The association between early arterial oxygenation and mortality post cardiac surgery

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SUMMARY

Many studies have been conducted to investigate the relationship between hyperoxia and mortality in cohorts of intensive care unit (ICU) patients with varied and often contradictory results. The impact of early hyperoxia post ischaemia remains uncertain in various ICU cohorts. We aimed to investigate the association between arterial oxygenation (PaO₂) in the first 24 hours in ICU and mortality in patients following cardiac surgery, using a retrospective cohort study of data from the Australian and New Zealand Intensive Care Society adult patient database. Participants were adults admitted to the ICU following cardiac surgery in Australia and New Zealand between 2003 and 2012. Patients were divided according to worst PaO₂ level or alveolar-arterial O₂ gradient in the 24 hours from admission. We defined ‘hyperoxia’ as PaO₂ ≥300 mmHg, ‘hypoxia/poor O₂ transfer’ as either PaO₂ <60 mmHg or ratio of PaO₂ to fraction of inspired oxygen <300 and ‘normoxia’ as between hypoxia and hyperoxia. The primary outcome was mortality at hospital discharge. Secondary outcomes were ICU mortality and ICU and hospital length-of-stay. Of the 83,060 patients 12,188 (14.7%) had hyperoxia, 54,420 (65.5%) had hypoxia/poor O₂ transfer and 16,452 (19.8%) had normoxia. There was no association between hyperoxia and in-hospital or ICU mortality compared to normoxia. There was a small increased hospital and ICU length-of-stay for hyperoxic compared to normoxic patients. We concluded that there was no association between mortality and hyperoxia in the first 24 hours in ICU after cardiac surgery.

Key Words: intensive care unit, cardiac surgery, cardiopulmonary bypass, mortality, oxygen therapy, hyperoxia
reported that, in both rat hearts and patients undergoing cardiopulmonary bypass, a high arterial oxygenation (PaO2) leads to myocardial reperfusion damage. Kaneda et al concluded that maintaining a more physiologic PaO2 during reperfusion following ischemia may attenuate reperfusion injury. However, no further studies have been done to analyse this hypothesis. Reperfusion injury may indeed be present in organs throughout the body following cardiac surgery, in addition to the heart, with similar inflammatory consequences secondary to O2-free radical development.

The hypothesis is that during cardiopulmonary bypass there is ischemia of myocardial tissue. As such, following removal of cardiopulmonary bypass there will be reperfusion injury to myocardial tissue similar to that of other causes of cardiac arrest. This injury could be greater still in patients undergoing emergency cardiac surgery, where an underlying acute ischemic pathology may be present (e.g., emergency coronary artery bypass grafting). The effect of hyperoxia in these settings is unknown and could indeed cause harm. It is also hypothesized that hypoxia will be harmful in this population. The aim of this study was to examine the relationship between PaO2 and outcome in patients admitted to the ICU following cardiac surgery.

METHODS

A retrospective cohort study of data extracted from the Australian and New Zealand Intensive Care Society Adult Patient Database (ANZICS-APD) was performed. Patients were adults admitted to the ICU following cardiac surgery in Australia and New Zealand between 2003 and 2012. Patients with missing vital status at discharge, blood gas information and Acute Physiology and Chronic Health Evaluation (APACHE) III information were excluded. The study protocol was considered and approved by the ANZICS Centre for Outcome and Resource Evaluation Management Committee. ANZICS Centre for Outcome and Resource Evaluation publication and data access policies require the lead investigator to obtain low risk ethics approval from their own institution, in this case the Alfred Hospital Ethics Committee (Low Risk Project No.: 204/12).

Oxygen values

Within all arterial blood gases available in the first 24 hours of ICU admission, one PaO2 value was automatically selected according to APACHE II and III methodology. Using this methodology for intubated patients with a fraction of inspired oxygen (FiO2) ≥0.5, the PaO2 associated with the arterial blood gas with the highest alveolar-arterial gradient was selected as the index of worst oxygenation. For non-intubated patients or intubated patients with FiO2 <0.5, the lowest arterial blood gas PaO2 level was recorded.

Patients were divided into three groups according to worst PaO2 level or alveolar-arterial O2 gradient in the first 24 hours after ICU admission. “Hypoxia/poor O2 transfer” was defined as either PaO2 <60 mmHg or a ratio of PaO2/FiO2 <300, “hyperoxia” as PaO2 ≥300 mmHg and “normoxia” as any value between hypoxia and hyperoxia.

Data extraction

The sizes, types and locations of the hospitals were recorded. At the patient level, the following variables were extracted: demographics, comorbidities according to APACHE II and III classifications, 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, hospital discharge destination and an APACHE III risk of death (ROD) score. As a marker of severity of illness independent of PaO2, we calculated an adjusted APACHE III index of illness severity (AP3no-ox), in which the O2 component of the APACHE III scoring system was removed.

Outcomes

The primary outcome was the association between PaO2 in the first 24 hours in the ICU and mortality at hospital discharge in patients admitted to ICU following cardiac surgery. Secondary outcomes were ICU mortality, ICU length-of-stay (LOS) and hospital LOS.

Statistical analyses

Assuming a minimum of 12,000 patients per subgroup, this study had an 80% power to detect a difference in mortality between any two subgroups equal to 0.5% (2.0% versus 1.5%), with a two sided P-value of 0.05. Statistical analysis was performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). Group comparisons were made using chi-square tests for equal proportions with results presents as n (%) and analysis of variance or Kruskal–Wallis tests, with results presented as means (standard deviation) or as medians (interquartile range), respectively. Analysis of mortality was performed using logistic regression with results reported as odds ratios (OR) (95% confidence interval [CI]). Analysis of LOS was performed using linear modelling on log-transformed...
lengths-of-stay, with results reported as geometric means (95% CI). All analysis was adjusted for patient severity. To facilitate a measure of patient severity that was independent of the PaO₂:FiO₂ ratio, an APACHE III ROD score was recalculated with all oxygen components removed. A two-sided $P$-value of 0.05 was considered to be statistically significant.

### RESULTS

Overall, 115,451 patients met the inclusion criteria of being ventilated and admitted to the ICU post cardiac surgery. A total of 32,391 patients were excluded, primarily because they did not have a measure of patient severity: age <17 ($n=235$), readmission ($n=1782$), missing mortality ($n=2045$), missing PaO₂ or FiO₂ ($n=2908$) or missing APACHE III ROD ($n=25,451$).
Of the remaining 83,060 patients 12,188 (14.7%) had hyperoxia, 54,420 (65.5%) had hypoxia/poor O₂ transfer and 16,452 (19.8%) had normoxia. The mean age of patients was 66.8 years (standard deviation 12.2), with 72.2% (59,948) male. The patients were from tertiary public ICUs (61.6%) and private ICUs (38.4%). The majority of patients were elective cases (95.7%) and the majority of patients were admitted to hospital from home (76.8%) (Table 1). The median APACHE III ROD was 1.36% and median APACHE III (no-ox) ROD was 0.94%.

ICU and hospital mortality

There was no association between hyperoxia in the first 24 hours in ICU and mortality at hospital discharge in patients admitted to ICU following cardiac surgery compared to normoxia (OR 0.9 [95% CI 0.7 to 1.1]). There was also no association between hyperoxia and ICU mortality compared to normoxia (OR 0.9 [95% CI 0.7 to 1.2]). Hypoxia patients had a significantly increased risk of in-hospital death (OR 1.5 [95% CI 1.2 to 1.7]) and ICU death (OR 1.8 [95% CI 1.5 to 2.2]) compared to normoxic patients. The overall in-hospital and ICU mortality rates were 2.0% and 1.3%, respectively (Tables 2 and 3).

ICU and hospital LOS

There was a small, statistically significant increase in hospital and ICU LOS for hyperoxic compared to normoxic patients. Hypoxia/poor O₂ transfer was associated with increased in-hospital and ICU mortality and increased hospital and ICU LOS (Tables 2 and 3).

DISCUSSION

Key findings

There was no association between hyperoxia in the first 24 hours in ICU and mortality at hospital discharge in patients admitted to ICU following cardiac surgery. Hyperoxia was not associated with an increase in ICU mortality, however, there was a slight increase in ICU and hospital LOS in patients with hyperoxia. As hypothesised, hypoxia/poor O₂ transfer was associated with increases in both mortality and LOS.

Comparison with other studies

There are no other published studies that have examined the effect of arterial oxygenation on outcome in patients admitted to the ICU post cardiac surgery. As such, this is the first study of its kind on this subject. In recent years, there have been a number of studies regarding the effect of hyperoxia on various cohorts of critically ill patients, the results of which have been varied and often contradictory. This study of patients post cardiac surgery has produced results consistent with cohorts of ICU patients post ischaemic stroke, cardiac arrest or being ventilated. Each of these studies included an adjustment for disease severity and found no mortality difference from early hyperoxia in patients from these cohorts. Conversely, our results are inconsistent with Kilgannon et al’s studies of patients post cardiac arrest. These studies suggested a harm effect for hyperoxia post cardiac arrest, however, did not adjust for disease severity in the cohorts of patients they were analysing.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Raw results</th>
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<tbody>
<tr>
<td>All</td>
<td>Hypoxia</td>
</tr>
<tr>
<td>ICU LOS (days)</td>
<td>1.9 [1.0–2.9]</td>
</tr>
<tr>
<td>ICU mortality (1.3%)</td>
<td>1041</td>
</tr>
<tr>
<td>Hospital mortality (2.0%)</td>
<td>1659</td>
</tr>
</tbody>
</table>

Length-of-stay presented as median [interquartile range]. Mortality presented as n (%). ICU=intensive care unit, LOS=length-of-stay.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Adjusted results</th>
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<tr>
<td>Hypoxia:Normoxia</td>
<td>Hyperoxia:Normoxia</td>
</tr>
<tr>
<td>Odds ratios</td>
<td>Raw</td>
</tr>
<tr>
<td>ICU mortality</td>
<td>2.3 (1.9–2.9)</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>1.8 (1.5–2.1)</td>
</tr>
<tr>
<td>Geometric means</td>
<td>Hypoxia</td>
</tr>
<tr>
<td>ICU LOS (days)</td>
<td>1.9 (1.9–1.9)</td>
</tr>
<tr>
<td>Hospital LOS (days)</td>
<td>11.6 (11.5–11.6)</td>
</tr>
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Mortality analysis used logistic regression, presented as odds ratios (95% confidence interval). Length-of-stay analysis used linear modelling on log-transformed lengths of stay, presented as geometric means (95% confidence interval). All analysis was adjusted for patient severity. All outcomes were statistically significantly different between groups P <0.0001. ICU=intensive care unit, LOS=length-of-stay.
Study significance

This study has confirmed the detrimental effect of hypoxia post cardiac surgery. Hypoxic patients had more than one and a half times the risk of in-hospital death compared to normoxic patients. As this is a retrospective cohort study, no comment can be made as to whether this represents a marker of severity of illness or the effect of hypoxia in this cohort. However, it is important to note the result that 65.5% of patients had hypoxia/poor O_2 transfer during the first 24 hours from ICU admission post cardiac surgery. It is well established that open cardiac surgery is associated with significant risk of lung injury and acute pulmonary oedema postoperatively. This is thought to be multifactorial, with extracorporeal circulation, anaesthesia and surgical techniques all contributing to lung injury. In order to decrease the mortality difference in the hypoxia/poor O_2 transfer group, a systematic, multifactorial approach must be undertaken, as described by Apostolakis et al.

Mortality results seen in the hyperoxia group were inconsistent with the hypothesis that hyperoxia could be harmful post cardiac surgery. However, a slight increase in ICU and hospital LOS may indicate a trend towards harm. This study is unable to determine any specific reason for this increased LOS. The increase could be related to actual lung/systemic damage caused by hyperoxia, increased (whether actual or perceived) severity of illness, as well as other unidentified factors.

Strengths and limitations

This is a large, multicentre study, which can be generalised to practice in public and private ICUs in Australia and New Zealand. It is well powered, with over 83,000 patients, to measure effect in a cohort of patients with an already low mortality. It increases its strength and relevance by adjustment of results for severity of illness. Being the first study of oxygenation post cardiac surgery, it provides a strong base of knowledge in a field not previously researched.

The study was limited by the variables available for analysis in the ANZICS-APD and by missing data in the database. Missing data resulted in a large number of patients being excluded from the study. Assessment of oxygenation in the study used the ‘worst’ PaO_2 and the peak and mean PaO_2 in the first 24 hours of ICU stay.

The use of the APACHE III ROD has some limitations as a measure of patient severity within a cohort of cardiac surgery patients. However, while the APACHE III ROD underestimates the true ROD for modern Australian and New Zealand cardiothoracic patients, it does remain a discriminatory risk adjustment tool (area under the receiver operating characteristic curve 0.80). As such, it can still be used in a logistic regression model to assess the independent effects of another factor on mortality (in this case, oxygenation status) after accounting for patient severity. Unfortunately, alternative risk scoring systems, like the European System for Cardiac Operative Risk Evaluation, were not possible in this study.

Some small differences in baseline characteristics were observed between the patient cohorts (Table 1). Many of these were included in the APACHE III adjustments, however the others may influence the results presented. Other information not included in the ANZICS-APD includes cardiopulmonary bypass time and cause of mortality, which would be interesting to correlate with other data presented. No causal influences for the results presented can be determined.

CONCLUSIONS

In a large multicentre cohort study of patients admitted to the ICU post cardiac surgery, there was no association between hyperoxia in the first 24 hours of ICU admission and in hospital or ICU mortality, however, due to study design, a small difference may not be detected. Hyperoxic patients had a slightly increased hospital and ICU LOS. Hypoxia/poor O_2 transfer was associated with increased hospital and ICU mortality as well as ICU and hospital LOS.

REFERENCES


