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 PaO_2 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.

Participants: Adults ventilated for ischaemic stroke in 129 ICUs in Australia and New Zealand, 2000–2009.

Main outcome measures: The primary outcome was the odds ratio for inhospital mortality associated with "worst" PaO_2 considered as a categorical variable, with data divided into deciles and compared with the mortality of the 10th decile. For patients on an FiO_2 of $\geqslant 50\%$ at any time in the first 24 hours, "worst" PaO_2 was defined as the PaO_2 associated with the highest alveolar–arterial (A–a) gradient. For patients on an FiO_2 of $<50\%$, it was defined as the lowest PaO_2. 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" PaO_2 was 117 mmHg (interquartile range, 87–196 mmHg). There was no association between worst PaO_2 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.

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Stroke is the second most common cause of mortality and a major cause of disability.[1] Apart from thrombolysis in highly selected patients,[2] the only general interventions that influence outcome are aspirin[3] and general supportive measures provided by dedicated stroke units.[4] Thus, it is desirable to identify therapeutic interventions that are effective and safe, and that can be routinely administered to all patients with stroke.

Strokes can be divided into ischaemic and haemorrhagic subtypes, with the former accounting for more than 80% of all strokes.[5] During the development of an ischaemic stroke, nerve cells lose the ability to maintain ionic homoeostasis as free radicals accumulate and degrade cell membranes.[6] These changes eventually lead to nerve cell death. This occurs rapidly in some patients and more gradually in others, over a matter of hours or days.[7] This phenomenon of gradual progression is due to the existence of areas of marginally viable brain (the "ischaemic penumbra") and has led to interest in various forms of oxygen therapy that may protect reversibly injured brain cells.[8] These potential benefits are weighed against a risk of free radical-mediated damage.[9]

The effect of oxygen administration soon after intensive care unit admission on outcome in critically ill patients ventilated after ischaemic stroke has not been previously reported. The appropriate oxygen therapy target for these patients is not clear. To address this important issue, we examined the relationship between PaO_2 in the first 24 hours in ICU and outcome in ventilated stroke patients in the Australian and New Zealand Intensive Care Society Adult Patient Database (ANZICS APD). We hypothesised that early hypoxia would be associated with increased mortality, and that early hyperoxia may be associated with either benefit or harm.

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.[10]

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 FiO_2 and PaO_2 are entered in the database. If the FiO_2 is $\geqslant 0.5$, the PaO_2 associated with the highest alveolar–arterial (A–a) gradient is selected, and if the FiO_2 is < 0.5, the measurement with the lowest PaO_2 is selected. If arterial blood gases are taken on both an $FiO_2 < 0.5$ and an $FiO_2 \geqslant 0.5$ during the first 24 hours, the PaO_2 derived from measurements taken on $\geqslant 0.5$ is used. In our study, this PaO_2 value was defined as the "worst" PaO_2.

To explore the relationship between the worst PaO_2 recorded in the adult patient database and the peak, median and mean PaO_2 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.[11] 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.

Table 1. Baseline characteristics

Characteristic	
Mean age (SD)	65.6 (14.6)
Male, no. (%)	1584 (60%)
Mean APACHE III score (SD)	75.8 (27.9)
Treatment limitation or palliative, no. (%)	92 (3%)
Chronic conditions, no. (%)	
Cardiovascular disease	306 (12%)
Liver disease	18 (1%)
Renal disease	54 (2%)
Respiratory disease	89 (3%)
ICU admission source, no. (%)	
Emergency	1420 (54%)
Theatre	46 (2%)
Other hospital	586 (22%)
Ward	586 (22%)
Vital signs, mean (SD)	
Glasgow Coma Scale score	7.07 (4.1)
Heart rate	88.8 (38.0)
MAP	99.5 (32.7)

APACHE = Acute Physiology and Chronic Health Evaluation. ICU = intensive care unit. MAP = mean arterial pressure.

Outcomes

The primary outcome was the odds ratio for the risk of inhospital mortality associated with the worst PaO_2 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 PaO_2 and mortality was not masked by confounding variables, multivariate analysis was conducted using logistic regression for mortality adjusting PaO_2 levels for FiO_2 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.[12]

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 PaO_2 levels in the first 24 hours in ICU, with mortality levels across the 10 deciles of PaO_2 ranging between 50% (5th decile, PaO_2 range 103–117 mmHg) and 63% (2nd decile, PaO_2 range 69–83 mmHg). (Figure 1). After adjustment for FiO_2 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 PaO_2 and mortality (Figure 2), as no decile was significantly different from the reference category (10th decile, PaO_2 range 341–611 mmHg). There was also no apparent relationship between PaO_2 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 PaO_2 are shown in Table 2.

After adjustment for confounding variables, there were no differences in inhospital mortality between the PaO_2 deciles for any of the predefined subgroups (Table 3).

Figure 1. Hospital mortality by PaO_2 decile

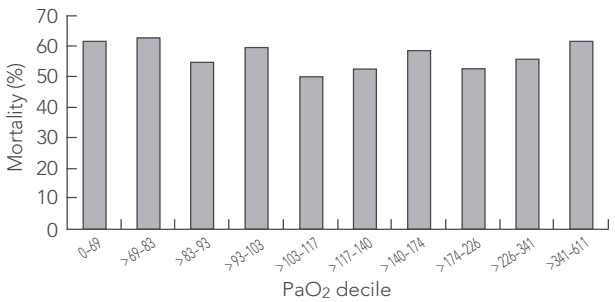
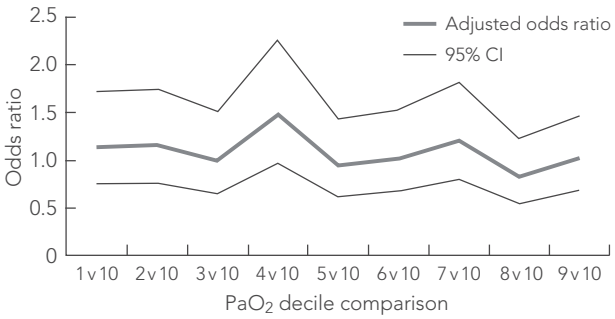


Figure 2. Odds ratios for PaO_2 deciles adjusted for FiO_2 level, AP3-no-ox and year of admission



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.

Table 2. Outcomes associated with deciles of "worst" PaO_2

Worst PaO_2, mmHg	Median ICU LOS (IQR), hours	Median hospital LOS (IQR), hours	Inhospital mortality, no. (%)	Adjusted* OR for inhospital mortality (95% CI)	OR for failure to discharge to home (95% CI)	Adjusted* OR for failure to discharge to home (95% CI)
0–69	60.5 (31.5–111.1)	162.4 (65.0–476.8)	163/264 (62%)	1.14 (0.76–1.72)	0.84 (0.55–1.30)	0.93 (0.57–1.51)
> 69–83	65.1 (318.0–121.7)	162.3 (67.0–428.9)	165/264 (63%)	1.15 (0.76–1.74)	0.91 (0.59–1.40)	0.98 (0.60–1.6)
> 83–93	70.8 (39.7–142.7)	178.0 (75.3–563.1)	145/265 (55%)	0.99 (0.65–1.51)	0.66 (0.43–1.00)	0.82 (0.51–1.33)
> 93–103	63.8 (32.8–118.5)	180.0 (73.8–435.3)	159/264 (60%)	1.48 (0.97–2.26)	0.84 (0.55–1.30)	1.20 (0.73–1.97)
> 103–117	75.9 (41.9–120.9)	233.6 (93.2–594.3)	133/264 (50%)	0.94 (0.62–1.43)	0.71 (0.47–1.08)	0.97 (0.60–1.58)
> 117–140	57.3 (32.1–116.0)	210.8 (66.3–518.5)	141/265 (53%)	1.01 (0.67–1.53)	0.78 (0.51–1.19)	1.05 (0.64–1.71)
> 140–174	58.1 (32.0–115.2)	187.5 (68.0–394.6)	156/264 (59%)	1.20 (0.80–1.81)	0.83 (0.54–1.27)	1.03 (0.64–1.66)
> 174–226	55.5 (32.0–124.4)	190.8 (64.8–569.3)	141/265 (53%)	0.82 (0.55–1.22)	0.78 (0.51–1.19)	0.89 (0.56–1.42)
> 226–341	63.8 (29.9–138.4)	188.8 (72.3–515.0)	148/264 (56%)	1.01 (0.69–1.47)	0.91 (0.59–1.4)	1.08 (0.68–1.71)
> 341–611	57.2 (27.0–98.0)	165.6 (63.3–491.5)	163/264 (62%)	1.00	1.00	1.00

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 FiO_2 levels, AP3-no-ox and year of admission. All odds ratios are relative to the 10th worst PaO_2 decile.

Table 3. Adjusted odds ratios* (95% CI) for inhospital mortality across deciles of PaO_2 for predefined subgroups

"Worst" PaO_2, mmHg	Admitted to hospital from home	Admitted to hospital from residential care or transferred from another hospital	Admitted to ICU from ward	Admitted to ICU from ED
0–69	1.33 (0.80–2.21)	0.87 (0.42–1.79)	1.72 (0.78–3.79)	1.04 (0.58–1.87)
> 69–83	0.99 (0.59–1.66)	1.49 (0.73–3.03)	1.66 (0.72–3.86)	0.77 (0.43–1.37)
> 83–93	1.12 (0.66–1.88)	0.83 (0.40–1.72)	1.82 (0.78–4.25)	0.78 (0.44–1.39)
> 93–103	1.52 (0.91–2.54)	1.34 (0.63–2.82)	1.74 (0.73–4.13)	1.34 (0.76–2.36)
> 103–117	0.94 (0.56–1.56)	0.92 (0.44–1.93)	1.13 (0.47–2.70)	0.82 (0.46–1.45)
> 117–140	1.00 (0.60–1.69)	1.04 (0.51–2.12)	1.71 (0.69–4.24)	0.82 (0.47–1.44)
> 140–174	1.30 (0.78–2.15)	1.05 (0.52–2.13)	1.5 (0.65–3.44)	0.91 (0.52–1.59)
> 174–226	0.89 (0.54–1.47)	0.76 (0.39–1.48)	1.06 (0.47–2.37)	0.76 (0.44–1.32)
> 226–341	1.05 (0.66–1.66)	0.91 (0.46–1.79)	1.51 (0.71–3.2)	0.77 (0.45–1.30)
> 341–611	1.00	1.00	1.00	1.00

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. ED = emergency department. ICU = intensive care unit. AOR = adjusted odds ratio.
* Adjusted for FiO_2 levels, AP3-no-ox and year of admission. All odds ratios are relative to the 10th worst PaO_2 decile.

The median worst PaO_2 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 PaO_2 defined in the database correlated well with the peak PaO_2 measured in the first 24 hours ($r = 0.79$), and the mean PaO_2 measured in the first 24 hours ($r = 0.68$), although there was a weaker correlation with the median PaO_2 measured in the first 24 hours ($r = 0.49$). The correlation between the worst PaO_2 and the mean and median PaO_2 for the entire ICU stay was $r = 0.46$ and $r = 0.30$, respectively. For 86% of these patients the worst PaO_2 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 $FiO_2 \geqslant 0.5$.

Discussion

We found no evidence that in mechanically ventilated patients with ischaemic stroke, differing levels of the worst PaO_2 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 PaO_2 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[13] and in patients with traumatic brain injury.[14] Hyperoxia also prevents degradation of the blood–brain barrier during focal cerebral ischaemia.[15] It has been proposed that hyperoxia shunts blood from regions of normal brain to ischaemic brain.[16] 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.[17] In animals subjected to focal cerebral ischaemia, eubaric hyperoxia causes upregulation of antioxidant enzymes[18] and glutamate transporters[19] and alters expression of inflammatory cytokines.[20]

Conversely, oxygen can reduce cerebral blood flow[21] and, when resulting in hyperoxia, can increase oxidative stress through the production of oxygen free radicals[22] that may be important in the pathogenesis of ischaemic stroke.[9] 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[23] and, more generally, by the demonstration that in critically ill patients mortality increases with increasing levels of hyperoxia.[24]

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.[17-21,25] 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.[16,26,27] The largest controlled trial of eubaric 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.[26] In this study, there was no significant difference in 1-year survival between the oxygen and the room air groups.[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]; $P = 0.02$). 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]; $P = 0.54$).[26]

Chiu and colleagues investigated the feasibility of eubaric hyperoxia therapy among a group of 46 patients with severe ischaemic stroke involving more than one-third of the middle cerebral artery territory.[27] In a non-randomised trial, they compared 40% oxygen administered via a Venturi mask with 2 L 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).[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.[16]

Given the correlation between worst PaO_2 and peak PaO_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.[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_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_2, regardless of FiO_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_2 was moderately well correlated with the peak and mean PaO_2 in the first 24 hours, and was usually taken from an early blood gas measurement taken on an FiO_2 of $\geqslant 0.5$. As a result, we consider that this measure is an acceptable surrogate for the PaO_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.[28]

Our data do not provide any information about the potential benefits or harms of eubaric 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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