-workers’ study investigating decline in cognitive function in COPD over two years demonstrated the ongoing deterioration that can be expected in severe COPD (Incalzi et al., 1998). Taking this into consideration, even finding no change in cognitive function over a six-month period may indicate a beneficial effect of LTOT – the fact that some improvement was indeed detected in Heaton and colleagues’ study (Heaton et al., 1983) lends even more support to the hypothesis that LTOT improves cognitive function in hypoxaemic COPD.
Hjalmarsen and colleagues performed a battery of 13 neuropsychological tests before and three months after starting LTOT in a group of ten hypoxaemic COPD patients (Hjalmarsen et al., 1999). Despite finding no statistically significant changes in any of the 13 tests, they concluded that there was a minor improvement in brain functioning following three months of LTOT. Whilst this conclusion is clearly inappropriate from the data presented, the small patient numbers (n=10) also indicate the possibility for a type-II error where the power of the study was not enough to demonstrate a real effect.

There is very limited data assessing the cognitive effects of short term administration of oxygen therapy – the study of Wilson et al (Wilson et al., 1985) is the only well-controlled study available. They assessed the acute effects of oxygen therapy upon information processing ability in a group of ten hypoxaemic COPD patients. Each patient was subjected in randomized turn to inhaled air and inhaled oxygen (sufficient to ensure oxygen saturation of at least 90%) over a period of twenty minutes, and separately over six hours. After each stage a battery of neuropsychologic tests specifically selected to assess information processing ability was performed. Specifically, the tests assessed auditory perception and memory (repetition test), visual perceptual/sensory function (critical flicker fusion test) and depth of processing and memory (story recall test).

Their blinded, crossover design allowed each subject to serve as his or her own control. They found no significant effect of oxygen nor of duration of oxygen therapy on any of the test performances over and above inhaled air, and concluded that acute oxygen therapy does not reverse information processing deficits observed in hypoxaemic COPD. They acknowledged the low patient numbers as a limitation of the study, however there are some other problems which may limit the applicability of the findings.

Firstly, they did not compare their COPD patient group results with an appropriate control group to demonstrate that they did indeed have baseline information processing deficits. Secondly, they stated that all patients had a current prescription for oxygen therapy which raises the possibility that the reason for the lack of cognitive improvement after acute oxygen therapy was that their LTOT had already
caused a reversal in their assumed ‘information processing deficits’, as was
described by other workers investigating effects of long-term oxygen treatment
(Heaton et al., 1983, Krop et al., 1973). And finally, the cognitive domains
investigated may not be relevant to all aspects of neurocognitive function, in
particular, they may not be pertinent in investigating the acute effects of oxygen
therapy on driving performance

Gerard and co-workers studied 24 healthy, young subjects at altitude to determine
the effect of oxygen enrichment (as opposed to supplemental oxygen therapy) on
neuropsychological function (Gerard et al., 2000). They performed a battery of 16
neuropsychological tests after 50 minutes exposure to an inspired oxygen partial
pressure of 78 mmHg, and again after 50 minutes at an oxygen partial pressure of
100 mmHg in a blinded and randomized order. The average arterial oxygen
saturations were 82% and 93% respectively. They found a modest, but statistically
significant improvement in psychomotor vigilance, with a mean improvement of 16
milliseconds in reaction time. They also found a significant improvement in
compensatory tracking, which provides an assessment of eye-hand coordination.
They also found improvements in the subjects’ sense of effectiveness and well-
being, but no other aspects of neuropsychological function were improved.

As discussed in Section 4.8, it may not be appropriate to extrapolate such findings
in young, healthy and presumably normoxaemic subjects to chronically
hypoxaemic COPD subjects. The cognitive effects of long-term hypoxaemia in
COPD are arguably quite different to those caused by short-term hypoxaemia, and
therefore acute reversal may elicit substantial differences in the two groups. Whilst
the data from Gerard and co-workers (Gerard et al., 2000) does suggest that acute
oxygen enrichment can improve some aspects of neuropsychological function, to
conclude that these findings are applicable to the hypoxaemic COPD population
may be erroneous.

6.13. Techniques for Assessment of Driving Performance

The guidelines for health professionals in Australia for assessing fitness to drive
recommend that driver assessment by trained occupational therapists be performed
where there is a medical concern about the patient’s ability to drive safely
(Austroads, 2006). A key component of this is the practical assessment performed
on the road in a dual-controlled vehicle accompanied by the occupational therapist. The assessment is designed to assess the impact of injury, illness or the ageing process on driving skills including judgment, decision-making skills, observation and vehicle handling (Austroads, 2006). Whilst a standard approach is taken with these on-road evaluations, the assessment can be designed to meet individual needs. This type of driving assessment does not lend itself to utility in the research setting since it is impossible to replicate exact conditions, and it is also difficult to objectively quantify performance.

George (George, 2003) reviewed the utility of driving simulators in clinical practice, particularly in the area of sleep medicine and studying the effects of fatigue. He points out that while simulators offer advantages such as greater degree of experimental control and more reliable and precise performance measures such as lane position variability, they do not provide all the visual, vestibular, and proprioceptive information of real-world driving which they simulate.

The question of how assessment of driving performance using driving simulators compares with on-road performance was investigated by Lee and colleagues (Lee et al., 2003). They studied a group of 129 elderly drivers both on the road and using a computerised simulator and found that an assessment index based upon the simulator performance could explain over two-thirds of the variability in on-road performance. The validity of the driving simulator as a driving assessment tool was supported by their data and they suggested that driving simulation is safer and more economical than on-road assessment.

To summarize, problems associated with real-world, on-road driving assessment include:

- lack of ability to standardize the driving task
- lack of ability to provide identical, or near identical, test conditions for assessing interventions
- physical dangers associated with on-road conditions
- difficulty in providing effective and reliable performance measures

Driving simulators overcome all these problems, but offer the following disadvantages:
• lack of authenticity compared with real-world driving
• lack of awareness that the driver’s safety is consequent to driving performance
• lack of data establishing how the results compare with real-world driving


The AusEd driving simulator was developed as a simple, inexpensive PC-based driving simulation system appropriate for and conducive to driver fatigue (Desai et al., 2007). It comprises a standard desktop computer with audio speakers, a steering wheel and dual foot pedal interface, and software to display the simulation from the driver’s perspective. In addition to the road view, the computer monitor also displays the vehicle speed as a speedometer at the top left of the screen. Being located outside the line of sight of the road, this represents a divided attention task. Software for analysing data collected during the simulation is also included in the system.

The driving task simulates a dual roadway at night and the driver’s instructions are to maintain suitable lane position, and to maintain the target speed of between 60 and 80 kilometres per hour. Trucks appear at random times, and the driver is required to brake as soon as they appear – this allows assessment of reaction times. Crashes are defined in three ways:

• veering outside off-road reference points (right or left)
• truck collisions
• ‘stand still’ where no movement is detected for ten seconds

The simulator provides user selectable options for such variables as total duration, duration of straights and curves, number of trucks appearing and seed number used to derive the course layout.

The utility of the simulator system in the clinical assessment of driver fatigue was evaluated by Desai and colleagues (Desai et al., 2007) who found it to be sensitive to performance decrement from driver fatigue. The AusEd driving simulator measures have also been found to be sensitive at detecting performance decrements due to such factors as sleep deprivation (Desai et al., 2006, Howard et al., 2007), alcohol (Banks et al., 2004, Banks et al., 2005, Howard et al., 2007), circadian
influences (Desai et al., 2006) and sleepiness (Banks et al., 2005). The reproducibility of the simulation was also found to be acceptable (Desai et al., 2007).

Primary outcome measures for the AusEd simulation system include variations in lane position, variations in speed, reaction times for braking in response to the on-screen appearance of trucks, and number and types of crashes. In their evaluation of the AusEd system in assessing sleep apnoea, Desai and colleagues found lane position variation, reaction times and crash data to be most sensitive in discriminating between their sleep apnoea and control groups (Desai et al., 2007). Similarly, lane position variability during driving simulation was found to be the most sensitive measure for assessing and quantifying driving impairment in another study evaluating patients with obstructive sleep apnoea (Risser et al., 2000).

Whilst the utility of the AusEd driving simulator as a tool for investigating driver fatigue has been demonstrated in a variety of conditions (Banks et al., 2004, Banks et al., 2005, Desai et al., 2006, Desai et al., 2007, Howard et al., 2007) there are no data specifically evaluating the system as a predictor of real, on-road driving performance. Whilst data from Lee and colleagues indicates that driving simulation is strongly associated with on-road performance (Lee et al., 2003), care should clearly be taken in extrapolating AusEd performance to on-road performance.

6.15. The Psychomotor Vigilance Task (PVT)

The psychomotor vigilance task was originally developed as a simple method of monitoring vigilance (Wilkinson and Houghton, 1982). It has received wide acceptance as a measure of neurobehavioral performance, particularly in the assessment of the effects of sleep loss and fatigue. The task involves responding to a visual stimulus that appears at random times by pressing a response button. The instruction to the subject is to press the response button as soon as possible after the stimulus and to continue to do so for the duration of the task, which is typically set at ten minutes. The PVT device records reaction times for analysis after completion of the study.
The PVT device was originally designed to utilise a mixed digital/analog cassette recorder, but was re-created as a fully digital system (Dinges and Powell, 1985) which was marketed commercially by Ambulatory Monitoring Inc as the model PVT-192 device. The PVT-192 has been the device of choice for most PVT research over the past 2 decades however more recently the test has become available as a software package for download to a Palm-type device to further improve portability and reduce costs (Thorne et al., 2005).

The test duration used for the PVT is typically set at ten minutes, however it is recognised that, particularly in field-based studies, it may not be practical to dedicate this period of time for vigilance assessment. Several studies have investigated the utility of a five-minute test and found that the abbreviated test does provide similar results to the ten-minute test in assessing the effects of sleep deprivation (Lamond et al., 2005, Loh et al., 2004, Roach et al., 2006). However it is noted that the ten-minute test should remain as the standard for laboratory assessment since it is more sensitive to sleepiness (Loh et al., 2004), but the five-minute version does provide a useful substitute where there are specific time restraints (Lamond et al., 2005).

The PVT is one of the most widely used neurobehavioral tests in studies of sleep and circadian rhythm research (Drummond et al., 2005). Amongst other factors, it has been shown to be sensitive to age (Philip et al., 1999, Urrila et al., 2004), caffeine use (Wright et al., 1997), bright light (Wright et al., 1997), sleep deprivation (Drummond et al., 2005, Howard et al., 2007, Lamond et al., 2005, Urrila et al., 2004), driving trip duration (Philip et al., 1999), alcohol ingestion (Howard et al., 2007) and oxygen supplementation (Gerard et al., 2000). The PVT result is generally considered to reflect the arousal and attentional state of the individual (Drummond et al., 2005).

There are a number of measures obtained from PVT assessment, all derived from the raw reaction time measurements. Those parameters found to best reflect neurocognitive function include mean or median reaction time and number of lapses in vigilance – usually defined as a reaction time of greater than 500 milliseconds.
The magnitude of change in mean reaction time caused by extended wakefulness ranges from approximately 16 milliseconds for 18-21 hours wakefulness in professional drivers (Howard et al., 2007), to more than 200 milliseconds after 40 hours of wakefulness (Urrila et al., 2004). Effects of alcohol ingestion have been found to increase mean reaction time by approximately 13 milliseconds at 0.03% blood alcohol content (BAC), to approximately 33 milliseconds at 0.05% BAC (Howard et al., 2007).

The PVT has also been used as an objective performance indicator to assess relationships between driving risk factors and performance (Philip et al., 1999). When assessing drivers who drove into a rest stop area, Philip and colleagues found a small, but statistically significant relationship between duration of drive and reaction time measurements. This indicates that the PVT device can be effectively used outside the laboratory environment to enable objective assessment of neurocognitive performance consequent to ‘real-world’ environment (i.e. actual driving duration scenarios).

The PVT has been used to assess neurocognitive effects of oxygen supplementation (Gerard et al., 2000) where mean reaction time was improved by 16 milliseconds – the consequences of this magnitude improvement on overall ability to control a motor vehicle are unknown, however it is comparable to the magnitude of change found with increased blood alcohol content of 0.03% BAC (Howard et al., 2007).

6.16. Summary

It is clear that cognitive dysfunction is common in subjects with chronic obstructive pulmonary disease, and probably more so in those with concomitant hypoxaemia. The types of neurocognitive deficits observed (such as decision making and motor-sensory abilities) are those likely to affect motor vehicle driving performance. Duration and severity of disease, duration of hypoxaemia prior to treatment, duration of LTOT and number of hours used per day are all factors which influence the magnitude of the neurocognitive deficit in COPD.

Whilst long-term oxygen therapy over a period of months to years does appear to provide improvements in the cognitive dysfunction observed in this subject group,
there is little objective evidence that acute oxygen therapy (over the period of minutes to hours) provides any beneficial effects to neuro-cognitive function. In fact there are data that indicate that 4 hours off supplemental oxygen therapy does not cause a decrement in neurocognitive performance suggesting that, from a neurocognitive perspective, driving performance would not be expected to be affected for driving over this time period or less.

Despite the lack of objective supportive evidence, the medical recommendations for hypoxaemic patients indicate that portable oxygen therapy be used whilst driving. There are important safety and economic implications involved in these recommendations, and so it is considered important to investigate whether acute oxygen therapy is likely to provide objective improvement in driving performance or in cognitive function in this patient group. The utility of the AusEd driving simulator and the psychomotor vigilance task appear to provide suitable investigative metrics to enable such an assessment to be performed in an objective manner.

7. Aims of This Study

The primary aim of this study is to objectively investigate whether acute administration of supplemental oxygen therapy produces measurable improvement in neurocognitive performance in hypoxaemic subjects with COPD. Assessment of performance on a motor vehicle simulation task and of reaction time measurements will be used to determine the effects of this intervention.

The rationale behind this investigation is to enable evidence-based recommendations to be made about the use of supplemental oxygen therapy whilst driving a motor vehicle in this patient group.
8. Methods

8.1. Subject Selection and Recruitment

Given the aim of the study was to investigate the effects of supplemental oxygen on driving and cognitive performance in drivers who were eligible for long-term oxygen therapy, it was clearly appropriate to recruit subjects who qualify for the provision of this therapy. The relevant guidelines for LTOT provision in Australia are those of the Thoracic Society of Australia and New Zealand (McDonald et al., 2005) and the primary qualification is demonstration of significant hypoxaemia breathing room air at rest. This is defined as an arterial oxygen partial pressure of less than or equal to 55 mmHg, or less than 60 mmHg with evidence of hypoxic organ damage (McDonald et al., 2005). A further requirement was that the hypoxaemia could be reversed to above 60 mmHg with the provision of relatively low-flow intranasal oxygen supplementation (of up to 4 L/min).

The predominant indication for provision of LTOT in Australia and New Zealand is COPD (McDonald et al., 2005), and in an effort to maximise the generalisability of study results, as well as to maximise potential to recruit subjects, it was considered important to limit recruitment to those with COPD only. Subjects were therefore required to have a clinical diagnosis of COPD as well as documented airflow obstruction demonstrated by spirometry (Abramson et al., 2006).

With the primary aim of the study to assess effects on driving performance it was considered important to recruit only those subjects who held current driver’s licences. It was not considered essential that subjects continue to be active and/or regular drivers, but that they could potentially take control of a motor vehicle – hence the requirement for currency in licensing.

Ability to provide informed consent for participation in the study was a further inclusion criterion, as was physical ability to perform the driving simulation and PVT testing procedures. To summarise, inclusion criteria for recruitment into the study were:

- Documented arterial hypoxaemia on room air ($\text{PaO}_2 \leq 55$ mmHg or $\text{PaO}_2 < 60$ mmHg with evidence of hypoxic organ damage)
- Clinically diagnosed COPD with spirometric evidence of airflow obstruction as defined by FEV1/FVC ratio of less than 70%
- Current driver’s licence

Exclusion criteria were:
- Inability to provide informed consent
- Inability to comprehend the purposes and requirements for the study in the English language
- Inability to adequately perform the driving simulation and PVT testing procedures

Subjects were primarily recruited from the Domiciliary Oxygen Clinic within the Department of Respiratory and Sleep Medicine at the Austin Hospital. This Clinic is involved in assessment of patients considered suitable for long-term oxygen therapy, and in those current LTOT patients undergoing regular review. Clinic staff were informed about the eligibility for inclusion in the study and asked to contact the study coordinator when suitable patients were identified. To further expand ability to recruit suitable subjects, information about the study and eligibility criteria was also provided to clinicians in Department of Respiratory and Sleep Medicine outpatient clinics at Austin Hospital.

Once recruited into the study, each subject was given an appointment to attend for conduct of the testing procedures and supplied with taxi vouchers to simplify attendance and return home. There was no financial reward offered for participation in the study. Subjects reported to the Austin Hospital Department of Respiratory and Sleep Medicine where testing procedures were performed within the Heidelberg House Sleep Laboratory. All testing was performed during normal working hours and in total, all testing procedures for the study were usually completed in approximately 2.5 hours.
8.2. Ethical Considerations, Approval and Trial Registration

Approval for the study was obtained from the Ethics Committees of Austin Hospital (project number H2004/01857) where the research project was carried out, and of Charles Sturt University (protocol number 2006/303). These committees operate under the guidelines of the National Health and Medical Research Council and the study was carried out in accordance with the National Statement on Ethical Conduct in Research Involving Humans (NHMRC, 1999). Copies of applications and letters of approval from both committees are included in the appendix.

An essential component of the ethics approval process involves the information provided in the ‘Participant Information Sheet’. The overall aim of this information sheet is to allow potential participants to make a conscious, informed, rational decision about participation without unnecessary pressure. The ‘Participant Information Sheet’ used for recruitment for this study is included in the appendix.

For participation in this study a fundamental requirement was demonstration of arterial hypoxaemia and documentation of adequacy of supplemental oxygen therapy, both of which require arterial blood sampling. However it is important to note that these tests were not performed as part of the research study, rather, they were being performed as part of each subject’s routine medical management. Subjects were specifically recruited from the Domiciliary Oxygen Clinic after they had undertaken these tests and after it had been demonstrated that they had met the selection criteria for inclusion in the study. It was therefore not necessary to document the risks involved in arterial blood sampling in the participant information sheet.

The only potential risk identified as being involved with this study, and as indicated in the ‘Participant Information Sheet’ was a theoretical risk that acute oxygen therapy can lead to a reduction in the rate or depth of breathing and may lead to increased blood carbon dioxide levels. It was pointed out that the participant had previously undergone formal determination of the oxygen flow rate that was appropriate and safe for them, and that oxygen would only be given at this safe flow rate for the purposes of this study.
Also in accordance with the NHMRC guidelines (NHMRC, 1999) and in accordance with the ethics committees’ requirements, all subjects recruited for the study were required to provide informed consent which was achieved by way of witnessed signature on the ‘Consent Form to Participate in Research’ – a copy of which is provided in the appendix.

The International Committee of Medical Journal Editors published a joint editorial in 2004 stating that results from any interventional trials would only be published if they had been previously registered in a publically accessible clinical trials registry (De Angelis et al., 2004). Their definition of ‘clinical trial’ was:

*Any research project that prospectively assigns human subjects to intervention and comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome.*

It was considered for the proposed study that oxygen therapy could be considered as a ‘medical intervention’ and that cognitive function and driving performance could reasonably be considered a ‘health outcome’. In any event, the Australian and New Zealand Clinical Trials Registry states that ‘if in doubt, registration is recommended’ (ANZCTR, 2007). As such, the *Effects of acute oxygen therapy on cognitive and driving performance in hypoxaemic COPD* trial was registered in August 2005 with the clinical trials registration number ACTRN12605000249651, with the trial acronym name *DriveOx*.

### 8.3. Testing Techniques

#### 8.3.1. Spirometry

An essential requirement for a diagnosis of chronic obstructive pulmonary disease to be made is demonstration of airflow obstruction which has been defined as an FEV₁/FVC ratio of less than 70% (Abramson et al., 2006, Pauwels et al., 2001). Furthermore, the FEV₁ when expressed as a percentage of the mean predicted value can be used to characterise the severity of the airflow obstruction (Pellegrino et al., 2005). Spirometry is therefore a fundamental requirement in the diagnosis and management of COPD.
All subjects asked to participate were required to have had documented evidence of airflow obstruction and spirometry was performed to ensure this. Standard laboratory procedures (Pretto, 2004) were followed in the performance of spirometry using either a wedge bellows spirometer (Vitalograph Ltd, Buckingham, UK) or a mass-flow sensor-based spirometer (Sensormedics Corporation, Yorba Linda, USA). These procedures were based upon the guidelines of the American Thoracic Society (ATS, 1995). The spirometric indices of FEV₁ and FVC were compared with the mean predicted values derived from the normal reference values of Knudson (Knudson et al., 1983). In non-caucasian subjects, correction of the predicted values for ethnicity were made as recommended by the American Thoracic Society (ATS, 1991).

8.3.2. Arterial Blood Gases

Arterial blood gas analysis provides the ultimate test of respiratory function in that it allows quantification of the adequacy of the lungs to perform their primary function – that is to adequately oxygenate the blood whilst appropriately excreting carbon dioxide. The technique used for arterial blood gas (ABG) sampling and analysis used for this study was in accordance with the Austin Hospital Respiratory Laboratory Methods Manual (Guy, 2003) and involves anaerobically taking an approximately 1-millilitre blood sample from the radial artery. Samples are taken using the Rapidlyte arterial blood gas sampling kit (Ciba Corning Diagnostics Corporation, Massachusetts, USA). The plastic syringes included in these kits have dry, lyophilized heparin included within the syringe to prevent clotting.

To minimise trauma a 25-gauge needle was used. Also in accordance with standard Austin Hospital methodology, no local anaesthetic was used for sampling since this has not been found to reduce the pain associated with arterial puncture (Tran et al., 2002). On completion of sampling care was taken to remove any air bubbles prior to gentle agitation to ensure adequate mixing of the heparin.

The arterial sample was analysed using a calibrated, semi-automated blood gas analyser (Radiometer model ABL500, Radiometer Medical ApS, Denmark) which
was operated in accordance with the Royal College of Pathologists Australia with full accreditation from the National Association of Testing Authorities (NATA). All analysis was performed within 10 minutes of sampling to minimise potential errors due to ongoing metabolism by the living cells within the sample, and due to diffusion of oxygen and carbon dioxide through the syringe walls (Pretto and Rochford, 1994).

The ABL500 blood gas analyser incorporates a co-oximeter for direct measurement of arterial saturation (SaO₂), as opposed to calculated values that blood gas analysers without co-oximeters produce. This provides a more accurate estimate of true oxygen saturation since it is directly measured and does not rely on assumptions made in the calculation method.

Blood gas sampling was performed in a comfortable, seated position whilst breathing room air – at least 15 minutes of rest was allowed prior to sampling to allow adequate time to return to the resting cardiopulmonary state.

Adequacy of oxygen therapy was documented by repeating ABG sampling and analysis whilst supplemental oxygen was delivered via intranasal prongs. In accordance with the TSANZ position statement on domiciliary oxygen therapy (McDonald et al, 2005), the target PaO₂ for supplemental oxygen was above 60 mmHg. The flow rate of oxygen supply was generally initiated at 2 L/min, except for when hypercapnia (defined as a PaCO₂ of above 45 mmHg) was found on room air ABG analysis – in this case a reduced flow rate of 1 to 1.5 L/min was delivered. At least ten minutes of rest whilst on supplemental oxygen was allowed prior to ABG sampling to allow adequate equilibration for the step change in inspired oxygen concentration.

The alveolar-arterial oxygen gradient, P(A-a)O₂, was calculated as:

\[ P(A-a)O_2 = PAO_2 - PaO_2 \]

Where PaO₂ is the measured arterial oxygen partial pressure in mmHg, and PAO₂ is the partial pressure of oxygen in the alveolar space in mmHg and is calculated using the simplified ideal air equation (Ruppel, 2009):
\[ PAO_2 = (PB - 47) \times \text{FiO}_2 - PaCO_2 / R \]

Where PB is the barometric pressure in mmHg, 47 is the assumed partial pressure of water vapour in the lungs in mmHg, FiO₂ is the fractional inspired oxygen concentration, PaCO₂ is the measured arterial carbon dioxide partial pressure in mmHg and R is the respiratory exchange ratio and assumed to be equal to 0.8.

Given that the exact FiO₂ is not known whilst breathing intranasal oxygen (since it is dependant upon unknown factors such as inspiratory flow-rates and timing, oro-nasal breathing patterns etc.), the P(\(A-a\))O₂ gradient is calculated from the baseline ABG sample collected whilst breathing room air.

8.3.3. Other Subject Information Obtained

Other information considered relevant to the study and obtained from all subjects recruited included:

- Demographics/anthropometry - standing height without shoes to the nearest centimetre, dressed weight and date of birth were obtained to enable calculation of predicted values for respiratory function test indices (FEV₁ and FVC)
- Driving history - number of years experience in motor vehicle driving was recorded. Whilst all participants had current driving licences, not all continued to drive – date and reason for stopping were also recorded. For those continuing to drive, an estimate of the average number of car driving trips undertaken per week was also obtained.
- Smoking history - including whether current, never or ex smoker and estimates of smoking rates and duration. These data was used to quantify smoking history in terms of pack years (where one pack year is the equivalent of smoking 20 cigarettes per day for one year). The following equation is used to calculate pack years (where P is the number of pack years, Y is the number of years smoked for and C is the average number of cigarettes per day over those years):

\[ P = C \times Y / 20 \]
- Long-term oxygen therapy history - whether the subject was on LTOT, and the duration of LTOT at the time of the study.
- Gas preference – at the completion of the study each subject was asked whether they believed that they had performed better on the driving simulator or on the PVT device on one gas over the other. Their preference was recorded as gas 1 or gas 2, or as no noticeable difference.

8.3.4. Delivery of Supplemental Gases

A key component in the provision of the supplemental gases required for the experiment involved the double-blinding of which gas was being supplied during testing. To achieve this, sealed envelopes were prepared by a colleague not involved in the testing procedures which included a small datasheet indicating the order of gases to be received by each subject. Randomization was performed using a published table of random numbers (Swinscow, 1996) to generate the order for each gas delivery – an odd number indicated oxygen to be used first, and an even number indicating air first. The front of the envelope indicated the subject number only. Figure 8.1 shows the order of testing procedures for each subject visit.
After completion of the familiarisation simulation and PVT session, a colleague (not involved in the project) was asked to open the sealed envelope allocated for each subject, and to connect the intranasal prongs to the gas indicated to be used initially.

Medical grade oxygen and air cylinders were used to supply the test gases (BOC Australia, Preston, Victoria). The cylinders were located next to each other and the gas cylinder flow-meters and regulators were concealed with a drape after connection. The arrangement was such that neither the operator nor the subject was able to determine which gas was being delivered. Given that oxygen is not discernibly different in taste or smell from air, it was possible to ensure complete blinding of the subject to the gas being delivered.

After a five-minute wash-in period, the colleague used a pulse oximeter (Nellcor model N595, Tyco Healthcare Group, Pleasanton, Ca., USA) via finger-probe to measure arterial oxygen saturation. The average saturation was recorded on the datasheet (appendix) included in the sealed envelope. Care was taken to ensure that neither the subject nor the operator were aware of the saturation readings.
At the completion of the second series of tests, the colleague was also asked to stop the original gas supply, and in a similar fashion to that performed for the first gas, to switch to the second gas for the third series of measurements. Again, arterial saturation values were measured and recorded after a further five-minute wash-in period.

8.3.5. Driving Simulation

Driving performance was assessed using a computer-based driving simulator (AusEd software, Woolcock Institute of Medical Research, Sydney, Australia), which utilizes a steering wheel and foot pedals connected to a standard desktop computer with a 19-inch monitor (Figure 8.2). The view is of a dual-carriage rural road at night from the driver’s perspective, with a speedometer displayed in the top corner of the screen. Subjects were instructed to maintain a position in the centre of the left hand lane and to maintain a speed between 60 and 80 km/h. The software generates a pseudorandom course for each test session; however, the same random number seed was used for all testing, which allowed similar but not predictable courses to be generated for each assessment.

Driving assessments were performed in a quiet, darkened room with the computer monitor and driving controls set up with minimal distractions. The steering wheel height was not adjustable, however seat height adjustment and position from the steering wheel allowed a comfortable driving position to be established. Some subjects also used a pillow behind the back to make a comfortable driving position.

Prior to the first of the three driving simulations, a practice period of approximately three to five minutes was allowed to instruct each subject in the conduct of the test. This was considered an appropriate practice period given that the first simulation (familiarisation session) was effectively a full-length practice simulation. The duration of each of the three simulations was 20 minutes. No subject had previous experience using a driving simulator.
Trucks appear in the near distance on the road at random times during the simulation task. The instructions given to the subject are to brake immediately that these trucks are seen. The AusEd software provides reaction time measurements indicating the time elapsed between the truck appearance and the brake pedal being pressed. Unfortunately many subjects had significant difficulty in accurately pressing the brake pedal and these data was thought to be too unreliable to be useful. Given that reaction time assessment was performed separately using the PVT device, it was decided that reaction time from the driving simulation would not be included in the analysis. Whilst the truck braking reaction time data was not to be used, the number of trucks appearing during the simulation was kept identical for all subjects.

The simulation is performed using the ‘Sampler’ computer program which forms the basis of the AusEd software. This program has a number of user-selectable
options which set the conditions of the simulation. The settings used for all testing for this project were:

- **Total time = 20 minutes.** This is the total duration of each simulation.
- **Chicanes = 5.** This determines the number of minutes spent driving through chicanes in the simulation task.
- **Straights = 2.** This sets the number of minutes spent on driving on straights.
- **Trucks = 10.** This sets the total number of trucks that appear at random times during the duration of simulation.
- **Random number seed = 153.** This setting determines the physical or geographical arrangement of the driving simulation task in terms of positions of straights, chicanes and corners. The same random number seed was used for all simulations to enable similar, but not identical nor predictable, courses to be used for all testing.

The familiarisation data was not used for analysis. Furthermore, the initial 7 minutes of each simulation was also excluded from analysis for two specific reasons. Firstly to overcome the initial variability in driving performance associated with the ‘start-up’ period of the simulation. And secondly, to allow an additional ‘wash-in’ period for the inhaled gas during the conditions of driving simulation. Whilst at least five minutes was allowed breathing the test gas prior to starting the driving simulation, it was thought that an additional period whilst driving was warranted to ensure ‘steady-state’ conditions were achieved.

There were three primary measurement outcomes for driving performance used for the purposes of this study:

1. **Steering variation.** This is calculated by the AusEd system as the total area in vehicle position away from the centre of the left lane over the duration of the simulation. To account for differences in interpretation of ‘the centre of the lane’ between subjects, the AusEd software also calculates the steering deviation from the median lane position during the drive (excluding crashes). This is expressed as the total area of deviation away from the median for the duration of the simulation.
(expressed in cm$^2$). This metric is labelled as *PosMedArea* in the AusEd analysis output file.

2. Speed variation. The instructions given to the subjects was to maintain speed within the target zone of 60-80 kilometres per hour (km/h), hence it is appropriate to express speed variation as variation outside this range, rather than variation away from the 70 km/h average target value. There are two calculations performed by the AusEd software which represent speed variation – the average speed deviation outside the target range (expressed in km/h), and the total area outside the target range over the duration of the simulation (expressed as km$^2$/h$^2$). These indices are labelled as *Sp60-80Avg* and *Sp60-80Area* respectively in the AusEd analysis output file. Given that the speed indicator is outside the line of sight of the driver, these metrics are considered to represent a divided attention task (Desai et al., 2007).

3. Number of crashes. Crashes are defined within the AusEd software as follows (Desai et al., 2007):
   - Off-road events, which are defined as the vehicle being located outside the allowable limits of either left or right lane (which are located 540 cm to the left and 900 cm to the right of the lane centre position respectively).
   - Stand still, where the vehicle has remained completely stationary for a period of ten seconds.
   - Truck collision, where the vehicle collides with the presented truck obstacle.

### 8.3.6. Psychomotor Vigilance Task

The handheld PVT-192 monitor (Ambulatory Monitoring Inc., Ardsley, NY, USA) measures and stores reaction times to visual stimuli, which occur randomly over the period of the test (Figure 8.3). The visual stimulus is a red light-emitting diode (LED) counter/timer which starts counting at random times. The device provides immediate feedback to the subject for each reaction time measurement by displaying the measured reaction time in milliseconds. Each PVT test session was set to a duration of ten minutes with the minimum time between stimuli set at 2 seconds and the maximum set at 4 seconds.
Figure 8.3: The PVT-192 monitor. The LED display provides immediate feedback for each response by displaying the reaction time in milliseconds.

The instructions given to each subject are to watch the display, and to press the button to stop the timer as quickly as possible. The subjects are informed of the total time for testing, but no feedback regarding time elapsed nor time remaining is provided. Each subject is also advised not to try to predict or anticipate the stimulus appearing. The device detects and records anticipations if the button is pressed prior to the stimulus appearing.

The PVT device stores data for the three test runs, which is downloaded for analysis with the provided software (PVTcomm) at the completion of testing. The data is then analysed using further software supplied with the device (PVT React). The analysis program creates a list of measured reaction times, then analyses these data to produce textual and graphical results. The key measurements obtained from this software are:

- Reaction times in milliseconds. These are expressed as medians or means of valid data (that data not considered an anticipation nor lapse
error as described below). Reaction times can also be expressed as mean or median of the fastest 10% of valid measurements, which has been described as reflecting the ‘optimum response’ (Dinges and Powell, 1989). Alternatively the mean or median of the slowest 10% of valid measurements can also be used – this has been found to be sensitive to physiological changes even in the absence of changes in median or fastest 10% reaction time (Wright et al., 2002).

- Lapse errors – the number of reaction times of more than 500 milliseconds. These are considered to represent lapses in concentration.

- Anticipation errors – the number of times the button is pressed prior to the stimulus appearing. In addition, reaction times that are considered to be physiologically impossible (defined as less than 100 milliseconds) are also classified as anticipation errors.
8.4. Statistical considerations

Sample size calculations were performed using PVT data as the primary outcome variable. The reason why driving simulation data was not used for sample size calculations was because, at the time of study design, there was little published data describing variability and significant changes in AusEd driving simulator data. Variables used for the sample size calculation were a minimum meaningful change of 25 msec in median reaction times, power of 90% and an alpha value of 5% (Bach and Sharpe, 1989). These calculations indicated that 27 subjects would be sufficient to detect changes in median reaction times with a power of 90% at a 5% significance level. It was decided that the subject recruitment target be set at 30 participants.

Since the time of study design there has been a number of publications using the AusEd driving simulation system. Post-hoc power calculations confirmed that the sample size achieved (30 subjects) resulted in a power of better than 95% to detect similar changes in driving parameters to those observed in low-level alcohol ingestion (Banks et al., 2004), and to detect similar reaction time changes in response to sleep deprivation (Drummond et al., 2005).

Because of the non-normal distribution of most PVT-derived reaction time measurements and driving simulation data, non-parametric analyses were used to compare air with oxygen values - Wilcoxon signed rank tests for paired data were used for these comparisons. Parametric statistics (means and standard deviations) were used for less critical and approximately normally-distributed data, such as baseline demographic, anthropometric, smoking and driving histories and spirometric values. Other variables which were clearly skewed away from a normal shape (such as LTOT duration) were described as median values. Parametric correlations (Pearson) were performed to assess relationships between variables given that the distributions of median data from the 30 subjects were approximately normal. A p-value of less than 0.05 was considered to be significant for all tests. Statistical analyses were performed using Sigmaplot software (Systat Software Inc., version 9.0, San Jose, CA, USA) and Microsoft Excel (Microsoft Office Excel 2003 SP3, Seattle, WA, USA).
9. Results

9.1. Subject Recruitment

A total of 44 subjects were identified as meeting the inclusion criteria and were approached to consider participating in the trial. Figure 9.1 shows the progression of subjects through each stage of recruitment and participation in the trial and includes the breakdown of reasons for subjects who did not complete the trial. There was one subject who was interested in participating but could not attend due to work commitments. The two subjects who did not complete testing withdrew because of a feeling of nauseous ‘motion sickness’ during the baseline driving simulation – no further testing was conducted in these subjects and none of the data from these subjects were used in the analysis. All results for the following section are derived from the data collected from the thirty subjects completing the study.
Figure 9.1: Number of subjects involved at each stage of recruitment and testing.

N = 44 subjects invited to participate

- N = 4 not interested
- N = 1 interested but unable to attend
- N = 4 too unwell and/or clinically unstable

N = 35 booked for testing

- N = 2 did not attend testing

N = 33 commenced testing

- N = 2 did not complete testing

N = 31 completed testing

- N = 1 data omitted due to O2 failure

N = 30 complete data obtained
9.2. Baseline Subject Characteristics

9.2.1. Demographics/Anthropometry

Table 9.1 shows mean values for all subjects for height, weight, age, body mass index (BMI, calculated as weight in kilograms divided by the square of height in metres) and the gender breakdown. All subjects recruited for the study were of caucasian ethnicity.

The average age of participants was relatively high at 72 years. This was expected given the relatively prolonged lead time for COPD to develop, and to become sufficiently severe to achieve hypoxaemia serious enough to achieve LTOT eligibility. For example, the trend data showing the relationship between tobacco usage and COPD incidence suggests an approximately 20-year delay between smoking initiation and development of COPD (AIHW, 2009).

Figure 9.2 shows the distribution of BMI for 29 of the 30 subjects (missing weight data for subject #1). Only 7 of 29 subjects (24%) were within the healthy BMI range, with 62% being overweight or obese. The average subject was overweight, which is not typically associated with the cachexia and low BMI often seen in severe COPD and contributing to increased mortality (Celli et al., 2004).

Table 9.1: Mean and range of demographic and anthropometric data for the 30 subjects.

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>male/female</td>
<td>22 / 8</td>
</tr>
<tr>
<td>Age</td>
<td>years</td>
<td>72 (7.9)</td>
</tr>
<tr>
<td>Height</td>
<td>cm</td>
<td>167.0 (7.5)</td>
</tr>
<tr>
<td>Weight</td>
<td>kg</td>
<td>80.1 (21.3)</td>
</tr>
<tr>
<td>BMI</td>
<td>kg/m²</td>
<td>28.8 (9.4)</td>
</tr>
</tbody>
</table>
9.2.2. Smoking History

Table 9.2 indicates the smoking history for the subject group. As expected given the primary aetiology of COPD, all participants had been heavy smokers of cigarettes with an average of just over 50 pack years. Only one subject was an active smoker at the time of the study (at 10 cigarettes per day).

Table 9.2: Smoking history summary for the 30 subjects.

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>Ex / Current</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>How long stopped</td>
<td>Years</td>
<td>9.4 (9.6)</td>
<td>0.2 – 32.0</td>
</tr>
<tr>
<td>Smoking history</td>
<td>Pack years</td>
<td>51.5 (19.7)</td>
<td>20 - 96</td>
</tr>
<tr>
<td>Smoking status</td>
<td>Ex / Current</td>
<td>29 / 1</td>
<td>-</td>
</tr>
</tbody>
</table>
9.2.3. Spirometry

Means and ranges for spirometric data are shown in Table 9.3. Spirometric values are compared with the mean predicted values derived using height, age and gender (Knudson et al., 1983). All subjects were of caucasian ethnicity hence no corrections to predicted values for spirometry were required.

Table 9.3: Spirometric data for the 30 subjects.

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>( FEV_1 ) Litres BTPS</td>
<td>1.04 (0.53)</td>
<td>0.42 – 2.46</td>
</tr>
<tr>
<td>( FEV_1 % ) Pred</td>
<td>41 (18.0)</td>
<td>19 - 98</td>
</tr>
<tr>
<td>( FVC ) Litres BTPS</td>
<td>2.83 (0.90)</td>
<td>1.50 – 5.10</td>
</tr>
<tr>
<td>( FVC % ) Pred</td>
<td>86 (19.1)</td>
<td>57 - 138</td>
</tr>
<tr>
<td>( FEV_1/FVC ) %</td>
<td>36 (11.9)</td>
<td>15 - 67</td>
</tr>
</tbody>
</table>

Figure 9.3 shows the breakdown of severity of airflow obstruction using the severity categorization recommendations of the ATS and ERS (Pellegrino et al., 2005). The distribution of subjects is clearly skewed towards more severe airflow obstruction with 22 of the 30 subjects being classified as severely obstructed. This categorization of severity is based upon the \( FEV_1 \) as a percentage of the mean predicted value. Using the \( FEV_1 / FVC \) ratio to characterise severity of obstruction, as was commonly performed prior to the ATS/ERS publication (Pellegrino et al., 2005), there is a similar skewness towards more severe airflow obstruction (data not shown).
9.2.4. Arterial Blood Gases

Results from analyses of arterial blood gases whilst resting breathing room air, and whilst breathing supplemental oxygen are shown in Table 9.4. As expected given the eligibility criteria for entry into the study, arterial oxygen partial pressures were reduced significantly below the predicted values (Harris et al, 1978) such that the average difference between the predicted PaO2 and actual PaO2 on room air was 34.2 mmHg.

The only significant differences between air and oxygen values were for PaO2 and SaO2 (p < 0.0001 for both). Alveolar-arterial oxygen gradient is calculated using the blood gas analyses whilst breathing room air. The mean data indicate that subjects were hypoxaemic with a widened P(A-a)O2 gradient, slightly
hypercapnoeic but with a normal pH whilst breathing room air. This indicates chronic alveolar hypoventilation.

Table 9.4: Data obtained from arterial blood gas analysis for the 30 subjects.

<table>
<thead>
<tr>
<th></th>
<th>Room Air</th>
<th>Supplemental O₂</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Range</td>
</tr>
<tr>
<td>pH</td>
<td>7.41 (0.03)</td>
<td>7.35 – 7.48</td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
<td>46.9 (7.8)</td>
<td>34.0 – 62.0</td>
</tr>
<tr>
<td>PaO₂ (mmHg)</td>
<td>50.5 (4.7)</td>
<td>41.0 – 60.2</td>
</tr>
<tr>
<td>P(A-a)O₂ (mmHg)</td>
<td>40.2 (10.1)</td>
<td>18.9 – 63.4</td>
</tr>
<tr>
<td>SaO₂ (%)</td>
<td>86.2 (3.5)</td>
<td>78.0 – 91.7</td>
</tr>
<tr>
<td>Predicted PaO₂ (mmHg)</td>
<td>84.8 (2.3)</td>
<td>80.9 – 90.9</td>
</tr>
<tr>
<td>Pred PaO₂-PaO₂ (mmHg)</td>
<td>34.2 (5.6)</td>
<td>23.1 – 44.0</td>
</tr>
<tr>
<td>Oxygen flow (L/min)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*significantly different (p < 0.0001) from room air values

The average improvement in oxygenation with supplemental oxygen amounted to 20.2 mmHg, without significant worsening in alveolar ventilation as evidenced by the small but not statistically significant increase of 0.8 mmHg in PaCO₂ (p = 0.09). Measured oxygen saturation values improved by an average of 8.4% on supplemental oxygen. Figure 9.4 shows the individual changes in arterial oxygen partial pressures for each subject.
Only one subject showed significant worsening of hypercapnia (defined as >5 mmHg increase) on supplemental oxygen – subject 23 who also demonstrated the worst degree of airflow obstruction (FEV₁ of only 20% of the predicted value and an FEV₁/FVC ratio of 15%). Most subjects (23 of 30) required a supplemental oxygen flow rate of 2 L/min to achieve adequate oxygenation.

**Figure 9.4: Change in arterial oxygen partial pressure on supplemental oxygen for each subject**
9.2.5. LTOT History

Whilst all subjects were eligible to receive long-term oxygen therapy by meeting diagnostic and blood gas criteria, nine of the thirty subjects were not on LTOT at the time of participation in the study (but were about to commence). Of those currently on LTOT, the median duration of this therapy was 31 months with a range of 0.5 to 129 months. The duration of LTOT for all subjects is shown as a histogram in Figure 9.5. These data reveal that most subjects on LTOT had been receiving the therapy for an extended period.

Figure 9.5: Histogram of LTOT duration for all 30 subjects completing the study.
9.2.6. Driving History

Whilst all subjects enrolled for the study had a current driver’s licence, not all continued to be regular drivers. Six of the thirty subjects were not currently driving and the reasons for ceasing driving are shown in Table 9.5. Time since last driving regularly for these six subjects is also indicated in the table – the median time since regular driving prior to participating in the study was 18 months. It is noteworthy that all decisions to cease driving were made by the individual and none were made in response to medical advice.

Table 9.5. Reasons for stopping driving and time since stopped for the 6 subjects who no longer drive regularly.

<table>
<thead>
<tr>
<th>Subject #</th>
<th>Reason for Stopping Driving</th>
<th>Duration Stopped</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>Too unwell - in and out of hospital</td>
<td>6 months</td>
</tr>
<tr>
<td>12</td>
<td>Having problems with eyesight</td>
<td>3 weeks</td>
</tr>
<tr>
<td>14</td>
<td>No longer needs to - wife drives</td>
<td>2 years</td>
</tr>
<tr>
<td>17</td>
<td>Lost confidence after starting LTOT</td>
<td>18 months</td>
</tr>
<tr>
<td>25</td>
<td>Not required to - uses a scooter</td>
<td>18 months</td>
</tr>
<tr>
<td>29</td>
<td>No particular reason.</td>
<td>10 years</td>
</tr>
</tbody>
</table>

All thirty subjects were highly experienced drivers with a minimum licensed driving history of 30 years (Table 9.6). Those who continued to drive regularly were also asked to estimate the average number of driving trips away from the home that they would drive on a normal week – driving away from home and returning was classified as one trip. These data are also shown in Table 9.6. None of the subjects had experience with driving simulators previously.

Table 9.6. Driving histories of all subjects and estimated number of driving trips per week for those who continued to drive.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years licensed to drive</td>
<td>30</td>
<td>50.1 (9.6)</td>
<td>30 - 67</td>
</tr>
<tr>
<td>Driving trips in a normal week</td>
<td>24</td>
<td>11.1 (8.1)</td>
<td>1 - 30</td>
</tr>
</tbody>
</table>
9.3. Air-Oxygen Driving Simulator Performance Comparisons

For all driving simulation measurements shown in the following section, a lower value for each parameter represents better driving performance.

9.3.1. Steering Variation

Median values for the measurements of steering variation on both test gases are shown in Figure 9.6. There was no significant difference between these measurements ($p = 0.39$, Wilcoxon signed-rank test).

Figure 9.6: Steering variation expressed as total area of lane position away from the median lane position (in cm$^2 \times 10^6$). The values expressed are the medians of the 30 subjects and the error bars show the interquartile ranges.
9.3.2. **Speed Variation**

Variations in speed are expressed in two distinct ways – as the total area away from the target speed range of 60 to 80 km/h, and as the average speed variation away from the target speed range. The median results whilst breathing the two test gases are shown in Figures 9.7 and 9.8 respectively. There were no statistically significant differences between the two test gases for either metric (p = 0.29 and p = 0.28 for area and average respectively, Wilcoxon signed-rank test).

**Figure 9.7:** Variation in speed expressed as total area of speed variation away from the target speed range (in km$^2$/h$^2$ x 10$^6$). The values expressed are the medians of the 30 subjects and the error bars show the interquartile ranges.
Figure 9.8: Variation in speed expressed as average speed variation away from the target speed range (in km/h). The values expressed are the medians of the 30 subjects and the error bars show the interquartile ranges.
9.3.3. Crashes

Total number of crashes (including off-road events, stand-stills and truck collisions) are indicated in Figure 9.9. There were no statistically significant differences between number of crashes whilst breathing intranasal oxygen compared with intranasal air (p = 0.44, Wilcoxon signed-rank test).

Figure 9.9: Number of crashes during the 20-minute driving simulation. The values expressed are the medians of the 30 subjects and the error bars show the interquartile ranges.
9.4. Air-Oxygen PVT Performance Comparisons

Psychomotor vigilance task data was not available for one of the 30 subjects (subject number 28) due to an error in downloading of the data. All results for PVT data are therefore limited to that from 29 subjects only.

9.4.1. Reaction Times

Reaction time measurements from the PVT data can be expressed in a number of different ways: medians of absolute values, medians of fastest 10% of reaction time measurements reflecting optimum performance (Dinges and Powell, 1989), and slowest 10% of reaction times. Figures 9.10, 9.11 and 9.12 show the group medians for these measures respectively. There were no statistically significant differences for any of these measures (\( p = 0.33, p = 0.40 \) and \( p = 0.12 \) respectively, Wilcoxon signed-rank test).

Figure 9.10: Absolute reaction time measurements expressed in milliseconds. The values expressed are the medians of the 29 subjects and the error bars show the interquartile ranges.
Figure 9.11: Fastest 10% of reaction time measurements expressed in milliseconds. The values expressed are the medians of the 29 subjects and the error bars show the interquartile ranges.

Figure 9.12: Slowest 10% of reaction time measurements expressed in milliseconds. The values expressed are the medians of the 29 subjects and the error bars show the interquartile ranges.
9.4.2. Lapse Errors

Lapses are defined as reaction times of more than 500 milliseconds and represent lapses in concentration over the PVT interval. Medians for the 29 subjects are shown in Figure 9.13 – there was no significant difference between air and oxygen values (p = 0.24, Wilcoxon signed-rank test).

Figure 9.13: Number of lapses in concentration during the PVT test. The values expressed are the medians of the 29 subjects and the error bars show the interquartile ranges.
9.4.3. Anticipation Errors

Anticipation errors indicate where the subject ‘jumps the gun’ or presses the button prior to the stimulus being presented and Figure 9.14 shows the median values on intranasal air and on intranasal oxygen. There was no significant difference between air and oxygen values ($p = 0.11$, Wilcoxon signed-rank test).

Figure 9.14: Number of anticipation errors during the PVT test. The values expressed are the medians of the 29 subjects and the error bars show the interquartile ranges.
9.5. Gas Preference

At the completion of the study, subjects were asked if they perceived that they performed better on the PVT and driving tasks on one gas over the other. Their responses were either ‘gas 1’, ‘gas 2’ or ‘no difference’. This question was answered without knowledge of which gas was oxygen and which gas was air. The distribution of responses is shown in Figure 9.15.

Figures 9.16, 9.17 and 9.18 illustrate the distributions of performance metrics for the PVT and driving tasks when grouped by gas preference. These graphs show that although there appeared to be a trend for participants to accurately assess performance in reaction time and steering variation changes, these relationships were largely not significant. Data for lapses and crashes are not shown since there were no numeric differences for the three groups (median of zero for all).

**Figure 9.15:** Responses to the question ‘Did you think you performed better on the PVT and driving tests on the first gas, the second gas, or no difference?’.
Figure 9.16: Distribution of changes in PVT reaction time measurements with oxygen grouped by gas preference. A negative value indicates improvement on oxygen. The lines and figures on the graph indicate the median values for each group and the comparisons between groups are using the Wilcoxon signed-rank test.

Figure 9.17: Distribution of changes in steering variation with oxygen grouped by gas preference. Units for the Y-axis are cm$^2 \times 10^6$. A negative value indicates improvement on oxygen. The lines and figures on the graph indicate the median values for each group and the comparisons between groups are using the Wilcoxon signed-rank test.
Figure 9.18: Distribution of changes in speed variation with oxygen grouped by gas preference. Units for the Y-axis are km²/h² x 10⁶. A negative value indicates improvement on oxygen. The lines and figures on the graph indicate the median values for each group and the comparisons between groups are using the Wilcoxon signed-rank test.

9.6. Order Effects

The question of whether there may have been order effects in the conduct of the driving simulation or the PVT test was investigated by comparing all driving and PVT data as obtained breathing gas 1 and gas 2, independently of the content of those gases. No significant differences could be found between gas 1 and gas 2 for any of the driving simulation data (steering deviation, speed variation or number of crashes) nor in PVT data (median and fastest 10% of reaction times or in number of lapses). This analysis suggests that learning and/or tiredness effects are not likely to be confounding factors in the analysis of the data.
9.7. Predicting Cognitive and/or Driving Performance Improvement

Despite there being no significant differences in group data between performance on intranasal oxygen and on intranasal air, it may be that there are some specific individuals who do have significant performance improvements with oxygen. In an effort to identify whether any baseline parameters could be used to predict those individuals who show performance improvements, correlations were performed with a range of baseline values against changes in neurocognitive and/or driving performance.

Parameters considered for this analysis were:

- Severity of baseline airflow obstruction as indicated by FEV$_1$ as a percent of the predicted value, and as a percentage of forced vital capacity.
- Baseline blood gas status as reflected in resting room air PaO$_2$ and PaCO$_2$.
- Improvements in resting blood gas status on supplemental oxygen therapy as indicated by differences in room air and supplemental oxygen PaO$_2$ and PaCO$_2$ values.
- Age, as a surrogate indicator of likely disease duration.

All of these identified parameters were correlated with the three primary measures of neurocognitive and driving performance in median reaction times, steering deviation and driving speed variation. Individual plots of these data are shown in Figure 9.19 (airflow obstruction severity based upon FEV$_1$ as % of predicted), Figure 9.20 (airflow obstruction severity based upon FEV$_1$/FVC ratio), Figure 9.21 (baseline arterial blood oxygen status), Figure 9.22 (baseline arterial blood carbon dioxide status), Figure 9.23 (improvement in blood oxygenation on supplemental oxygen), Figure 9.24 (change in arterial carbon dioxide level on supplemental oxygen) and Figure 9.25 (age). A summary of the individual correlation coefficients for all these analyses are shown in Table 9.7. In summary, there were no significant correlations found for any of these analyses.
Table 9.7  Summary of correlation coefficients (Pearson r-value) for baseline data versus changes in neurocognitive and/or driving performance. None of the correlations achieve statistical significance at the p = 0.05 level.

<table>
<thead>
<tr>
<th></th>
<th>Lane Position Variation Area</th>
<th>Speed Variation Area</th>
<th>Median PVT Reaction Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 30</td>
<td>n = 30</td>
<td>n = 29</td>
<td></td>
</tr>
<tr>
<td>FEV₁ % Predicted</td>
<td>0.11</td>
<td>0.07</td>
<td>0.31</td>
</tr>
<tr>
<td>FEV₁ / FVC</td>
<td>0.12</td>
<td>0.02</td>
<td>0.29</td>
</tr>
<tr>
<td>Resting PaO₂</td>
<td>0.13</td>
<td>0.14</td>
<td>0.03</td>
</tr>
<tr>
<td>Resting PaCO₂</td>
<td>0.23</td>
<td>0.01</td>
<td>0.35</td>
</tr>
<tr>
<td>Δ PaO₂ on Oxygen</td>
<td>0.13</td>
<td>0.07</td>
<td>0.20</td>
</tr>
<tr>
<td>Δ PaCO₂ on Oxygen</td>
<td>0.29</td>
<td>0.04</td>
<td>0.17</td>
</tr>
<tr>
<td>Age</td>
<td>0.07</td>
<td>0.11</td>
<td>0.13</td>
</tr>
</tbody>
</table>
Figure 9.19: Plots of performance change between intranasal air and intranasal oxygen (y-axes) versus severity of airflow obstruction (x-axes) as determined by FEV₁ as a percentage of the predicted value. Units for lane variation area and speed variation area are cm² x 10⁶ and km²/h² x 10⁶ respectively.
Figure 9.20: Plots of performance change between intranasal air and intranasal oxygen (y-axes) versus severity of airflow obstruction (x-axes) as determined by FEV₁/FVC ratio. Units for lane variation area and speed variation area are cm² x 10⁶ and km²/h² x 10⁶ respectively.
Figure 9.21: Plots of performance change between intranasal air and intranasal oxygen versus baseline resting arterial oxygenation. Units for lane variation area and speed variation area are cm$^2 \times 10^6$ and km$^2$/h$^2 \times 10^6$ respectively.

![Change in Lane Variation Area](image1)

$R^2 = 0.0168$

![Change in Speed Variation Area](image2)

$R^2 = 0.0184$

![Change in RT (msec)](image3)

$R^2 = 0.001$
Figure 9.22: Plots of performance change between intranasal air and intranasal oxygen versus baseline resting arterial carbon dioxide levels. Units for lane variation area and speed variation area are cm$^2 \times 10^6$ and km$^2$/h$^2 \times 10^6$ respectively.

![Graph 1](image1)

- Change in Lane Variation Area
- Baseline PaCO2 (mmHg)
- $R^2 = 0.0548$

![Graph 2](image2)

- Change in Speed Variation Area
- Baseline PaCO2 (mmHg)
- $R^2 = 5E-05$

![Graph 3](image3)

- Change in RT (msec)
- Baseline PaCO2 (mmHg)
- $R^2 = 0.1224$
Figure 9.23: Plots of performance change between intranasal air and intranasal oxygen versus changes in resting arterial blood oxygenation on supplemental oxygen. Units for lane variation area and speed variation area are cm² x 10⁶ and km²/h² x 10⁶ respectively.
Figure 9.24: Plots of performance change between intranasal air and intranasal oxygen versus changes in resting arterial blood carbon dioxide levels. Units for lane variation area and speed variation area are cm$^2 \times 10^6$ and km$^2$/h$^2 \times 10^6$ respectively.
Figure 9.25: Plots of performance change between intranasal air and intranasal oxygen versus age of subject. Units for lane variation area and speed variation area are cm² x 10⁶ and km²/h² x 10⁶ respectively.

![Graph showing change in lane variation area](image1)

![Graph showing change in speed variation area](image2)

![Graph showing change in RT (msec)](image3)
9.8. Comparisons with Other Published AusEd and PVT Data

Table 9.8 provides a summary of relevant published studies using the AusEd driving simulation system for comparison with data from the current study. The table indicates effects of various interventions and disease states on the metrics obtained.

Comparisons of PVT data from the current study with other published PVT data are given in tables 9.9 and 9.10. Table 9.9 shows subject group and methodological details with the average and/or median values for the measures obtained. Note that, apart from the current study, all studies indicated in this table where healthy and free from significant disease. See the discussion section for more details.

Table 9.10 illustrates the effects of various interventions on PVT measurements. The purpose of this comparison with the current study is to illustrate the fact that the effect size for interventions such as sleep deprivation, alcohol ingestion and oxygen enrichment is much larger than the effect size seen in the current study. See discussion for more detail.
Table 9.8: Summary of other published AusEd driving simulation data compared with the current study. SD indicates sleep deprivation.

<table>
<thead>
<tr>
<th></th>
<th>Banks et al</th>
<th>Desai et al</th>
<th>Howard et al</th>
<th>Current Study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Year published</strong></td>
<td>2004</td>
<td>2007</td>
<td>2007</td>
<td>2008</td>
</tr>
<tr>
<td><strong>Sim. Time</strong></td>
<td>70 mins</td>
<td>30 mins</td>
<td>30 mins</td>
<td>20 mins</td>
</tr>
<tr>
<td><strong>Subjects</strong></td>
<td>20</td>
<td>28 / 13</td>
<td>16</td>
<td>30</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>23</td>
<td>40 / 42</td>
<td>46</td>
<td>72</td>
</tr>
<tr>
<td><strong>Study Group</strong></td>
<td>Normal</td>
<td>Control/OSAS</td>
<td>Truck drivers</td>
<td>COPD</td>
</tr>
<tr>
<td><strong>Lane variability</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>-</td>
<td>102.9 / 152.4</td>
<td>44.0</td>
<td>-</td>
</tr>
<tr>
<td>SD</td>
<td>82.0</td>
<td>-</td>
<td>52.9</td>
<td>-</td>
</tr>
<tr>
<td>Alcohol</td>
<td>-</td>
<td>-</td>
<td>62.5</td>
<td>-</td>
</tr>
<tr>
<td>SD &amp; Alc.</td>
<td>92.9</td>
<td>-</td>
<td>75.8</td>
<td>-</td>
</tr>
<tr>
<td>Air</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>79.0</td>
</tr>
<tr>
<td>Oxygen</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>75.5</td>
</tr>
<tr>
<td><strong>Speed variability</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>-</td>
<td>-</td>
<td>1.4</td>
<td>-</td>
</tr>
<tr>
<td>SD</td>
<td>8.9</td>
<td>-</td>
<td>2.5</td>
<td>-</td>
</tr>
<tr>
<td>Alcohol</td>
<td>-</td>
<td>-</td>
<td>3.6</td>
<td>-</td>
</tr>
<tr>
<td>SD &amp; Alc.</td>
<td>10.5</td>
<td>-</td>
<td>5.6</td>
<td>-</td>
</tr>
<tr>
<td>Air</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6.9</td>
</tr>
<tr>
<td>Oxygen</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>7.3</td>
</tr>
<tr>
<td><strong>Crashes (per 20 minute period)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>-</td>
<td>0.1 / 0.4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sleep Dep.</td>
<td>0.7</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Alcohol</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SD &amp; Alc.</td>
<td>2.9</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Air</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2.0</td>
</tr>
<tr>
<td>Oxygen</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.5</td>
</tr>
</tbody>
</table>
Table 9.9: Summary of relevant recent studies using the PVT device compared with the data from the current study. All subjects from all studies except the current study were healthy and free from significant disease.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Mean Age</th>
<th>Number of Female/Male</th>
<th>Device Used</th>
<th>Test Duration</th>
<th>Mean/ Median RT</th>
<th>Slowest 10% RT</th>
<th>Fastest 10% RT</th>
<th>Lapses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gerard et al</td>
<td>2000</td>
<td>28</td>
<td>8 / 16</td>
<td>Not specified</td>
<td>10 mins</td>
<td>274</td>
<td>-</td>
<td>-</td>
<td>2.3</td>
</tr>
<tr>
<td>Urilla et al</td>
<td>2004</td>
<td>21</td>
<td>13 / 0</td>
<td>PVT-192</td>
<td>10 mins</td>
<td>230</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Urilla et al</td>
<td>2004</td>
<td>63</td>
<td>12 / 0</td>
<td>PVT-192</td>
<td>10 mins</td>
<td>283</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Loh et al</td>
<td>2004</td>
<td>22</td>
<td>8 / 7</td>
<td>PVT-192</td>
<td>10 mins</td>
<td>215</td>
<td>217</td>
<td>281</td>
<td>1.6</td>
</tr>
<tr>
<td>Drummeland et al</td>
<td>2005</td>
<td>27</td>
<td>8 / 12</td>
<td>Not specified</td>
<td>10 mins</td>
<td>269</td>
<td>388</td>
<td>330</td>
<td></td>
</tr>
<tr>
<td>Lamond et al</td>
<td>2006</td>
<td>~23</td>
<td>8 / 7</td>
<td>PDA</td>
<td>10 mins</td>
<td>222</td>
<td>-</td>
<td>181</td>
<td></td>
</tr>
<tr>
<td>Blatter et al</td>
<td>2006</td>
<td>25</td>
<td>8 / 8</td>
<td>PVT-192</td>
<td>5 mins</td>
<td>224</td>
<td>181</td>
<td>191</td>
<td></td>
</tr>
<tr>
<td>Blatter et al</td>
<td>2007</td>
<td>46</td>
<td>8 / 11</td>
<td>PVT-192</td>
<td>10 mins</td>
<td>238</td>
<td>191</td>
<td>383</td>
<td></td>
</tr>
<tr>
<td>Howard et al</td>
<td>2007</td>
<td>1 / 18</td>
<td>8 / 21</td>
<td>PVT-192</td>
<td>10 mins</td>
<td>218</td>
<td>-</td>
<td>444</td>
<td>4.0</td>
</tr>
<tr>
<td>Current study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
Table 9.10: Summary of relevant recent studies assessing effects of interventions on PVT measurements. All subjects from all studies except the current study were relatively healthy and free from significant disease.

<table>
<thead>
<tr>
<th>Change in Lapses</th>
<th>Change in Slowest 10%</th>
<th>Change in Fastest 10%</th>
<th>Change in RT (%)</th>
<th>Change in RT (msec)</th>
<th>Mean Age</th>
<th>Female / Male</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1.2 (-52%)</td>
<td>-</td>
<td>-</td>
<td>-6%</td>
<td>-16</td>
<td>28</td>
<td>8 / 16</td>
<td>Oxygen enrichment</td>
</tr>
<tr>
<td>-</td>
<td>+174</td>
<td>+26</td>
<td>+24%</td>
<td>+55</td>
<td>21</td>
<td>13 / 0</td>
<td>24 hour wakefulness</td>
</tr>
<tr>
<td>-</td>
<td>+90</td>
<td>+26</td>
<td>+24%</td>
<td>+63</td>
<td>63</td>
<td>12 / 0</td>
<td>24 hour wakefulness</td>
</tr>
<tr>
<td>+2.3 (+148%)</td>
<td>-374</td>
<td>+14</td>
<td>+10%</td>
<td>+22</td>
<td>22</td>
<td>8 / 7</td>
<td>24 hour wakefulness</td>
</tr>
<tr>
<td>-</td>
<td>+4</td>
<td>-</td>
<td>+44%</td>
<td>-23</td>
<td>8 / 7</td>
<td>8 / 12</td>
<td>24 hour wakefulness</td>
</tr>
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<td>+65</td>
<td>65</td>
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<td>+81</td>
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<tr>
<td>-</td>
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<td>+15%</td>
<td>-374</td>
<td>40</td>
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</tr>
<tr>
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<td>+39</td>
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<tr>
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<td>-</td>
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<td>-1</td>
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</tr>
<tr>
<td>+1 (+25%)</td>
<td>-5</td>
<td>-</td>
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<td>-2%</td>
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<td>18-21 hour wakefulness</td>
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10. Discussion

COPD is a common disease with an estimated 16,000 Australians dying from it in 2008 (Access Economics, 2008). The total number of people in this country with COPD is estimated at over 2 million affecting 18.6% of people aged over 40 (Access Economics, 2008). Furthermore, the incidence is projected to steadily increase over the coming decades with the number of people with non-trivial forms of the disease predicted to more than double by the year 2050 (Access Economics, 2008).

In its most severe form, COPD results in significant reductions in blood oxygen levels. The most effective form of treatment for this condition is long-term oxygen therapy, a costly but demonstrably useful intervention shown to increase survival, improve quality of life and provide healthcare cost effectiveness (Access Economics, 2008). In hypoxaemic COPD LTOT should be used for 15 to 18 hours per day (McDonald et al., 2005). It is estimated that the number of Australians eligible for provision of LTOT in 2008 was approximately 15,000, and this was projected to rise to 33,000 by the year 2050 (Access Economics, 2008).

A difficult to estimate but sizeable proportion of COPD patients receiving LTOT continue to drive motor vehicles and for the thousands of such people in this country an important consideration is whether oxygen therapy should continue to be used whilst driving. This has important implications since hypoxaemia is known to adversely affect neurocognitive performance and driving ability may be consequently affected. Additionally, there are economic and safety issues involved in using oxygen whilst driving. Austroads, the association of Australian and New Zealand road transport and traffic authorities, have addressed this issue and make the recommendation that such drivers should probably use their oxygen whilst driving (Austroads, 2006). This recommendation is based primarily on the findings that long-term provision of oxygen therapy improves neuropsychological function (Block et al., 1974, Borak et al., 1996, Heaton et al., 1983, Krop et al., 1973). There is no evidence that short-term oxygen administration results in such improvement, in fact the only well-controlled study investigating this found the contrary (Wilson et al., 1985). There are no valid, objective data in the literature investigating whether acute oxygen therapy affects driving performance in hypoxaemic subjects, hence the aim of this study was to provide this missing body
of evidence. The hope was that recommendations regarding using supplemental oxygen whilst driving could be based on sound evidence.

This study has not demonstrated any effect of supplemental oxygen on driving performance using a computerised driving simulator in a group of hypoxaemic COPD patients. Additionally, no change in cognitive function as assessed using psychomotor reaction times was found. These findings are in agreement with the only other published study investigating the acute effects of oxygen therapy on neurocognitive function in hypoxaemic COPD. Wilson and colleagues (Wilson et al., 1985) assessed information processing ability in 10 hypoxaemic COPD subjects whilst breathing air and oxygen sufficient to improve oxygen saturation to above 90% and showed no significant difference in any measured parameter. They specifically assessed auditory and visual perception, sensory function, and memory and depth of processing. They did not assess driving ability. The findings from their well-controlled study contrast with observed improvements in neuropsychological functions following oxygen therapy of at least 4 weeks duration (Block et al., 1974, Borak et al., 1996, Heaton et al., 1983, Krop et al., 1973). It may well be that LTOT over extended periods is required to allow reparative processes to occur to enable measurable improvements in cognition, rather than the acute improvements in oxygenation achieved in Wilson’s study (Wilson et al., 1985) and this current study.

All of the subjects in Wilson’s study (Wilson et al., 1985) and 70% of those in the current study had been on LTOT at the time of the study. Duration of LTOT required to achieve neurocognitive improvement is not clearly described. Whilst improvements in neuropsychological function have been documented after six months of LTOT (Heaton et al., 1983), and after 12-months (Borak et al., 1996), others have found measurable improvements after only 4 weeks of LTOT (Block et al., 1974, Krop et al., 1973). Only one of the 21 subjects on LTOT in the current study had been on this therapy for less than one month, with 16 (76%) being on LTOT for more than one year. These data indicate that most subjects had been receiving this therapy for periods of time sufficient to allow the longer-term beneficial effects of LTOT on neurocognitive function to have been realised. It could therefore be argued that the reason that no neurocognitive improvements were observed in either this or Wilson’s study (Wilson et al., 1985) was that the
previous LTOT had already reversed the neurocognitive deficits attributable to hypoxaemia as demonstrated by others (Block et al., 1974, Borak et al., 1996, Heaton et al., 1983, Krop et al., 1973), and consequently there was little margin for further improvement with acute therapy. Whilst this certainly may be the case, the question of whether using oxygen whilst driving in patients who would normally be on LTOT is still relevant and we believe that our findings specifically indicate that no benefit in driving performance is obtained with concurrent oxygen usage, at least in COPD patients with resting PaO₂ of greater than or equal to 40 mmHg.

The conclusions that no changes could be detected in driving or neurocognitive performance are based upon the group data as a whole, however there were clearly some individuals who did perform better on supplemental oxygen than others. In an effort to try to predict those individuals, and thereby perhaps enable targeted recommendations regarding using oxygen whilst driving, correlations between baseline data and changes in performance on oxygen were performed. The rationale for this was that perhaps those with more severe disease were more likely to elicit a performance improvement with supplemental oxygen. The contrary may also have been possible, that is, that those with less severe disease may be more likely to have reversible cognitive impairments. The baseline parameters considered likely to yield positive correlations and therefore subjected to this analysis were degree of airflow obstruction (expressed as both FEV₁ as a percentage of the predicted value and as a percentage of FVC), degree of baseline hypoxaemia (PaO₂) and degree of adequacy of alveolar ventilation (PaCO₂). In addition, it was considered reasonable that the magnitude of blood gas response to supplemental oxygen might also be a predictor of performance improvement. The correlation analysis was therefore also performed using change in PaO₂ and change in PaCO₂ as predictor variables.

None of the calculated correlation coefficients achieved statistical significance. Of the 21 correlations performed (Figures 9.19 to 9.25) the best correlation was that of change in PVT reaction time versus baseline PaCO₂ ($r = 0.35$, $p = 0.06$). Even if we consider that a $p$-value at this level indicates a possible relationship between these two variables, it is apparent from the wide distribution of these data (Figure 9.22) that attempting to predict change in reaction time on supplemental oxygen from baseline PaCO₂ would be ill-advised. This analysis indicates that, not only
are there no systematic changes in either driving performance or in neurocognitive performance with supplemental oxygen, there does not appear to be a way to predict those individuals likely to perform better on supplemental oxygen. Overall, this suggests that acute supplemental oxygen has no general effect on these performance measures in this patient group.

It is well established that acute hypoxaemia is associated with decline in neurocognitive function, so the question of why acute reversal of hypoxaemia did not elicit a measurable change in driving and cognitive performance in this study needs to be addressed. One possible hypothesis is that a long-term effect of prolonged hypoxaemia is to produce structural and/or organic changes in the neurological system such that short-term interventions have no demonstrable effect. This effect, suggested by Grant et al to result from insufficient oxygenation of brain tissue (Grant et al., 1982), is exacerbated by disease duration rather than severity (Incalzi et al., 1993) and in our subject group with an average age of 72 years is likely to play a significant role. This hypothesis may certainly be true, however when it comes to deciding whether to use oxygen whilst driving, the results of this study are still relevant – the fact that no discernible difference in performance could be detected still indicates that there is no evidence to support the recommendation that this therapy be used whilst driving.

Another possible reason why no measurable effect on neurocognitive function was detected on short term oxygen therapy is that the neurocognitive reparative effects of LTOT may have a carry-over effect for some hours after temporarily stopping LTOT. It may be that if all oxygen therapy had been avoided for days or perhaps weeks then acute improvements may have been measured. No data about recent LTOT use prior to the study was collected from study participants to directly address this question. However, if this argument is valid we would expect to find that those study participants who had yet to initiate LTOT (9 of the 30 subjects) might demonstrate improvements on acute oxygen therapy. Analysis of the data revealed not only no such improvements for any of the PVT or driving simulation outcomes in the LTOT-naïve subjects, but also no differences in the pattern of responses between this group and the LTOT group. This suggests that this explanation for the lack of overall response is not likely to be applicable.
No data were collected for this study describing co-morbidities which might impact on driving and cognitive performance. One particular condition which might be expected to play a significant role is the presence of sleep disordered breathing. The disruption to sleep architecture caused by sleep apnoea is known to adversely affect daytime neurocognitive function (Guilleminault et al., 1978) and the periodic oxygen desaturation in this condition also causes reduced overall oxygenation. Further, relative hypoventilation is a normal feature of REM sleep and this can cause marked oxygen desaturation in COPD. Overnight oximetry monitoring provides a relatively simple method for quantifying the extent of sleep disordered breathing, and in retrospect, such data may have proved useful in more fully describing characteristics of the subject group relevant to the study outcomes. In particular, subgroup analysis of those with more profound overnight desaturation may have revealed capacity to predict those likely to show either worse driving and cognitive performance, or those likely to benefit most from acute oxygen therapy. Further research in this area might be beneficial.

It is important to note that the aim of this study was to determine whether driving and/or neurocognitive performance is measurably improved in hypoxaemic drivers with the addition of supplemental oxygen. I have not assessed whether the driving performance of hypoxaemic drivers is any different to non-hypoxaemic drivers, and as such no conclusions can be made about the safety of driving in this patient group. A comparison with an adequately matched (particularly from an age perspective) control group would be required to do this. The dependence of the same driving metrics used for this study on subject age has not been previously investigated, so it is not possible to perform a historical or previously published comparison. However Orth and colleagues compared COPD patients with an age matched control group using a different driving simulator (Orth et al., 2008) and found impairments in the COPD patients. Their patients had less hypoxaemia than those in the current study (average PaO2 of 69 mmHg). Given the likely additional decline in neurocognitive function to be expected in a hypoxaemic COPD group, we could speculate that hypoxaemic COPD patients would have even worse driving performance than their healthy counterparts. The important question of whether drivers with hypoxaemic COPD pose an overall risk on the road remains to be answered. In addition, extrapolating driving simulation data to real, on-road driving performance in an effort to predict crash or road-safety related events is
also problematic since no formal evaluation of the link between these issues has been conducted for the AusEd system or for other driving simulators. Evaluation of this link would provide a further research opportunity for the future.

Another way to evaluate the driving simulation performance of this group of hypoxaemic COPD subjects is to compare the data with other published datasets using the same AusEd system. Table 9.8 compares published AusEd data for the three primary measurements obtained using this system. It is likely that driving simulation performance deteriorates with age as the age-related neurocognitive decline progresses (as seen in reaction time measurements, for example) (Blatter et al., 2006, Urrila et al., 2004). Direct comparisons of the AusEd metrics shown in Table 9.8 are therefore problematic given that the mean ages of all other studies is significantly lower than in the current study.

It should be stressed that a proper comparison of these simulation data should really be made with an age-matched control group, and the data in Table 9.8 should not be interpreted as indicating that the hypoxaemic COPD drivers perform at similar levels to that of sleep-deprived and alcohol-affected drivers.

The data in Table 9.8 do provide an indication of the relative magnitudes of change that can be induced by various interventions and/or disease states. It can be seen from these data that the size of effect of supplemental oxygen compared with air from the current study is not only statistically not significant, but also functionally insignificant.

The PVT device has been utilised much more widely than the AusEd driving simulator system and there are published data with which comparisons can be made to the hypoxaemic COPD group recruited for this study. As pointed out by Thorne et al, absolute values of reaction times are critically dependent upon the characteristics of the instrument used to measure them, with factors such as stimulus characteristics, mechanical, electronic and optical features affecting the reaction time measurements (Thorne et al., 2005). This means that direct comparisons of absolute measurements can only reliably be made when all testing is performed using the same instrument. Up until relatively recently, the PVT-192 instrument with its associated software for analysis (as used for this study) has been
widely used as the primary instrument to measure psychomotor vigilance, hence published data to enable comparisons with the data from this study are available. One further confounding factor is the duration of the PVT task with published data ranging from 2-minute durations (Loh et al., 2004) to 20-minutes (Van Dongen and Dinges, 2005). Table 9.9 summarises findings from a number of relevant recent studies using the PVT device together with the findings from the current study.

This table shows that the median reaction times for the current study were higher than for most studies listed. Urilla’s elderly group (Urrila et al., 2004) had higher values. This may be a consequence of the fact that they were all female, as females have been shown to have slower reaction times than males (Blatter et al., 2006). Drummond’s younger group also had higher mean reaction times, but in this case the device used for PVT measurements may have been different as it was not clearly identified in their report (Drummond et al., 2005). Gerard’s study, the only other published data showing effects of oxygen concentration on reaction time measurements, also showed a higher mean reaction time however the PVT device used was not the PVT-192, and the baseline measurement conditions in this study were at reduced inspired oxygen concentration.

Of the studies in Table 9.9 where slowest 10% reaction times were quoted, the median for the current study were the worst of all at 444 milliseconds. Again this probably reflects the fact that average age for the current study was the highest, with an additional factor being that all other studies involved healthy subjects. The magnitude of the effect that chronic, severe lung disease has on reaction times is not known, nor is the average effect of hypoxaemia on reaction times. There is a similar pattern in fastest 10% of reaction times where (apart from the Drummond study where the device used may be different to that used in the other studies) the current subject group has the worst results.

The fastest 10% reaction time data obtained from the PVT measurements is used to isolate the overall reaction time measurements from the effects of large lapses in concentration and is said to represent the ‘optimum response domain’ (Loh et al., 2004). The optimum response domain is thought to be less sensitive to performance decrement in response to interventions, however it still has been found to deteriorate in response to sleep deprivation (Dinges and Powell, 1989, Lisper and
The slowest 10% of reaction times is largely dependent upon lapses in concentration and is said to represent the ‘lapse domain’ (Loh et al., 2004). The question of which of the reaction time data provides the most relevant metric is a difficult one, however it has been found that changes in some reaction time parameters can exist without changes in others. For example, slowest 10% reaction times have been found to track changes in performance associated with body temperature variations whereas fastest and median reaction times did not (Wright et al., 2002). Irrespective of how the reaction time data are represented or analysed, whether as indicating optimum response domain, lapse response domain or as an overall median value, there were no significant changes induced by breathing supplemental oxygen in comparison with supplemental air.

Table 9.10 summarises the effects of specific interventions on PVT-derived measurements from a selection of relevant and recent studies, in comparison with the average effects on these measurements from the current study. The reason for this comparison is to illustrate the magnitude of effect that these interventions (predominantly wakefulness) have on the respective PVT measurements. Whilst the magnitude of responses varies somewhat, the minimum change observed in all these studies was a worsening in response time of 21 milliseconds in response to 18-21 hours of wakefulness (Howard et al., 2007). Whilst the data from the current study showed no statistically significant difference in reaction times between supplemental air and oxygen, the absolute change of only 5 millisecond shows that this difference is also insignificant from a functional perspective when comparisons are made with the observed changes of between 21 and 203 milliseconds from the other studies. As a percentage change, interventions such as sleep deprivation and alcohol ingestion caused upwards of 10% change in reaction time. The current study only revealed a difference of 2%. Examining the effects on other PVT measures such as fastest or slowest 10% of reaction times, and numbers of lapses revealed a similar outcome – the magnitude of changes in the current study were far below those observed for other interventional studies.

Gerard’s study is particularly relevant in that it is the only other study investigating effects of inspired oxygen concentration on reaction time performance (Gerard et al., 2000). Gerard and colleagues investigated 24 healthy young subjects after two days at altitude where oxygen saturation averaged 82% and assessed the response to
50 minutes of oxygen enrichment where saturation rose to an average of 93% (Gerard et al., 2000). They found a modest but significant improvement in mean reaction times of 16 milliseconds. The major difference between the current study and Gerard’s is in the age and health of the subject group investigated and in the duration that the subjects had been exposed to hypoxia. Extrapolating their findings in young, healthy subjects to elderly, chronically ill subjects is problematic. Furthermore, the cognitive effects of the long-term hypoxaemia experienced in COPD are arguably quite different to those caused by the short-term hypoxaemia involved in 2-days at altitude, and therefore acute reversal of hypoxaemia may elicit substantial differences in the two groups. In any event, the magnitude of effects on reaction times in Gerard’s study are relatively modest compared with the effects of other interventions as shown in Table 9.10.

It is noteworthy that there was a high degree of interest in this study from those invited to participate. Only 4 of 44 subjects (9%) invited to consider volunteering expressed no interest in the study. Of the 40 that did express a desire to participate, five could not be enrolled due to other factors (four were too unwell or clinically unstable and one subject was unable to attend due to ongoing work commitments). Only two of 35 subjects booked in for testing failed to attend – both claimed to be too busy to keep the appointments but it was suspected that they had lost interest and did not wish to continue with the study.

In any event, to achieve a total of 33 subjects entering the trial from an invited total of 44 (75% success rate) is considered to be a highly successful recruitment process. The skills in screening and offering of initial invitations by the Austin Hospital staff involved, particularly those from the Domiciliary Oxygen Clinic, clearly played an important role in this recruitment success and are much appreciated.

Two of the 33 subjects participating experienced nausea which was described as ‘motion sickness’ during the initial practice runs on the driving simulator. This has not been previously described in the literature with the AusEd simulation system. Both subjects were unwilling to continue with this aspect of the study, so testing was abandoned and no test data was collected. The feeling of nausea was short-lived and ceased when the driving simulation was stopped. The baseline
spirometric, smoking and driving data in these two subjects was not substantially different from the group data, however it was noted that one of the subjects had the highest room air PaCO₂ of all subjects (63 mmHg), and that both subjects had significantly lower BMI than the means for the rest of the group (17.9 and 20.6 kg/m²). The significance of these findings is unknown, however motion sickness occurring in two of 33 subjects (6%) should be allowed for in future projects in this patient group. Furthermore, future participant information sheets and consent forms should disclose short-lived motion sickness or nausea as a possible side effect or complication during driving simulations. Motion sickness and/or nausea has not been previously described using the AusEd driving simulator.

Data from one subject were not included in the analysis since it was discovered at the completion of the study that the oxygen supply had failed during the inhaled oxygen part of the study. Data obtained from this subject was therefore not included in the analysis and an extra subject was recruited to ensure the target of 30 participants was achieved.

Being odourless, tasteless and colourless, oxygen is indistinguishable from air hence it allows a simple study design where treatment modality can be easily blinded from the subject. Furthermore, providing specific care is taken to screen the operator from the supply gas and from oximeter readings, double-blinding of received treatments can also be achieved quite simply.

In addition, the rapid wash-in and wash-out periods for changes in inspired oxygen concentration, shown to be around five minutes in other studies in similar patient groups (Alvisi et al., 2003a, Naughton et al., 1995), enables the study to be easily conducted as a crossover study without prolonged time difficulties. As such, each subject acts as his or her own control enabling paired data comparisons.

Randomly allocating the order of the received treatments overcomes any potential biases that may be associated with treatment order effects. Analysis of the data showed that no order effects could be found, further strengthening the major findings. The study can therefore be considered as a valid double-blinded, randomized, crossover design study.
Given that the subjects were blinded from the order of gases that they received, the question ‘Did you think you performed better on the first or second gas, or no difference?’ provides an objective assessment of how the subjects perceived changes in performance. It is interesting that seven subjects (23%) could detect no discernible difference in performance and that nine subjects (30%) perceived that they performed better on inhaled supplemental air. The overall result was less than 50% of subjects thought that they performed better on oxygen. The analysis provided in figures 9.15, 9.16 and 9.17 show that whilst there appeared to be a group trend for participants to correctly identify which gas they performed better on (at least for PVT reaction time and for lane variation), there was little difference between the groups. Furthermore, the substantial overlap of the data between groups indicates that an individual’s ability to correctly nominate better-performing gas for the neurocognitive and driving performance measurements is limited.

Comparing the findings of this study with others assessing effects of oxygen levels on driving performance is problematic due to the paucity of data available, and to the methodological problems with those studies. The only other published data available (Sung et al., 2005) has significant methodological problems which make interpretation problematic. In that study, subjective fatigue and reaction times were found to be improved whilst breathing 30% oxygen compared with 18% oxygen in a group of young, healthy drivers, however no driving simulation data was provided (Sung et al., 2005). The modest reduction in inspired oxygen content in this subject group is unlikely to have resulted in substantial hypoxaemia, hence the study is more an evaluation of the effects of hyperoxia than of hypoxia. Also, there is little detail provided regarding the statistical analyses performed which further makes interpretation and comparison with the current study findings difficult.

There are also a limited number of studies investigating effects of oxygen levels on measurements of reaction time. Gerard et al found in a group of young, healthy subjects at altitude that oxygen enrichment (increasing oxygen saturation from 82% to 93%) caused a modest but significant improvement in PVT-measured reaction time of an average of 16 milliseconds (Gerard et al., 2000). One possible reason why no such difference was found in the current study may be because of the substantial differences in the two subject groups. The cognitive effects of long-term hypoxaemia in COPD are arguably quite different to those caused by short-
term hypoxaemia in young, healthy subjects resulting from acute altitude exposure, and therefore acute reversal may elicit substantial differences in the two groups. For this reason, extrapolation of findings in usually normoxaemic subjects made acutely hypoxaemic to predict what happens in chronically hypoxaemic COPD subjects made acutely normoxaemic (or at least closer to normoxaemic) may be inappropriate.

One of the limitations of this study is that a driving simulator was used as a surrogate for real-world driving. There are substantial differences between simulators compared with real-world driving due to factors such as lack of visual, proprioceptive and vestibular sensory information, however the validity of simulators as a driving assessment tool in the elderly has been previously demonstrated (Lee et al., 2003). The primary reason for using a simulator for this study was that it provides a greater degree of experimental control and enables more reliable and precise performance measurements to be made. Simulators are therefore particularly effective in assessing effects of interventions such as oxygen therapy. The AusEd program used in this study has been shown to be sensitive to decrements in performance due to factors such as sleep deprivation and alcohol use (Banks et al., 2004, Banks et al., 2005). To our knowledge, it has not been previously used in the investigation of the effects of supplemental oxygen therapy or in the investigation of the effects of hypoxaemia.

One further potential limitation of using the AusEd driving simulation system for this study involved the physical effort required to operate the simulator. The steering wheel used in this simulator offers very low resistance to movement and requires very little physical exertion to operate – less than that of a real steering wheel. Arterial oxygen desaturation on exertion is a common manifestation of advanced COPD and the physical effort involved in controlling a motor vehicle could potentially cause further deterioration in hypoxaemia, and thereby exacerbate cognitive dysfunction. Given the predominance of power-assisted steering in modern cars it was considered that the amount of effort required to drive a motor vehicle is unlikely to be sufficient to cause significant worsening of hypoxaemia. There are however no published observations to support this assumption. In any event, it was considered that the reduced effort involved in operating the driving simulator was unlikely to substantially interfere with the conclusions reached.
One limitation of the current study may be that adequate time was not allowed after changes in inspired oxygen before the PVT and driving simulation measurements were made. The ‘wash-in/wash-out’ period incorporated into the study design was based upon published data indicating that ‘steady state’ conditions are achieved in ventilatory parameters and in blood gas values after only 5 minutes following change in inspired oxygen concentration in similar patient groups (Alvisi et al., 2003b, Naughton et al., 1995). However it could be that the effects of changes in blood oxygen levels on neurological performance may take longer than the achievement of ‘steady state’ to be fully realised. To my knowledge, there are no published data investigating the time course of neurocognitive changes in response to changes in oxygenation allowing an informed decision to be made on this.

In an effort to overcome this potential limitation, analysis of the driving simulation data was restricted to the last 13 minutes of the 20-minute simulation. This allowed an extra seven minutes of breathing each supplemental gas prior to the any data analysis being performed. The study design specified that at least five minutes be allowed on the supplemental gas prior to driving simulation beginning. In practice, the average time between starting the gas and starting the driving simulation amounted to between seven and ten minutes (although precise measurements were not taken). With the additional seven minutes of driving prior to measurements being used, the end result was that most subjects were exposed to around 15 minutes of gas wash-in and wash-out before measurements were made. Again, whilst it is unknown whether this represents a suitable period of time in terms of neurological effects, it does represent a longer period than the five minutes stated in the study design.

On the other hand, the wash-in and wash-out periods for the PVT measurements were significantly longer given they were always performed after the driving simulation. The total time for breathing each supplemental gas for PVT analysis was estimated at around 30 minutes: seven to ten minutes wash-in / wash-out, plus 20 minutes driving simulation, plus one to two minutes changeover time.

Further, the duration of the driving simulation task used for this study was 20 minutes per data collection period which was the same as in one other study.
assessing effects of oxygen therapy (Patel et al, 2003), but of shorter duration than the 30 to 70 minutes used in other studies using the AusEd system (Banks et al., 2004, Desai et al., 2007, Howard et al., 2007). A 20-minute driving task was chosen to ensure that fatigue and/or sleepiness due to prolonged simulation time was avoided, and that the primary intervention under investigation (i.e. oxygen therapy) was providing the predominant stimulus for change in performance. It may well be that different results may have been obtained had a longer duration for driving simulation been used, however given that the typical driving trip duration of the study participants was noted to be very short, the study findings remain valid in that the 20-minute test is representative of typical driving patterns in this patient group. There is a theoretical possibility that oxygen therapy may delay the onset of fatigue and/or sleepiness and as such there remains the possibility that oxygen therapy may potentially be of value during longer trip durations. Further research investigating this possibility may be warranted to determine whether oxygen therapy should be recommended for longer duration trips in this patient group.

Whilst the number of hypoxaemic drivers is likely to be relatively small compared with all road users, the ageing of the community and projected increases in COPD incidence (Access Economics, 2008, Pauwels et al., 2001) suggests that the importance of this issue will intensify over coming years. I would estimate that approximately one in three patients eligible for LTOT due to COPD-induced hypoxaemia would continue to hold a driver’s licence. Using Crockett’s estimation of the number of Australian residents eligible for LTOT in 2008 (Access Economics, 2008), this would equate to around 5,000 Australians for whom the advice regarding whether to use oxygen whilst driving is relevant. The future projections for COPD incidence in this country would see this figure rising to around 15,000 drivers by the year 2050. Clearly the findings for this investigation are relevant for a sizeable number of individuals. Furthermore, the safety aspects involved in decisions made about using oxygen whilst driving affect not only these thousands of hypoxaemic drivers, but also the many more thousands of road users with whom the roads are shared. I believe that, from a safety and welfare perspective, it is important that any recommendations or advice that are given to individual patients about using oxygen whilst driving should be based on accurate and objective data. This study has provided the first objective investigation of this issue.
A further consideration is that not all patients on LTOT are supplied with portable oxygen suitable for use in the car. There would be significant cost implications if all drivers who qualify for LTOT were also required to have appropriate oxygen supply equipment to use whilst driving. This would include small, preferably lightweight oxygen cylinders along with some form of oxygen conservation device, or alternatively a portable oxygen concentrator suitable for use in the car – additional costs for these over and above the provision of oxygen in the home could become substantial. Clearly the need to establish whether this recommendation should be made becomes an economic issue as well as a safety-related clinical issue.

11. Conclusions

In a double-blinded, randomized, crossover study designed to assess changes in driving simulator and neurocognitive performances, I have been unable to demonstrate any systematic effects of acute supplemental oxygen therapy in a group of hypoxaemic subjects with COPD. These data do not support the recommendation that drivers with hypoxaemic COPD should use supplemental oxygen therapy whilst driving.
## Appendices

### 12.1. Abbreviations used in this Exegesis

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABG</td>
<td>Arterial blood gas</td>
</tr>
<tr>
<td>ANZCTR</td>
<td>Australian and New Zealand Clinical Trials Registry</td>
</tr>
<tr>
<td>ANZSRS</td>
<td>Australian and New Zealand Society of Respiratory Science</td>
</tr>
<tr>
<td>APSR</td>
<td>Asia Pacific Society of Respirology</td>
</tr>
<tr>
<td>ATS</td>
<td>American Thoracic Society</td>
</tr>
<tr>
<td>BAC</td>
<td>Blood alcohol content</td>
</tr>
<tr>
<td>BTS</td>
<td>British Thoracic Society</td>
</tr>
<tr>
<td>CO₂</td>
<td>Carbon dioxide</td>
</tr>
<tr>
<td>COHb</td>
<td>Carboxyhaemoglobin</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>CSU</td>
<td>Charles Sturt University</td>
</tr>
<tr>
<td>EEG</td>
<td>Electroencephalograph</td>
</tr>
<tr>
<td>FEV₁</td>
<td>Forced expiratory volume in one second</td>
</tr>
<tr>
<td>FiO₂</td>
<td>Fractional concentration of inspired oxygen</td>
</tr>
<tr>
<td>FVC</td>
<td>Forced vital capacity</td>
</tr>
<tr>
<td>GP</td>
<td>General physician</td>
</tr>
<tr>
<td>h</td>
<td>Hour</td>
</tr>
<tr>
<td>HMRS</td>
<td>Proton magnetic resonance spectroscopy</td>
</tr>
<tr>
<td>km/h</td>
<td>Kilometres per hour</td>
</tr>
<tr>
<td>L</td>
<td>Litre</td>
</tr>
<tr>
<td>L/min</td>
<td>Litres per minute</td>
</tr>
<tr>
<td>LED</td>
<td>Light-emitting diode</td>
</tr>
<tr>
<td>LOE</td>
<td>Level of evidence</td>
</tr>
<tr>
<td>LTOT</td>
<td>Long-term oxygen therapy</td>
</tr>
<tr>
<td>min</td>
<td>Minute</td>
</tr>
<tr>
<td>mmHg</td>
<td>Millimetres of mercury pressure</td>
</tr>
<tr>
<td>MRC</td>
<td>Medical Research Council</td>
</tr>
<tr>
<td>ms</td>
<td>Millisecond</td>
</tr>
<tr>
<td>NATA</td>
<td>National Association of Testing Authorities</td>
</tr>
<tr>
<td>NHMRC</td>
<td>National Health and Medical Research Council</td>
</tr>
<tr>
<td>NOTT</td>
<td>Nocturnal oxygen therapy trial</td>
</tr>
<tr>
<td>O₂</td>
<td>Oxygen</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>-------------</td>
</tr>
<tr>
<td>OSAS</td>
<td>Obstructive sleep apnoea syndrome</td>
</tr>
<tr>
<td>P(A-a)O$_2$</td>
<td>Alveolar - arterial oxygen gradient</td>
</tr>
<tr>
<td>PaCO$_2$</td>
<td>Partial pressure of carbon dioxide in arterial blood</td>
</tr>
<tr>
<td>PaO$_2$</td>
<td>Partial pressure of oxygen in arterial blood</td>
</tr>
<tr>
<td>PAO$_2$</td>
<td>Partial pressure of oxygen in alveolar air</td>
</tr>
<tr>
<td>PB</td>
<td>Barometric pressure</td>
</tr>
<tr>
<td>PO$_2$</td>
<td>Partial pressure of oxygen</td>
</tr>
<tr>
<td>PVT</td>
<td>Psychomotor Vigilance Task</td>
</tr>
<tr>
<td>R</td>
<td>Respiratory exchange ratio</td>
</tr>
<tr>
<td>SaO$_2$</td>
<td>Arterial oxygen saturation (measured by haemoximetry)</td>
</tr>
<tr>
<td>SO$_2$</td>
<td>Oxygen saturation</td>
</tr>
<tr>
<td>SpO$_2$</td>
<td>Arterial oxygen saturation (measured non-invasively by pulse oximetry)</td>
</tr>
<tr>
<td>TSANZ</td>
<td>Thoracic Society of Australia and New Zealand</td>
</tr>
<tr>
<td>V/Q</td>
<td>Ventilation to perfusion ratio</td>
</tr>
</tbody>
</table>
DEPARTMENT OF THE ACADEMIC SECRETARY
Academic Secretariat
Private Mail Bag 29
Panorama Avenue
Balmain NSW 2192
Australia

11 December 2006

Mr Jeffrey Pretto
Respiratory Laboratory
Austin Hospital
PO Box 5444
HEIDELBERG VIC 3084

Dear Mr Pretto,

The Ethics in Human Research Committee has approved your proposal “Effects of acute oxygen therapy on cognitive and driving performance in hypoxaemic COPD” for a twelve month period from Monday, 11 December 2006.

The protocol number issued with respect to this project is 2006/303. Please be sure to quote this number when responding to any request made by the Committee.

Please note that the Committee requires that all consent forms and information sheets are to be printed on Charles Sturt University letterhead. Students should liaise with their Supervisor to arrange to have these documents printed.

You must notify the Committee immediately should your research differ in any way from that proposed.

You are also required to complete a Progress Report form, which can be downloaded from www.csu.edu.au/research/forms/ehrc_annrep.doc, and return it on completion of your research project or by 11/12/2007 if your research has not been completed by that date.

The Committee wishes you well in your research and please do not hesitate to contact the Executive Officer on telephone (02) 6338 4628 or email ethics@csu.edu.au if you have any enquiries.

Yours sincerely

Julie Hicks
Executive Officer
Ethics in Human Research Committee

www.csu.edu.au
Dear Mr Pretto

Further to my letter of 25 February 2004 concerning the above detailed project, I am writing to acknowledge that your response to the issues raised by the by the Human Research Ethics Committee at their meeting on 19 February 2004 is satisfactory. This project now has full ethical approval.

It is now your responsibility to ensure that all people associated with this particular project are made aware of what has actually been approved. Any changes to the original application will require a submission of a protocol amendment to the Committee for consideration as this approval only relates to the original application as detailed above.

The Committee has requested me to make arrangement for progress reports to be submitted by the Investigator to the Committee at the end of twelve (12) months, or sooner if the project is completed within twelve (12) months. Should your study not commence twelve (12) months from the date of this letter this approval will lapse. A resubmission to the Human Research Ethics Committee would then be necessary before you could commence.
The Radiation Safety Committee must also receive a 12 monthly report if your study includes the use of ionising radiation.

The Committee wishes to be informed immediately of any untoward effects experienced by any participant in the trial where those effects in degree or nature were not anticipated by the researchers.

DETAILS OF ETHICS COMMITTEE:

It is the policy of the Committee not to release personal details of its members. However, I can confirm that at the meeting at which the above project was considered, the Committee fulfilled the requirements of the National Health and Medical Research Council in that it contained men and women encompassing different age groups and included people in the following categories:

Chairman
Lay Man
Lay Woman
Minister of Religion
Lawyer
Person with Research Experience
Person with Counselling Experience

Additional members include:
- Nursing Administrator
- Surgeon
- Pharmacologist
- Pharmacist

I confirm that the Principal Investigator or Co-Investigators were not involved in the approval of this project. I further confirm that all relevant documentation relating to this study is kept on the premises of Austin Health for more than three years.

The Committee is organised and operates according to the *Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)*, annotated with TGA comments, and *The National Statement on Ethical Conduct in Research Involving Humans* (NHMRC The National Statement) and the applicable laws and regulations; and the Health Privacy Principles in *The Health Records Act 2001*. This hospital is registered under the United States DHHS Federal Wide Assurance number 00001363.

Could you please sign and return the attached copy of this letter, to indicate you accept the conditions of approval.
PLEASE NOTE: The Committee requests that the Administrative Secretary Ms Pauline Jacklin (Pauline.Jacklin@austin.org.au) is informed of the actual starting date of the study as soon as the study commences. A written notice (e-mail, fax or letter) is considered the appropriate format for notification.

Dr K (Humsha) Naidoo

I acknowledge that I have read the above conditions and agree to abide by them:

Signed:  

Researcher
12.3. **Participant Information Sheet**

---

**Research Study Participant Information Sheet**

**Version 4, March 4, 2004**

---

**Full Project Title:**

Effects of Acute Oxygen Therapy on Cognitive and Driving Performance in Hypoxaemic COPD.

---

**Chief Investigators:**

Mr Jeff Pretto  
Senior Respiratory Scientist  
Department of Respiratory & Sleep Medicine, Austin Hospital  
Phone: 9496 5754  
email: jeff.pretto@austin.org.au

Associate Professor Christine McDonald  
Director, Respiratory Laboratory  
Department of Respiratory & Sleep Medicine, Austin Hospital  
Phone: 9496 5739  
email: christine.mcdonald@austin.org.au

---

**1. Your Consent**

You are invited to take part in this research project which investigates simulated driving performance in people like yourself with low blood oxygen levels. This Participant Information Sheet contains detailed information about the research project - its purpose is to explain to you as openly and clearly as possible all the procedures involved in this project before you decide whether or not to take part in it. Please read this document carefully and feel free to ask questions about any aspect of the project. You may also wish to discuss the project with a relative or friend or your local health worker. Once you understand what the project is about and if you agree to take part in it, you will be asked to sign the Consent Form. By signing the Consent Form, you indicate that you understand the information provided and that you give your consent to participate in the research project. You will be given a copy of the Participant Information and Consent Form to keep as a record.

**2. Purpose of This Study**

The purpose of this study is to determine whether driving performance in people with low blood oxygen levels is improved by breathing extra oxygen. Rather than performing the evaluation on the road with a real car, we will be using a computerised driving simulator (a little like a video game) to assess driving performance, and also a computer to measure your reaction times.

**3. Procedures**

If you agree to participate we will require you to attend our laboratory for a testing session of about 2½ hours in total. During this time you will undergo the driving and reaction time tests 3 times – the first time is to assess your normal driving performance and reaction times, and these tests are repeated whilst breathing air via nasal prongs, and oxygen via nasal prongs. You will be given time to familiarize yourself with the simulator before testing commences. The oxygen flow that you receive will be the same as that prescribed for you to use at home, as determined during your oxygen assessment tests. Note that this study does *not* require any blood sampling. You will be given cabcharge vouchers for transport to and from the Hospital without cost to you.
4. Possible Risks or Side Effects
There are no known risks, side effects or discomforts associated with the computer tests. Whilst there is a theoretical risk that acute oxygen therapy can lead to a reduction in the rate or depth of breathing and may lead to increased blood carbon dioxide levels, you have already undergone formal determination of the oxygen flow rate which is appropriate and safe for you. At no time during this project will you be given oxygen at flow rates different to this safe level. Since the computer tests take a total of 1½ hours over the total 2½ hour attendance time, there are many opportunities to take a break if you feel you need it. If you choose, you can also request to stop the testing at any stage for any reason.

5. Alternatives to Participation
No alternative or standard treatments will be withheld as a result of participation in the study.

6. Privacy, Confidentiality and Disclosure of Information
Any information obtained in connection with this research project which can identify you will remain confidential and will only be used for the purpose of this research project. It will only be disclosed with your permission, except as required by law. We plan to publish the results of the study in medical journals and present the findings at medical conferences. However, information in any publication or presentation will be provided in such a way that you cannot be identified. Records will be retained in password-locked computer databases and securely stored within the Department of Respiratory & Sleep Medicine at The Austin Hospital. The project managers will be the only individuals to have access to the personal details of participants. The study data will be retained for 7 years after which time it will be destroyed.

7. More Information
If you have any specific questions about this project, please feel free to ask either of the study investigators listed above. If you wish to contact someone, independent of the study, about ethical issues or your rights, you may contact:
Mr. Stephen Duns
Chairman of the Austin Health Human Research Ethics Committee
Phone: (03) 5427 0427.

8. Participation is Voluntary
Participation in any research project is voluntary. If you do not wish to take part you are not obliged to. If you decide to take part and later change your mind, you are free to withdraw from the study. Your decision whether to take part or not will not affect your routine treatment, your relationship with the treating you or your relationship with The Austin Hospital. Before you make your decision, a member of the research team will be available so that you can ask any questions you may have about the research project. The Consent Form should only be signed after you have had a chance to ask your questions and have received satisfactory answers.

9. Ethical Guidelines
This project will be carried out according to the National Statement on Ethical Conduct in Research Involving Humans (June 1999) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies. The ethical aspects of this research project have been approved by the Human Research Ethics Committee here at the Austin Hospital.
12.4. Consent Form

Consent Form to Participate in Research

Date: 19/09/2006

Project Title:
Effects of Acute Oxygen Therapy on Cognitive and Driving Performance in Hypoxaemic COPD.

I, .......................................................................................................................... have been invited to participate in the above study which is being conducted under the direction of Mr Jeff Presto (Principal Investigator, Respiratory Laboratory, Austin Hospital, ph: 9496 5754). I understand that while the study will be under his/her supervision, other relevant and appropriate persons may assist or act on his/her behalf.

My consent is based on the understanding that the study involves:

- The performance of computer-based driving simulation and reaction time measurements whilst having oxygen and air supplied via nasal prongs.

The study may involve the following risks, inconvenience and discomforts, which have been explained to me:

- There is a theoretical risk that breathing supplemental oxygen may cause a reduction in breathing rate leading to increased blood carbon dioxide levels. This is highly unlikely to occur given that oxygen will only be supplied at a rate previously shown to be safe to me. Attendance at the laboratory for approximately 2½ hours will be required. There are no known risks or discomforts associated with the computer tests.

I have received and read the attached ‘Participant Information Sheet’ and understand the general purposes, methods and demands of the study. All of my questions have been answered to my satisfaction. I understand that the project may not be of direct benefit to me. I can withdraw or be withdrawn by the Principal Investigator from this study/project at any time, without prejudicing my further management. I consent to the publishing of results from this study provided my identity is not revealed.

I hereby voluntarily consent and offer to take part in this study.

Signature (Participant) .................................................. Date: ................. Time: .............
Witness to signature ............................................................ Date: ................. Time: .............
Signature (Investigator) ..................................................... Date: ................. Time: .............

One copy to be given to participant, one copy filed in participant’s medical record

Charles Sturt University’s Ethics in Human Research Committee has approved this study. I understand that if I have any complaints or concerns about this research I can contact:

Executive Officer
Ethics in Human Research Committee
Academic Secretariat, Charles Sturt University
Private Bag Day 29
Bathurst NSW 2795
Phone: (02) 6338 4628 Fax: (02) 6338 4194
### 12.5. Worksheets and Other Forms

#### 12.5.1. Study Details Worksheet

**DriveOx Study Patient Details**

**Smoking History**
- Never smoked
- Ex-smoker: Stopped: __/__/____
- Current: ____ cigs/day
- Pack years: ______

**Arterial Blood Gases**

<table>
<thead>
<tr>
<th>Room Air</th>
<th>Intranasal Oxygen</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td></td>
</tr>
<tr>
<td>PaCO2</td>
<td></td>
</tr>
<tr>
<td>PaO2</td>
<td></td>
</tr>
<tr>
<td>SaO2</td>
<td></td>
</tr>
<tr>
<td>COHb</td>
<td></td>
</tr>
<tr>
<td>Hb</td>
<td></td>
</tr>
</tbody>
</table>

**Driving History**
- Current driver: ☐ Yes ☐ No
- Trips/week: ______
- Date stopped: __/__/____
- Reason stopped: ______
- License duration: ______

**Driving Data**

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Gas 1</th>
<th>Gas 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pos med Area</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pos Med Ave</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sp 60-80 Area</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sp 60-80 Ave</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crashes</td>
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</table>

**PVT Data**

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<thead>
<tr>
<th>Median KT</th>
<th>Errors</th>
<th>Lapses</th>
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</table>

<table>
<thead>
<tr>
<th>Trans. Lapses</th>
<th>Slowest 10%</th>
<th>Fastest 10%</th>
<th>RRT v Min slope</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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12.5.2. Forms included in sealed envelopes

**DriveOx Study Data Sheet**

 Patient #:  
 Name:  
 Date:  

**GAS 1**

**OXYGEN**

- Time:  
- Flowrate:  L/min
- SpO2:  

**GAS 2**

**AIR**

- Time:  
- Flowrate:  L/min
- SpO2:  

Comments:  

[Image]
Acute oxygen therapy does not improve cognitive and driving performance in hypoxaemic COPD

JEFFREY J. PRETTO1,2 AND CHRISTINE F. MCDONALD1

1Institute for Breathing and Sleep, Department of Respiratory and Sleep Medicine, Austin Hospital, Heidelberg, Victoria, and 2Department of Respiratory and Sleep Medicine, John Hunter Hospital, Newcastle, New South Wales, Australia

Acute oxygen therapy does not improve cognitive and driving performance in hypoxaemic COPD

PRETTO JJ, MCDONALD CF. Respirology 2008; 13: 1039–1044

Background and objective: Cognitive and neuropsychological function may be adversely affected by low blood oxygen levels and this has been previously demonstrated in hypoxaemic COPD. The aim of this study was to assess whether supplemental oxygen therapy while driving a motor vehicle is justified in hypoxaemic COPD. We therefore used computer-based driving simulation to investigate whether acute intranasal oxygen therapy improves the cognitive and driving performance of such patients.

Methods: Thirty hypoxaemic COPD subjects with a current driving licence performed a 20-min computer-based driving simulation task and a 10-min psychomotor vigilance task (PVT) at baseline, and while breathing intranasal oxygen or intranasal air in a randomized, double-blind, cross-over protocol.

Results: The mean (SD) age of the subjects was 72 years (8) and their mean driving experience was 50 years (10). Mean FEV1 was 41% (18) of predicted and PaO2 was 50.5 mm Hg (4.7) on air and 70.7 mm Hg (9.1) on oxygen. There were no statistically significant differences in any measure of driving performance or in reaction time measurements while breathing oxygen compared with air.

Conclusions: Acute oxygen therapy does not improve simulated driving performance or neuropsychological function as assessed by PVT in patients with hypoxaemic COPD. These data do not support the recommendation that oxygen should be used by this patient group while driving.

Key words: automobile driving, COPD, cognitive manifestation, hypoxaemia, oxygen therapy.

INTRODUCTION

It has been recognized since early last century that cognitive function is adversely affected by hypoxaemia.1 Several studies have demonstrated reduced neuropsychological performance in patients who suffer chronic hypoxaemia due to respiratory disease, particularly COPD.2-5 The question as to whether acute reversal of hypoxaemia with supple-

mental oxygen therapy leads to improved neurocognitive function has not been adequately studied. In one of the few controlled trials investigating this question, Wilson et al. found that acute oxygen therapy did not reverse information processing deficits in hypoxaemic COPD.6

Controlling a motor vehicle is a complex task requiring advanced cognitive, perceptual, motor and decision-making skills. These are precisely the neurocognitive factors that have been demonstrated to be negatively affected by hypoxaemia. It is therefore not unreasonable to expect that motor driving skills may be compromised in hypoxaemic drivers; however, there is a lack of formal investigation into the effects of hypoxaemia on driving performance.

Hypoxaemic patients who are treated with long-term oxygen therapy (LTOT) commonly use ambulatory oxygen equipment when away from the home. It is unclear whether this portable oxygen should be used while driving. Austroads, the association of Australian and New Zealand road transport and
traffic authorities, is one of the few groups to address this issue. Its medical recommendations for assessing fitness to drive state ‘individuals requiring LTOT should probably use their oxygen while driving.’ However, there is no published evidence to support this recommendation.

The aim of the current study was to help determine whether it is safe for COPD patients on LTOT to withhold their oxygen therapy while driving, by examining whether acute supplemental oxygen therapy improves driving or cognitive performance, and therefore whether the recommendation that oxygen be used while driving is justified.

METHODS

Patients with documented COPD who held a current driver’s licence were invited to participate in the study if they met the Thoracic Society of Australia and New Zealand (TSANZ) requirements for provision of domiciliary oxygen therapy, the prime requirement for which is significant arterial hypoxaemia (PaO₂ of ≤55 mm Hg or PaO₂ of ≤60 mm Hg with evidence of hypoxic organ damage). Patients were recruited from the hospital domiciliary oxygen clinic or from respiratory outpatient clinics.

Spirometry was performed in accordance with the recommendations of the American Thoracic Society, and arterial blood gases were sampled from the radial artery at least 15 min of rest, both while breathing room air and while breathing intranasal oxygen. The oxygen flow rate was adjusted to achieve a PaO₂ of at least 80 mm Hg in accordance with the TSANZ recommendations.

Driving simulator

Driving performance was assessed using a computer-based driving simulator (AutoEd software, Woolcock Institute of Medical Research, Sydney, Australia), which utilizes a steering wheel and foot pedals connected to a standard desktop computer with a 19-inch monitor. The view is of a dual-carriage rural road at night from the driver’s perspective, with a speedometer displayed in the top corner of the screen. Subjects were instructed to maintain a position in the centre of the left hand lane and to maintain a speed between 60 and 80 km/h. The software generates a pseudo-random course for each test session; however, the same random number seed was used for all testing, which allowed similar but not predictable courses to be generated for each assessment. This tool has previously been used to assess the effects on driving performance of such factors as sleep deprivation, alcohol use and inebriation exacerbations in cystic fibrosis. Driving assessments of 20-min duration were performed in a quiet, darkened room with no distractions. Primary measurement outcomes for driving performance were variation in lane position, variation in speed around the target value and the number of off-road events (crashes).

Psychomotor vigilance task

This test was originally developed as a measure of sustained attention and has been widely used over the past two decades in research on sleep and fatigue. Although to our knowledge, it has not been used to investigate the neurocognitive effects of hypoxaemia, psychomotor vigilance task (PVT) results are generally interpreted as providing a measure of an individual’s arousal and attention state. The handheld PVT-192 monitor (Ambulatory Monitoring Inc., Ardsley, NY, USA) measures and stores reaction times to visual stimuli, which occur randomly over 2–4 s intervals. It provides immediate feedback to the subject for each reaction time measurement. Each PVT assessment was made over a 10-min interval, with reaction times and the number of lapses in concentration (defined as a reaction time of more than 500 ms) being used as the primary measurement outcomes.

After providing informed consent to participation in the study, which was approved by the institutional medical research ethics committee, subjects underwent baseline driving simulator assessment for 20 min, followed by assessment of PVT performance for 10 min. Subjects were then randomized to receive either intranasal air or intranasal oxygen which were provided in a double-blind fashion for a period of at least 5 min prior to and during repeat driving and PVT assessments. Finally, subjects received the alternate gas via nasal prongs, and after a similar wash-in period, underwent the same driving and PVT assessments, during which the alternate gas was inhaled. The baseline measurements (with no intranasal gas) were used as a practice run and these data were not used in the analysis. This randomized, double-blind, cross-over study design therefore allowed comparisons between breathing air and oxygen, with each subject acting as his/her own control. The testing session for each subject lasted approximately 2.5 h in total.

Wilcoxon rank-sum tests were used to compare measurements while subjects were breathing air and oxygen, and Pearson correlations were performed to assess relationships between variables with \(P < 0.05\) being considered significant. Statistical analyses were performed using SigmaPlot software, version 9.0 (Systat Software Inc., San Jose, CA, USA). Sample size calculations were performed using PVT data as the primary outcome variable and a minimum meaningful change of 25 ms in median reaction times. These calculations indicated that 27 subjects would be sufficient to detect significant changes in PVT measurements with a power of 90% at an \(\alpha\) of 5%. Post hoc power calculations confirmed that the sample size resulted in power >95% to detect similar changes in driving parameters to those observed in response to low level alcohol ingestion, and to detect similar reaction time changes in response to sleep deprivation.

RESULTS

 Thirty-three subjects commenced the study, with two withdrawing due to nausea during the driving
Acute oxygen and driving in COPD

Table 1. Baseline characteristics of the 30 subjects who completed the study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>72</td>
<td>51-65</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>22/8</td>
<td></td>
</tr>
<tr>
<td>FEV$_1$ L (% predicted)</td>
<td>1.04 (41%)</td>
<td>0.42-2.46 (19-56)</td>
</tr>
<tr>
<td>FVC L (% predicted)</td>
<td>2.03 (86%)</td>
<td>1.5-5.1 (57-130)</td>
</tr>
<tr>
<td>FEV$_1$/FVC (%)</td>
<td>36</td>
<td>15-67</td>
</tr>
<tr>
<td>Smoking history (pack-years)</td>
<td>52</td>
<td>20-90</td>
</tr>
<tr>
<td>Driving experience (years licensed)</td>
<td>50</td>
<td>30-67</td>
</tr>
</tbody>
</table>

Predicted values for spirometry were obtained from the publication of Knudson et al.16

Table 2. Resting arterial blood gas measurements while breathing room air or supplemental intranasal oxygen

<table>
<thead>
<tr>
<th></th>
<th>Room air</th>
<th>Supplemental O$_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.41 (0.03)</td>
<td>7.49 (0.04)</td>
</tr>
<tr>
<td>PaCO$_2$ (mm Hg)</td>
<td>49.3 (7.8)</td>
<td>47.7 (8.3)</td>
</tr>
<tr>
<td>PaO$_2$ (mm Hg)</td>
<td>59.5 (4.7)</td>
<td>70.7 (9.1)</td>
</tr>
<tr>
<td>O$_2$ flow rate (L/min)</td>
<td>—</td>
<td>2.1</td>
</tr>
</tbody>
</table>

Values are means (SD).

Simulation, and data from one being omitted due to a failure in oxygen supply during the study. Baseline details for the remaining 30 subjects are shown in Table 1. Resting arterial blood gases on room air and on supplemental intranasal oxygen sufficient to increase PaO$_2$ to >60 mm Hg are shown in Table 2.

Figure 1 compares driving simulation data for the 30 patients, while breathing intranasal air or intranasal oxygen. Key measurements included the variation in lane position from the centre of the lane, expressed in units of area, the variation in speed around the target value of 70 km/h also expressed as an area, and the number of off-road events or crashes. There were no significant differences in any of these measurements when subjects were breathing intranasal air compared with intranasal oxygen.

Similarly, there were no significant differences in any of the PVT measurements, as shown in Figure 2. The primary PVT measurements were median reaction times, the fastest 10% of reaction times and lapses in concentration.

Twenty-one of the subjects tested had been prescribed LTOI at the time of the study, with nine either not receiving or about to commence LTOI. Of those on LTOI, the median duration of this therapy was 31 months (range 2 weeks to 129 months). Twenty-nine of the subjects were ex-smokers with a median of 6 years since quitting. Only one subject was an active smoker at the time of the study.

To investigate whether those patients with greater increases in PaO$_2$ while on oxygen demonstrated greater improvements in driving or PVT measurements, the changes in these measurements are plotted against each other in Figures 3 and 4. These data show no significant correlations, indicating that neither improvements in driving nor PVT performance were related to the magnitude of improvement in oxygenation. Similarly, there were no significant correlations between change in PaCO$_2$ on supplemental oxygen and performance. In addition, there was no order effect observed for any of the driving or PVT measurements.

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DISCUSSION

This study did not demonstrate any effect of supplemental oxygen on driving performance using a computerized driving simulator in this group of hypoxaemic COPD patients. Similarly, there was no change in cognitive function as assessed by psychomotor reaction times. These conclusions are based on the group data as a whole; however, there were no correlations between baseline data (including acute arterial blood gas changes on supplemental oxygen) and improvements in driving or neurocognitive function. It was therefore not possible to predict which individuals were likely to perform better on supplemental oxygen.

These findings are in agreement with the only other published study investigating the acute effects of oxygen therapy on neurocognitive function in hypoxaemic COPD. Wilson et al. assessed information processing ability in 10 hypoxaemic COPD subjects while breathing air or sufficient oxygen to improve SaO₂ to >95%, and showed no significant difference in any measured parameter. They specifically assessed auditory and visual perception and sensory function, memory and depth of processing but did not assess driving ability. The findings from that well-controlled study contrast with observed improvements in neuropsychological functions following oxygen therapy of at least 4 weeks' duration. It may well be that LiOT over extended periods is required to allow sufficient time for reparative processes and measurable improvements in cognition, rather than the acute improvements in oxygenation achieved in the current study and that of Wilson et al.

Compromised neurocognitive function is a well-documented feature of COPD in general, and of hypoxaemic COPD in particular. Heaton et al. found moderate to severe neurocognitive impairment in 42% of patients recruited for the landmark Nocturnal Oxygen Therapy Trial (NOTT) that assessed the efficacy of LiOT in hypoxaemic COPD. They found that higher cognitive functions were particularly affected, but also found significantly decreased motor speed and coordination in half the subjects. In a larger group of 203 NOTT patients, Grant et al. performed an age, gender and education-matched analysis and found that 77% of the hypoxaemic COPD patients had a neuropsychological deficit suggestive of cerebral dysfunction. The cause of the neuropsychological disturbance was not identified; however, the finding of significant correlations between degree of hypoxaemia and degree of neurocognitive impairment suggests a causative link between the two.

There is limited published data investigating the effects of hypoxaemia on driving performance. Ramsey found deterioration in reaction times after driving in commuter traffic for 90 min in a group of young healthy subjects and in older patients with respiratory disease. While he attributed this change to effective hypoxaemia caused by increased carboxyhaemoglobin, direct measurements of arterial oxygen were not made and there were other methodological problems that probably negate the findings of the study.

Sung et al. used a driving simulator to assess the effects of oxygen concentration on fatigue; however, blood oxygen levels were not measured and only subjective assessments of fatigue, but no driving performance data, was obtained. As with many other studies in this area, normal subjects (presumably normoxaemic) were acutely subjected to hypoxic gas to document the neuropsychological effects of hypoxaemia. The experimental conclusions drawn from such studies may not necessarily be applicable in assessing the effects of acute improvements in
blood oxygen levels in chronically hypoxaemic subjects. We believe that the present study is the first to objectively assess, in a controlled way, the acute effects of oxygen therapy on driving performance in hypoxaemic COPD patients.

While there are substantial differences in the use of driving simulators compared with real-world driving, due to factors such as the lack of visual, proprioceptive and vestibular sensory information, the validity of simulators as a driving assessment tool in the elderly has been demonstrated by Lee et al.25 Furthermore, simulators do provide a greater degree of experimental control and enable more reliable and precise performance measurements to be made. They are therefore particularly effective in assessing the effects of interventions such as oxygen therapy. The AusFed program used in this study has been shown to be sensitive to decrements in performance due to factors such as sleep deprivation and alcohol use.8,11,12 To our knowledge, it has not previously been used in the investigation of the effects of hypoxaemia.

While there were no statistically significant differences when subjects were on oxygen compared with air for any of the primary measurement outcomes, the magnitude of the differences was also small compared with the effects found for other interventions. For example, increases in PVT reaction times of approximately 90 ms (40%) were reported after 24 h of sleep deprivation,28 compared with the 5 ms improvement (2%) we observed in response to oxygen therapy.

All of the subjects in the study of Wilson et al.8 and 7% of those in the present study had been on LTOT at the time of the study. It could therefore be argued that the reason that no neurocognitive improvements were observed in either study was that the previous LTOT had already reversed the neurocognitive deficits attributable to hypoxaemia, as demonstrated by others,19-22 and consequently there was little margin for further improvement with acute therapy. While this certainly may be the case, we would suggest that the question of whether the use of oxygen while driving in patients who would normally be on LTOT is still relevant, and we believe that our findings specifically indicate that no benefit in driving performance is obtained with concurrent oxygen usage.

One limitation of this study was that the driving simulation was conducted over a 20-min period only, and hence performance was not assessed over longer duration trips. It could be argued that neurocognitive performance might decline further over longer time periods without supplemental oxygen; however, in our experience, patients on LTOT rarely drive long distances. While usual driving durations were not specifically quantified, the average weekly number of trips undertaken by these subjects was only 10, with most being of very short duration.

It should be stressed that the aim of this study was to determine whether driving and/or neurocognitive performance is measurably improved in hypoxaemic drivers with the use of supplemental oxygen. The question of whether the driving performance of hypoxaemic drivers is any different to that of non-hypoxaemic drivers was not addressed, and as such, no conclusions can be made about the safety of drivers in this patient group.

While the number of hypoxaemic drivers is likely to be relatively small compared with the total number of road users, the ageing of the community and projected increases in COPD incidence25 suggest that the importance of this issue will intensify over coming years. We did not find any differences in driving or cognitive performance while this patient group was breathing oxygen compared with air, indicating that driving without supplemental oxygen does not adversely affect driving performance. In this context the present findings do not support the recommendation that drivers with hypoxaemic COPD should use supplemental oxygen therapy while driving.

ACKNOWLEDGEMENTS

This study was supported by a grant from the Victorian Tuberculosis and Lung Association (Melbourne, Victoria, Australia). We are grateful to Liz Perry, Ito Moore and Katie Doan (Department of Respiratory and Sleep Medicine, Austin Hospital) for their assistance in the recruitment of subjects for this study.

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THE ACUTE EFFECTS OF OXYGEN THERAPY ON COGNITIVE AND DRIVING PERFORMANCE IN HYPOXAEIC COPD.
Jeffrey J. Prett and Christine F. McDonald
Department of Respiratory & Sleep Medicine, Austin Health and Institute for Breathing and Sleep, Heidelberg, Victoria 3084.

It has long been recognized that cognitive and neuropsychological function is adversely affected by low blood oxygen levels. Current Australian guidelines recommend that individuals requiring long-term oxygen therapy should probably use oxygen whilst driving, however there is little evidence to support this recommendation. This is a preliminary report investigating whether acute intranasal oxygen therapy improves cognitive and driving performance as assessed using computer-based simulation. Methods: Fifteen hypoxaeic subjects with COPD and current driver's licences performed a 20 minute computer-based driving simulation task (AusEd) and 10 minute psychomotor vigilance task (PVT) at baseline, and whilst breathing intranasal oxygen and intranasal air in a randomized, double-blinded, crossover manner. Paired comparisons (Wilcoxon) were made between air and oxygen data with p<0.05 considered significant. Results: Mean PaO2 was 51 mmHg on air and 71 mmHg on oxygen. The table shows key driving and PVT results whilst breathing intranasal air and oxygen, expressed as medians and interquartile ranges. There were no statistically significant differences in any performance measures.

<table>
<thead>
<tr>
<th></th>
<th>Driving Simulation</th>
<th>PVT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lane Variation</td>
<td>Speed Variation</td>
</tr>
<tr>
<td>Air</td>
<td>86 (55)</td>
<td>11.3 (5.8)</td>
</tr>
<tr>
<td>O2</td>
<td>84 (56)</td>
<td>9.5 (8.5)</td>
</tr>
</tbody>
</table>

Conclusion: Acute oxygen therapy does not improve simulated driving performance or neurocognitive function as assessed by PVT in hypoxaeic COPD. These data do not support the recommendation that oxygen should be used whilst driving in this patient group.

This study was supported by the Victorian Tuberculosis and Lung Association.
Keywords: Hypoxaeia, driving performance, COPD
12.8. Abstract for 2006 Congress of the APSR (Kyoto)

The Acute Effects of Oxygen Therapy on Cognitive and Driving Performance in Hypoxaemic COPD.
Jeffrey J. Pretto and Christine F. McDonald
Department of Respiratory & Sleep Medicine, Austin Health and Institute for Breathing and Sleep, Heidelberg, Victoria 3084.

Background: It has long been recognized that cognitive and neuropsychological function is adversely affected by low blood oxygen levels. Current Australian guidelines recommend that individuals requiring long-term oxygen therapy should probably use oxygen whilst driving, however there is little evidence to support this recommendation. The aim of this study was to investigate whether acute intranasal oxygen therapy improves cognitive and driving performance as assessed using computer-based simulation. Methods: Twenty-two hypoxaemic subjects with COPD and current driver’s licences performed a 20 minute computer-based driving simulation task (AnaEd) and 10 minute psychomotor vigilance task (PVT) at baseline, and whilst breathing intranasal oxygen and intranasal air in a randomized, double-blinded, crossover manner. Paired comparisons (Wilcoxon) were made between air and oxygen data with p<0.05 considered significant. Results: Baseline subject characteristics (mean, SD) were a subject age of 72 (8) years with 52 (8) years of driving experience. FEV1 was 42 (19) % of predicted and PaO2 was 50 (5) mmHg on air and 70 (9) mmHg on oxygen. There were no statistically significant differences in lane position variation, speed variation or in any other driving performance measurements whilst breathing oxygen compared with breathing air. Similarly, reaction time measurements and vigilance were not different between the 2 inhaled gases. Conclusion: Acute oxygen therapy does not improve simulated driving performance or neurocognitive function as assessed by PVT in hypoxaemic COPD. These data do not support the recommendation that oxygen should be used whilst driving in this patient group.

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THE ACUTE EFFECTS OF OXYGEN THERAPY ON COGNITIVE AND DRIVING PERFORMANCE IN HYPOXAEIC COPD.

Jeffrey J. Pretto and Christine F. McDonald
Department of Respiratory & Sleep Medicine, Austin Health and Institute for Breathing and Sleep, Heidelberg, Victoria 3084

Background: It has long been recognized that cognitive and neuropsychological function is adversely affected by low blood oxygen levels. Current Australian guidelines (AusRoads 2003) recommend that individuals requiring long-term oxygen therapy should probably use oxygen whilst driving, however there is little evidence to support this recommendation. The aim of this study was to investigate whether acute intranasal oxygen therapy improves cognitive and driving performance as assessed using computer-based simulation.

Methods: Twenty-two hypoxaemic subjects with COPD and current driver’s licences performed a 20 minute computer-based driving simulation task (AusEd) and 10 minute psychomotor vigilance task (PVT) at baseline, and whilst breathing intranasal oxygen and intranasal air in a randomized, double-blinded, crossover manner. Paired comparisons (Wilcoxon) were made between air and oxygen data with p<0.05 considered significant.

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This study was supported by the Victorian Tuberculosis and Lung Association.
ACUTE OXYGEN THERAPY DOES NOT IMPROVE COGNITIVE AND DRIVING PERFORMANCE IN HYPOXAEIC COPD.

JJ Pretto and CF McDonald
Institute for Breathing & Sleep, Department of Respiratory & Sleep Medicine, Austin Hospital, Heidelberg, Victoria 3084.

Introduction: Cognitive and neuropsychological function may be adversely affected by low blood oxygen levels and this has previously been demonstrated in hypoxaeic COPD. Consequently, current Australian guidelines for assessing fitness to drive recommend that individuals requiring long-term oxygen therapy should probably use oxygen whilst driving. There is however no evidence to support this recommendation. Aim: To investigate whether acute intranasal oxygen therapy improves cognitive and driving performance of patients with COPD and hypoxaeia as assessed using computer-based simulation. Methods: Thirty hypoxaeic subjects with COPD holding a current driving license performed a 20 minute computer-based driving simulation task and a 10 minute psychomotor vigilance task (PVT) at baseline, and whilst breathing intranasal oxygen and intranasal air in a randomized, double-blinded, crossover manner. Paired comparisons (Wilcoxon) were made between air and oxygen data with p<0.05 considered significant. Results: Baseline subject characteristics (mean, SD) were an age of 72 (8) years with 50 (10) years of driving experience. FEV1 was 41 (16) % of predicted and PaO2 was 50.5 (4.7) mmHg on air and 70.7 (9.1) mmHg on oxygen. There were no statistically significant differences in lane position variation, speed variation or in any other measures of driving performance whilst breathing oxygen compared with breathing air. Similarly, reaction time measurements were not different between the two inhaled gases. Conclusions: Acute oxygen therapy does not improve simulated driving performance or neurocognitive function as assessed by PVT in hypoxaeic COPD. These data do not support the recommendation that oxygen should be used whilst driving in this patient group. Supported by: Victorian Tuberculosis and Lung Association
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