The association between early arterial oxygenation and mortality in ventilated patients with acute ischaemic stroke

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ABSTRACT

Background: There are conflicting data that suggest that hyperoxia may be associated with either worse or better outcomes in patients suffering a stroke.

Objectives: To investigate the association between PaO2 in the first 24 hours in the intensive care unit and mortality among ventilated patients with acute ischaemic stroke.

Design: Retrospective cohort study.

Setting: Data were extracted from the Australian and New Zealand Intensive Care Society Adult Patient Database.


Main outcome measures: The primary outcome was the odds ratio for inhospital mortality associated with “worst” PaO2 considered as a categorical variable, with data divided into deciles and compared with the mortality of the 10th decile. For patients on an FiO2 of $\leq 50\%$ at any time in the first 24 hours, “worst” PaO2 was defined as the PaO2 associated with the highest alveolar–arterial (A–a) gradient. For patients on an FiO2 of $<50\%$, it was defined as the lowest PaO2.

Secondary outcomes were ICU and hospital length of stay and the proportion of patients in each decile discharged home.

Results: Of the 2643 patients eligible for study inclusion, 1507 (57\%) died in hospital. The median “worst” PaO2 was 117 mmHg (interquartile range, 87–196 mmHg). There was no association between worst PaO2 and mortality, length of stay or likelihood of discharge home.

Conclusions: We found no association between worst arterial oxygen tension in the first 24 hours in ICU and outcome in ventilated patients with ischaemic stroke.

Methods

Data were extracted from the ANZICS APD. This database is an established binational voluntary database, which contains data from more than one million ICU admissions.

Ventilated adult patients (>17 years of age) who were admitted to the ICU with a stroke at one of 129 participating centres between 1 January 2000 and 31 December 2009 were included. The primary Acute Physiology and Chronic Health Evaluation (APACHE) III diagnostic code 403 (stroke) was used to identify suitable patients. An alternative code (402) exists for intracerebral haemorrhage, so it is likely that our dataset exclusively comprises patients with ischaemic strokes. Readmissions and patients whose records did not contain arterial blood gas analysis, APACHE III risk of death, or vital status at discharge were excluded.

Access to the data was granted by the ANZICS Centre for Outcome and Resource Evaluation (CORE) Management Committee in accordance with standing protocols. Data are collected under the quality assurance legislation of Part VC.
of the *Health Insurance Act 1973* (Cwlth). In New Zealand, use of anonymous collected quality data for research is classified as low-risk audit activity and is exempt from requirements for formal ethics approval.

**Data for oxygen values**

All arterial blood gas measurements taken during the first 24 hours of ICU admission are collected and entered into a standard data collection system. In accordance with the APACHE III scoring system, the most abnormal set of arterial blood gas measurements by analysis of simultaneous recordings of FiO2 and PaO2 are entered in the database. If the FiO2 is \( \geq 0.5 \), the PaO2 associated with the highest alveolar–arterial (A–a) gradient is selected, and if the FiO2 is \( < 0.5 \), the measurement with the lowest PaO2 is selected. If arterial blood gases are taken on both an FiO2 \( < 0.5 \) and an FiO2 \( \geq 0.5 \) during the first 24 hours, the PaO2 derived from measurements taken on \( \geq 0.5 \) is used. In our study, this PaO2 value was defined as the “worst” PaO2.

To explore the relationship between the worst PaO2 recorded in the adult patient database and the peak, median and mean PaO2 measured during the first 24 hours and over the duration of the ICU stay in patients with stroke, we examined details of all recorded arterial blood gas measurements (906 measurements) for a convenience sample of 49 stroke patients admitted to five tertiary ICUs in Australia with a diagnosis of ischaemic stroke. The measurements were collected between 2000 and 2009, and, of these, 311 were collected from the first 24 hours of the ICU stay.

**Data extraction**

Data of the size, type and location of the hospital were collected. At a patient level, the following variables were extracted: demographics, APACHE III chronic comorbidities, hospital and ICU admission source, intubation, treatment limitation, year of admission, physiological and arterial blood gas parameters over the first 24 hours in the ICU, vital status at hospital discharge (alive or dead), discharge destination, and an APACHE III risk of death score. To apply a marker for severity of illness that was independent of arterial oxygenation, an adjusted APACHE risk of death (AP3-no-ox) was calculated for each patient, whereby the oxygen component of the APACHE III scoring system was removed and an adjusted score independent of oxygen was recalculated.

**Outcomes**

The primary outcome was the odds ratio for the risk of inhospital mortality associated with the worst PaO2 in the first 24 hours in ICU considered as a categorical variable with the data divided into deciles, and compared with the mortality of the 10th decile. We compared between deciles the proportion of patients who were discharged home, the ICU length of stay and the hospital length of stay as secondary outcome variables.

**Subgroup analyses**

We compared patients who were admitted to the ICU from the emergency department with those who were admitted to the ICU from the ward. We also compared patients who lived at home before admission with patients who were in hospitals or residential care facilities.

**Statistical analyses**

All analyses were performed using SAS, version 9.2 (SAS Institute Inc, Cary, NC, USA). Continuous data are presented as mean (SD) or median (interquartile range [IQR]), depending on the underlying distribution of the data. Categorical data are reported as number (%).

To ensure that the nature of the relationship between PaO2 and mortality was not masked by confounding variables, multivariate analysis was conducted using logistic regression for mortality adjusting PaO2 levels for FiO2 levels, illness severity (AP3-no-ox) and year of admission. All first-order interactions were tested for statistical significance, with none being significant. A two-sided \( P \) of 0.05 was considered statistically significant. Data are reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

**Results**

Overall, 3148 patients met the inclusion criteria of mechanical ventilation, age older than 17 years and admission to ICU with an ischaemic stroke. There were 505 patients who did not have available information for hospital mortality (163), arterial blood gas measurements (50), APACHE III risk of
death (277) or were readmissions (15). The remaining 2643 patients were drawn from ICUs of 129 contributing hospitals (33 rural, 33 metropolitan, 34 tertiary referral centre and 29 private hospitals). Most hospitals (75) were small to medium (<300 beds), 33 hospitals were large (300–500 beds) and 21 hospitals were extra-large (>500 beds). The median number of acute ischaemic stroke patients per hospital over the study period was 8 (IQR, 3–21).

The mean patient age was 66 years (SD, 15 years) and 1584 (60%) were men. A total of 1674 were living at home before admission (63%). The ICU admission source was the emergency department for 1420 patients (54%), the ward for 586 patients (22%), other hospitals 586 (22%) and the operating theatre for 46 (2%). Admission source data were missing for five patients (0.2%). Eighteen per cent of patients (476) had documented pre-existing APACHE III chronic comorbidities. The median APACHE III risk of death was 45% (IQR, 21%–69%) and 1507 patients died in hospital (57%). Baseline characteristics are shown in Table 1.

There was no apparent relationship between mortality and PaO2 levels in the first 24 hours in ICU, with mortality levels across the 10 deciles of PaO2 ranging between 50% (5th decile, PaO2 range 103–117 mmHg) and 63% (2nd decile, PaO2 range 69–83 mmHg). (Figure 1). After adjustment for FiO2 levels (odds ratio [OR], 1.44 [95% CI, 0.97–2.14]) AP3-no-ox (OR, 1.03 [95% CI, 1.03–1.04]) and year of admission (OR, 1.02 [95% CI, 1.00–1.04]), there was no relationship between PaO2 and mortality (Figure 2), as no decile was significantly different from the reference category (10th decile, PaO2 range 341–611 mmHg). There was also no apparent relationship between PaO2 and length of ICU stay, length of hospital stay or likelihood of being discharged home. Outcome data for each of the 10 deciles of worst PaO2 are shown in Table 2.

After adjustment for confounding variables, there were no differences in inhospital mortality between the PaO2 deciles for any of the predefined subgroups (Table 3).

### Table 2. Outcomes associated with deciles of “worst” PaO2

<table>
<thead>
<tr>
<th>Worst PaO2, mmHg</th>
<th>Median ICU LOS (IQR), hours</th>
<th>Median hospital LOS (IQR), hours</th>
<th>Inhospital mortality, no. (%)</th>
<th>Adjusted* OR for inhospital mortality (95% CI)</th>
<th>OR for failure to discharge to home (95% CI)</th>
<th>Adjusted* OR for failure to discharge to home (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–69</td>
<td>60.5 (31.5–111.1)</td>
<td>162.4 (65.0–476.8)</td>
<td>163/264 (62%)</td>
<td>1.14 (0.76–1.72)</td>
<td>0.84 (0.55–1.30)</td>
<td>0.93 (0.57–1.51)</td>
</tr>
<tr>
<td>&gt;69–83</td>
<td>65.1 (318.0–121.7)</td>
<td>162.3 (67.0–428.9)</td>
<td>165/264 (63%)</td>
<td>1.15 (0.76–1.74)</td>
<td>0.91 (0.59–1.40)</td>
<td>0.98 (0.60–1.6)</td>
</tr>
<tr>
<td>&gt;83–93</td>
<td>70.8 (39.7–142.7)</td>
<td>178.0 (75.3–563.1)</td>
<td>145/265 (55%)</td>
<td>0.99 (0.65–1.51)</td>
<td>0.66 (0.43–1.00)</td>
<td>0.82 (0.51–1.33)</td>
</tr>
<tr>
<td>&gt;93–103</td>
<td>63.8 (32.8–118.5)</td>
<td>180.0 (73.8–435.3)</td>
<td>159/264 (60%)</td>
<td>1.48 (0.97–2.26)</td>
<td>0.84 (0.55–1.30)</td>
<td>1.20 (0.73–1.97)</td>
</tr>
<tr>
<td>&gt;103–117</td>
<td>75.9 (41.9–120.9)</td>
<td>233.6 (93.2–594.3)</td>
<td>133/264 (50%)</td>
<td>0.94 (0.62–1.43)</td>
<td>0.71 (0.47–1.08)</td>
<td>0.97 (0.60–1.58)</td>
</tr>
<tr>
<td>&gt;117–140</td>
<td>57.3 (32.1–116.0)</td>
<td>210.8 (66.3–518.5)</td>
<td>141/265 (53%)</td>
<td>1.01 (0.67–1.53)</td>
<td>0.78 (0.51–1.19)</td>
<td>1.05 (0.64–1.71)</td>
</tr>
<tr>
<td>&gt;140–174</td>
<td>58.1 (32.0–115.2)</td>
<td>187.5 (68.0–394.6)</td>
<td>156/264 (59%)</td>
<td>1.20 (0.80–1.81)</td>
<td>0.83 (0.54–1.27)</td>
<td>1.03 (0.64–1.66)</td>
</tr>
<tr>
<td>&gt;174–226</td>
<td>55.5 (32.0–124.4)</td>
<td>190.8 (64.8–569.3)</td>
<td>141/265 (53%)</td>
<td>0.82 (0.55–1.22)</td>
<td>0.78 (0.51–1.19)</td>
<td>0.89 (0.56–1.42)</td>
</tr>
<tr>
<td>&gt;226–341</td>
<td>63.8 (29.9–138.4)</td>
<td>188.8 (72.3–515.0)</td>
<td>148/264 (56%)</td>
<td>1.01 (0.69–1.47)</td>
<td>0.91 (0.59–1.4)</td>
<td>1.08 (0.68–1.71)</td>
</tr>
<tr>
<td>&gt;341–611</td>
<td>57.2 (27.0–98.0)</td>
<td>165.6 (63.3–491.5)</td>
<td>163/264 (62%)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
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</table>

AP3-no-ox = adjusted Acute and Chronic Health Evaluation (APACHE) III risk of death, whereby the oxygen component of the APACHE III scoring system was removed and an adjusted score independent of oxygen was recalculated. ICU = intensive care unit. IQR = interquartile range. LOS = length of stay.

OR = odds ratio. * Odds ratio is adjusted for FiO2 levels, AP3-no-ox and year of admission. All odds ratios are relative to the 10th worst PaO2 decile.
The median worst PaO₂ value was 117 mmHg (IQR, 87–196 mmHg). Using data from 906 arterial blood gas measurements derived from 49 ventilated stroke patients in the ICU, we showed that the worst PaO₂ defined in the database correlated well with the peak PaO₂ measured in the first 24 hours (r=0.79), and the mean PaO₂ measured in the first 24 hours (r=0.68), although there was a weaker correlation with the median PaO₂ measured in the first 24 hours (r=0.49). The correlation between the worst PaO₂ and the mean and median PaO₂ for the entire ICU stay was r=0.46 and r=0.30, respectively. For 86% of these patients the worst PaO₂ value that would have been entered in the ANZICS CORE database was derived from an arterial blood gas measurement taken when the patient had an FiO₂ ≥ 0.5.

### Discussion

We found no evidence that in mechanically ventilated patients with ischaemic stroke, differing levels of the worst PaO₂ in the first 24 hours in ICU influenced mortality, length of ICU or hospital stay or the likelihood of being discharged home. The relationship between worst PaO₂ and mortality was similar for patients admitted to hospital from their own home compared with patients admitted from other hospitals and residential care facilities. It was also similar for patients admitted to ICU from the ward compared with patients admitted to ICU from the emergency department.

Eubaric hyperoxia has been shown to increase oxygen delivery to brain tissue in animal stroke models and in patients with traumatic brain injury. Hyperoxia also prevents degradation of the blood–brain barrier during focal cerebral ischaemia. It has been proposed that hyperoxia shunts blood from regions of normal brain to ischaemic brain. It does this by selectively vasoconstricting cerebral arteries that perfuse normal brain without affecting arteries in areas of ischaemic brain, thereby potentially protecting the ischaemic penumbra. Hyperoxia during ischaemia and reperfusion in rats subjected to middle cerebral artery occlusion leads to a reduction in infarct size and neurological scores. In animals subjected to focal cerebral ischaemia, eubaric hyperoxia causes upregulation of antioxidant enzymes and glutamate transporters and alters expression of inflammatory cytokines.

Conversely, oxygen can reduce cerebral blood flow and, when resulting in hyperoxia, can increase oxidative stress through the production of oxygen free radicals that may be important in the pathogenesis of ischaemic stroke. The potential harms of oxygen therapy in brain injured patients are suggested by recent evidence that, in patients with global hypoxic brain injury after cardiac arrest, hyperoxia increases mortality and, more generally, by the demonstration that in critically ill patients mortality increases with increasing levels of hyperoxia.

There is evidence that administration of high concentrations of oxygen under eubaric conditions may reduce the neurological deficit caused by an acute stroke in animal models. We were unable to assess for such an effect in critically ill patients with ischaemic stroke and could only use surrogate measures, such as discharge home, to assess neurological outcome.

However, experimental administration of oxygen in animal models differs from use of oxygen in ICU patients with stroke in two ways. Firstly, in many cases, animal models of stroke typically involve brief transient arterial occlusion rather than prolonged arterial occlusion as typically occurs in stroke patients. Secondly, administration of oxygen in models of stroke typically occurs at or soon after the onset of brain ischaemia, whereas, oxygen administration to ICU patients...
takes place many hours after the onset of ischaemia due to the time it takes for stabilisation and transfer to the ICU. We are unable to ascertain whether our measurements are reflective of oxygen measurements taken earlier on in the patient’s prehospital (ambulance) or hospital course.

Existing human data from stroke patients are limited and conflicting.\textsuperscript{16,26,27} The largest controlled trial of eobaric oxygen therapy was performed in a single centre in Norway and involved 550 patients with a stroke (of which 87.6\% were ischaemic) who were allocated by a quasi-randomised design to 24 hours of treatment with either 3 L of oxygen or room air.\textsuperscript{26} In this study, there was no significant difference in 1-year survival between the oxygen and the room air groups.\textsuperscript{26} However, in a subgroup analysis of patients with minor or moderate strokes, survival was lower in the oxygen group than the control group (82\% v 91\%; odds ratio, 0.45 [95\% CI, 0.23–0.90]; \textit{P}=0.02). For patients with the most severe strokes, treatment with oxygen did not have an effect on 1-year mortality (53\% v 48\%; odds ratio, 1.26 [95\% CI, 0.76–2.09]; \textit{P}=0.54).\textsuperscript{26}

Chiu and colleagues investigated the feasibility of eobaric hyperoxia therapy among a group of 46 patients with severe ischaemic stroke involving more than one-third of the middle cerebral artery territory.\textsuperscript{27} In a non-randomised trial, they compared 40\% oxygen administered via a Venturi mask with 2 L of oxygen administered via nasal prongs. No significant differences in mortality or other outcome measures were demonstrated, although the analyses were limited by low power.

Similar limitations applied in a pilot randomised controlled trial that investigated the effects of high-flow oxygen in 16 acute ischaemic stroke inpatients with perfusion–diffusion mismatch on magnetic resonance imaging (MRI) scan (an abnormality thought to correspond to the presence of ischaemic but potentially salvageable brain tissue).\textsuperscript{16} It demonstrated that during hyperoxia there were transient MRI and clinical improvements within the first 4 and 24 hours respectively; however, these improvements were not evident by the time of 1-week or 3-month follow-up.\textsuperscript{16}

Given the correlation between worst PaO\textsubscript{2} and peak PaO\textsubscript{2} in the first 24 hours, our findings suggest that peak arterial oxygen tension in the first 24 hours was not associated with a change in the risk of mortality, length of ICU or hospital stay, or likelihood of being discharged home among ventilated critically ill patients with ischaemic stroke. However, the retrospective nature of our study means that detailed clinical conclusions cannot be drawn. Furthermore, we cannot exclude the possibility of benefit or harm among particular subsets of patients such as those with less severe strokes, as suggested by the Norwegian study.\textsuperscript{26}

The major strength of our study is its power to detect an effect, with more than 2600 patients studied. Our findings are generalisable to ICU practice in that the data were contributed by 129 ICUs in Australia and New Zealand. They also included a multifaceted assessment of the independent relationship between hyperoxia and outcome with adjustment for illness severity. However, like other studies of association using a large database, it is limited by the nature of the data available. Additionally, 16\% of eligible records were not included in the analysis because of missing data.

The assessment of oxygenation status in the first 24 hours was based on the worst possible arterial blood gas result in accordance with the PaO\textsubscript{2} criteria used for this component of the APACHE III risk of death score. It would have been preferable to use the highest (or lowest) PaO\textsubscript{2}, regardless of FiO\textsubscript{2}; however, these data were not available in the ANZICS APD. However, in a validation study of arterial blood gas results from 49 patients with ischaemic stroke admitted to ICU, we determined that the “worst” PaO\textsubscript{2} was moderately well correlated with the peak and mean PaO\textsubscript{2} in the first 24 hours, and was usually taken from an early blood gas measurement taken on an FiO\textsubscript{2} of \textasciitilde 0.5. As a result, we consider that this measure is an acceptable surrogate for the PaO\textsubscript{2} levels in the first 24 hours of ICU care. An additional weakness of our data is that we did not adjust for carbon dioxide levels, which are known to influence cerebral perfusion.\textsuperscript{28}

Our data do not provide any information about the potential benefits or harms of eobaric hyperoxia in the early period after acute stroke or exclude a potential effect of such therapy in particular subgroups of patients. We only studied patients admitted to ICU. The mortality rate of over 50\% seen in our cohort of patients may reflect factors such as the severity of the stroke and underlying comorbidities or functional limitations that might drive clinicians to withdraw active therapy and may confound the detection of an effect of hyperoxia on outcome. Our results do not provide information about the usefulness or otherwise of hyperoxia in stroke patients in non-ICU settings.

Finally, we are unable to comment on the cause of death or consider other potential confounding variables that might have affected the relationship between oxygenation and mortality but were not collected as part of the ANZICS APD.

**Summary**

In a large multicentre cohort study of patients admitted to the ICU and ventilated after an ischaemic stroke, we found no significant association between worst arterial oxygen pressure in the first 24 hours of ICU admission and in hospital mortality, length of stay or likelihood of being discharged home.

**Competing interests**

None declared.
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References
1 Lopez AD, Mathers CD, Ezzati M, et al. Global and regional burden of
disease and risk factors, 2001: systematic analysis of population
2 Tissue plasminogen activator for acute ischaemic stroke. The National
Institute of Neurological Disorders and Stroke rt-PA Stroke Study
3 Chen ZM, Sandercock P, Han HC, et al. Indications for early aspirin use
in acute ischaemic stroke: a combined analysis of 40 000 randomized
patients from the Chinese acute stroke trial and the international
stroke trial. On behalf of the CAST and IST collaborative groups.
4 Govan L, Weir CJ, Langhorne P, for the Stroke Unit Trialists’ Collabora-
tion. Organized Inpatient (Stroke Unit) Care for Stroke. Stroke 2008;
Jun 12. [Epub ahead of print]
5 Feigin VL, Lawes CM, Bennett DA, Anderson CS. Stroke epidemi-
ology: a review of population-based studies of incidence, prevalence,
and case-fatality in the late 20th century. Lancet Neurol 2003; 2:
43-53.
6 Dirnagl U, Iadecola C, Moskowitz MA. Pathobiology of ischaemic
7 Fisher M, Takano K. The penumbra, therapeutic time window and
8 Singhal AB. Oxygen therapy in stroke: past, present, and future. Int J
9 Chan PH. Reactive oxygen radicals in signaling and damage in the
10 Stow PJ, Hart GK, Higlett T, et al. Development and implementation of
a high-quality clinical database: the Australian and New Zealand
Intensive Care Society Adult Patient Database. J Crit Care 2006; 21:
133-41.
system. Risk prediction of hospital mortality for critically ill hospitalized
12 von Elm E, Altman DG, Egger M, et al; STROBE Initiative. The
Strengthening the Reporting of Observational Studies in Epidemiology
(STROBE) statement: guidelines for reporting observational studies.
13 Shin HK, Dunne AK, Jones PB, et al. Normobaric hyperoxia improves
cerebral blood flow and oxygenation, and inhibits peri-infarct depo-
oxygen concentration as a factor in improved brain tissue oxygenation
and tissue lactate levels after severe human head injury. J Neurosurg
15 Liu W, Hendren J, Qin XJ, Shen J, Liu KJ. Normobaric hyperoxia
attenuates early blood-brain barrier disruption by inhibiting MMP-9-
mediated occludin degradation in focal cerebral ischemia. J Neuro-
16 Singhal AB, Benner T, Roccatagliata L, et al. A pilot study of
normobaric oxygen therapy in acute ischaemic stroke. Stroke 2005;
36: 797-802.
17 Henninger N, Bouley J, Nelligan JM, et al. Normobaric hyperoxia
delays perfusion/diffusion mismatch evolution, reduces infarct vol-
ume, and differentially affects neuronal cell death pathways after
Metab 2007; 27: 1632-42.
18 Bigdeli MR. Preconditioning with prolonged normobaric hyperoxia
induces ischaemic tolerance partly by upregulation of antioxidant
induces ischaemic tolerance and upregulation of glutamate transport-
ers in the rat brain and serum TNF-alpha level. Exp Neurol 2008; 212:
298-306.
20 Bigdeli MR, Khoshbaten A. In vivo preconditioning with normobaric
hyperoxia induces ischaemic tolerance partly by triggering tumor
necrosis factor-alpha converting enzyme/tumor necrosis factor-alpha/nuclear
21 Floyd TF, Clark JM, Gelfand R, et al. Independent cerebral vasocon-
strictive effects of hyperoxia and accompanying arterial hypocapnia at
22 Yusa T, Beckman JS, Crapo JD, Freeman BA. Hyperoxia increases
23 Kilgannon JH, Jones AE, Shapiro NI, et al. Association between arterial
hyperoxia following resuscitation from cardiac arrest and in-hospital
mortality. JAMA 2010; 303: 2165-71.
24 de Jonge E, Peelen L, Keijzers PJ, et al. Association between adminis-
tered oxygen, arterial partial oxygen pressure and mortality in
mechanically ventilated intensive care unit patients. Crit Care 2008;
12: R156.
25 Flynn EP, Auer RN. Eubotic hyperoxemia and experimental cerebral
26 Rønning OM, Guldvog B. Should stroke victims routinely receive
supplemental oxygen? A quasi-randomized controlled trial. Stroke
27 Chiu EH, Liu CS, Tan TY, Chang KC. Venturi mask adjuvant oxygen
28 Bulte DP, Chiarelli PA, Wise RG, Jezzard P. Cerebral perfusion response