RESEARCH PAPER

Hyperoxia may be related to delayed cerebral ischemia and poor outcome after subarachnoid haemorrhage

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ABSTRACT

Objective To determine the association between exposure to hyperoxia and the risk of delayed cerebral ischaemia (DCI) after subarachnoid haemorrhage (SAH).
Methods We analysed data from a single centre, prospective, observational cohort database. Patient inclusion criteria were age ≥18 years, aneurysmal SAH, endotracheal intubation with mechanical ventilation, and arterial partial pressure of oxygen (PaO_2) measurements. Hyperoxia was defined as the highest quartile of an area under the curve of PaO_2, until the development of DCI ($PaO_2 \geq 173$ mm Hg). Poor outcome was defined as modified Rankin Scale 4–6 at 3 months after SAH.
Results Of 252 patients, there were no differences in baseline characteristics between the hyperoxia and control group. Ninety-seven (38.5%) patients developed DCI. The hyperoxia group had a higher incidence of DCI ($p < 0.001$) and poor outcome ($p = 0.087$). After adjusting for modified Fisher scale, rebleeding, global cerebral oedema, intracranial pressure crisis, pneumonia and sepsis, hyperoxia was independently associated with DCI (OR, 3.16; 95% CI 1.69 to 5.92; $p < 0.001$). After adjusting for age, Hunt–Hess grade, aneurysm size, Acute Physiology and Chronic Health Evaluation II score, rebleeding, pneumonia and sepsis, hyperoxia was independently associated with poor outcome (OR, 2.30; 95% CI 1.03 to 5.12; $p = 0.042$).
Conclusions In SAH patients, exposure to hyperoxia was associated with DCI. Our findings suggest that exposure to excess oxygen after SAH may represent a modifiable factor for morbidity and mortality in this population.

INTRODUCTION

Supplemental oxygen is commonly administered to patients after subarachnoid haemorrhage (SAH) during the prehospital, emergency and critical care.[1] During mechanical ventilation, hyperoxia is not uncommon in the emergency room and intensive care unit during the management of SAH. Recent studies in patients after cardiac arrest and traumatic brain injury have suggested that hyperoxia is associated with worse outcomes.[2,3] Contrarily, others have suggested that hyperoxia may be of therapeutic benefit for patients with traumatic brain injury and ischaemic stroke.[4–7] The effect of hyperoxia on outcomes in patients with SAH has not been studied.

At supra-physiologic levels, oxygen may have toxic effects on the human brain through production of superoxide anion, hydrogen peroxide and hydroxyl radical.[8] The overproduction of these reactive oxygen species results in oxidative stress, a deleterious process which may lead to neuronal inflammation and necrosis as well as reduction of cerebral blood flow.[9,10] After SAH, these processes may contribute to the development of delayed cerebral ischaemia (DCI).

We hypothesised that hyperoxia may increase the risk of DCI after SAH. We aimed to investigate the association between exposure to hyperoxia and the incidence of DCI and poor 3-month outcome.

PATIENTS AND METHODS
Patients

Columbia University SAH Outcomes Database Project is a single centre, prospective observational cohort study. Data fields include demographics, clinical, radiological and outcome data for all adult spontaneous SAH patients. All data are prospectively collected by a dedicated investigator and are adjudicated by the study team in weekly meetings.[11,12] This retrospective analysis considered all SAH patients collected in our registry between August 1996 and April 2011. We included patients who (1) were 18 years of age or older; (2) had aneurysmal SAH confirmed by brain CT with angiography and/or CT angiography; (3) were endotracheally intubated with ventilators within 3 days after onset (excluding patients intubated solely for surgical interventions); (4) underwent arterial partial pressure of oxygen (PaO_2) measurements ≥3 times (to be able to calculate area under the curve) within 14 days, including twice or more within 3 days. We excluded patients who expired within 14 days after symptom onset because (1) early death would lead to less chance of DCI; (2) it was uncertain that the cause of early death was related to DCI; (3) severe hypoxia could precede death.

This study was approved by the institutional review board of our centre. Informed consents for this study were obtained from patients or their family members.

Clinical, radiological and laboratory assessment

We obtained demographics (age, sex and ethnicity), risk factors or underlying comorbidities

(hypertension, smoking, alcohol consumption, previous ischaemic or haemorrhagic stroke, cardiac disease, such as myocardial infarction and arrhythmia, and pulmonary disease, such as chronic obstructive pulmonary disease), clinical, radiological and laboratory findings on initial assessments (Glasgow coma scale (GCS), Hunt–Hess grade, modified Fisher scale,[13] Hijdra scale,[13] global cerebral oedema on initial CT,[14] APACHE II (Acute Physiology and Chronic Health Evaluation II) score, PaO_2, and arterial partial pressure of carbon dioxide), and acute complications of SAH on follow-up assessments (rebleeding,[15] global cerebral oedema on follow-up CT, hydrocephalus, intracranial pressure crisis, meningitis, pneumonia or pulmonary oedema, and sepsis), DCI, and modified Rankin Scale (mRS).[15]

Definitions of hyperoxia and other variables

Oxygen burden was defined as the area under the curve of PaO_2 divided by the observation period since the onset of SAH. The main objectives of this study were to investigate the effects of hyperoxia on DCI, which mostly occurs within the first 2 weeks. For this purpose, oxygen burden was calculated until the time point when each patient developed DCI. For patients who did not develop DCI, oxygen burden until postbleed day 6 was adopted for comparison. Six days were the median day from symptom onset to DCI in our study population. We further defined hyperoxia as the uppermost quartile of oxygen burden. The median oxygen burden was 146.5 mm Hg (IQR, 123–173 mm Hg) (figure 1). Thus, oxygen burden ≥173 mm Hg was considered as hyperoxia, as aforementioned. We chose these cutoff points, because (1) we investigated the 'excess' oxygen's effects and (2) there is no consensus on a specific cutoff point of hyperoxia in a human SAH population.

DCI was defined as either a symptomatic vasospasm (ie, clinical deterioration, such as a new focal deficit and/or a decrease of the level of consciousness, in the presence of vasospasm determined by conventional angiography or CT angiography) or development of new cerebral infarction which is not explained by other causes such as hydrocephalus, seizures, intracranial pressure crisis and infection.[16] This definition of DCI has been demonstrated to have a better predictive value for poor clinical outcomes than symptomatic, angiographic, or transcranial Doppler vasospasm.[16] mRS was obtained by in-person interview

Figure 1 Distributions of oxygen burden.

or phone interview either with the patient or with a surrogate if the patient was unable to participate. Poor outcome was defined as mRS 4–6 at 3 months after the onset of SAH.[16] We recorded the day of aneurysmal rupture as bleed day 0.

Clinical managements

The management of these patients followed guidelines set forth by the American Heart Association and has been described in detail previously.[15] Endotracheal intubation was performed and mechanical ventilator was applied to the patients whose respiratory drive or reflexes were abnormal. All patients underwent neurological examinations each day. Patients underwent conventional angiography on admission, and between postbleed days 4 and 8 if clinically indicated. Transcranial Doppler was performed daily, and CT angiography was performed for clinical purposes. Patients who developed DCI were treated with hypertensive hypervolemic therapy. Endovascular treatment, including intra-arterial verapamil hydrochloride injection and/or angioplasty, was attempted on patients who developed DCI and did not respond to medical treatment. We did not increase fraction of inspired oxygen as a modality of prevention or treatment of DCI.[15]

Data analysis

We compared demographics, risk factors and comorbidities, findings on initial and follow-up assessments, and the exposure to hyperoxia with the development of DCI, and also with poor outcome. For univariate analysis, we used Pearson's χ^2 test with the exact method, Student t test and the Mann–Whitney U test as appropriate. Multiple logistic regression analysis was performed after examining collinearity to estimate the independent contributions of variables to DCI and poor outcome. Variables with a p value <0.1 by univariate analysis were included in the multivariable model as candidate variables, and then removed by a backward stepwise selection procedure. We further performed all analysis using a forward selection procedure. A two-tailed p value of <0.05 was considered to indicate a significant difference in all statistical analysis. SPSS for Windows V.13.0 (SPSS, Chicago, Illinois) was used for all statistical analyses.

RESULTS

During the study period, 1140 patients with aneurysmal SAH were identified. Of those, 888 patients did not meet inclusion criteria and were excluded. Thus, the remaining 252 patients were included for the final analysis. Age was the only baseline characteristic that was different between 252 included and 888 excluded subjects, included patients being older (mean±SD, 56.7±13.9 years vs 53.7±14.7 years; p=0.005). SAH severity was more severe in included patients compared with excluded patients: GCS (median (IQR), 8 (6–10) vs 15 (12–15); p<0.001); Hunt–Hess grade (grade 1, 4% vs 29%; grade 2, 4% vs 22%; grade 3, 25% vs 30%; grade 4, 43% vs 9%; grade 5, 24% vs 10%; p<0.001); modified Fisher scale (group 0, 0% vs 4%; group 1, 10% vs 33%; group 2, 11% vs 9%; group 3, 41% vs 37%; group 4, 38% vs 17%; p<0.001); and APACH II score (mean±SD, 17.7±6.7 vs 10.6±7.2; p<0.001) (see online supplementary table S1).

Of the 252 included patients, 179 (71%) were women. A mean age was 56.7±13.9 years. The median time from symptom onset to the initial PaO_2 was 16.4 h (IQR, 10.3–25.9 h). The median frequency of PaO_2 measurements, within 14 days after symptom onset, was 23.0 (IQR, 15–31). Initial Hunt–Hess grade ranged from grade 1 to grade 5, with high grades predominant (table 1).
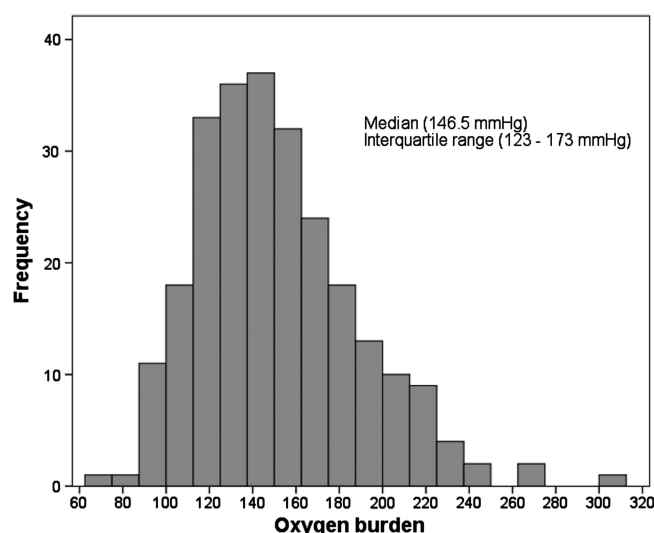
Table 1 Patient characteristics

	Delayed cerebral ischaemia		Poor outcome	
	No (n=155)	Yes (n=97)	No (n=94)	Yes (n=108)
Demographics				
Age, years	57.1±14.1	56.0±13.5	53.1±12.0	60.5±15.6
Gender, male	47 (30.3)	26 (26.8)	34 (36.2)	28 (25.9)
Ethnicity, white	68 (43.9)	41 (42.3)	45 (47.9)	51 (47.2)
Risk factors and comorbidities				
Hypertension	85 (54.8)	46 (47.4)	46 (48.9)	56 (51.9)
Smoking	61 (39.4)	34 (35.1)	40 (42.6)	29 (26.9)
Alcohol	14 (9.0)	11 (11.3)	12 (12.8)	6 (5.6)
Stroke	12 (7.7)	4 (4.1)	3 (3.2)	11 (10.2)
Cardiac disease	16 (10.3)	8 (8.2)	4 (4.3)	17 (15.7)
Pulmonary disease	10 (6.5)	4 (4.1)	6 (6.4)	7 (6.5)
Initial assessment				
GCS	8 (6–10)	8 (6–10)	9 (7–14)	7 (5–10)
Hunt–Hess grade				
1	5 (3.2)	4 (4.1)	8 (8.5)	1 (0.9)
2	7 (4.5)	3 (3.1)	7 (7.4)	1 (0.9)
3	41 (26.5)	23 (23.7)	24 (25.5)	28 (25.9)
4	64 (41.3)	44 (45.4)	41 (43.6)	41 (38.0)
5	38 (24.5)	23 (23.7)	14 (14.9)	37 (34.3)
Modified Fisher scale				
1	19 (12.3)	6 (6.2)	7 (7.4)	12 (11.1)
2	21 (13.5)	7 (7.2)	12 (12.8)	12 (11.1)
3	63 (40.6)	40 (41.2)	38 (40.4)	42 (38.9)
4	52 (33.5)	44 (45.4)	37 (39.4)	42 (38.9)
Hijdra scale	18.3±7.4	19.8±8.4	18.8±7.7	18.6±7.8
Global cerebral oedema, initial CT	41 (26.5)	32 (33.0)	26 (27.7)	28 (25.9)
Aneurysm size, mm	8.7±6.7	8.0±4.5	7.5±3.9	9.9±7.5
APACHE II score	17.5±7.0	18.0±6.2	16.2±6.5	19.3±6.7
Follow-up assessment				
Rebleeding	20 (12.9)	21 (21.6)	8 (8.5)	24 (22.2)
Global cerebral oedema, follow-up CT	111 (71.6)	85 (87.6)	60 (63.8)	92 (85.2)
Hydrocephalus	110 (71.0)	74 (76.3)	64 (68.1)	85 (78.7)
Intracranial pressure crisis	95 (61.3)	75 (77.3)	61 (64.9)	74 (68.5)
Meningitis	25 (16.1)	20 (20.6)	14 (14.9)	25 (23.1)
Pneumonia and/or pulmonary oedema	96 (61.9)	73 (75.3)	55 (58.5)	84 (77.8)
Sepsis	28 (18.1)	28 (28.9)	12 (12.8)	28 (25.9)
Exposure to hyperoxia	28 (18.1)	36 (37.1)	18 (19.1)	32 (29.6)
Exposure to hypocarbia	25 (16.1)	23 (23.7)	15 (16.0)	21 (19.4)

Values are number (column %), mean±SD, or median (IQR), as appropriate.
APACHE II, Acute Physiology and Chronic Health Evaluation II; GCS, Glasgow coma scale.

Hyperoxia and baseline characteristics

Among demographics, risk factors, underlying comorbidities and initial findings, there was no variable significantly related to hyperoxia (see online supplementary table S2).

Hyperoxia and DCI

Table 1 shows demographics, risk factors or comorbidities, findings on initial assessments, findings on follow-up assessments and an exposure to hyperoxia, assorted by DCI. DCI was observed in 97/252 (38.5%) patients, and the median time interval from symptom onset to the occurrence of DCI was 6.0 days (mean±SD, 6.4±3.1 days; IQR, 4–8 days) (figures 2 and 3). Table 2 shows factors associated with DCI: highest grade of modified Fisher Scale (p=0.012), global cerebral oedema on follow-up CT (p=0.004), intracranial pressure crisis (p=0.009), pneumonia and/or pulmonary oedema (p=0.030), sepsis

(p=0.046), and hyperoxia (p=0.001). Rebleeding was marginally associated with DCI (p=0.070). Increase in oxygen burden was related to high proportion of patients with DCI (figure 4). In multiple logistic regression analysis, modified Fisher Scale grade 3 (p=0.040) and grade 4 (p=0.005), global cerebral oedema on follow-up CT (p=0.004), pneumonia and/or pulmonary oedema (p=0.010) and hyperoxia (p<0.001) were independently associated with DCI.

Hyperoxia and poor outcome

mRS At 3 months was available in 202 (80.2%) patients (see online supplementary table S3). Poor outcome occurred in 108/202 (53.5%) patients. Table 3 shows the factors associated with poor outcome: older age (p<0.001), APACHE II score (p=0.001), higher Hunt–Hess grade (p<0.001), aneurysm size (p=0.006), rebleeding (p=0.011), global cerebral oedema on follow-up CT (p=0.001), pneumonia and/or pulmonary

Cerebrovascular disease
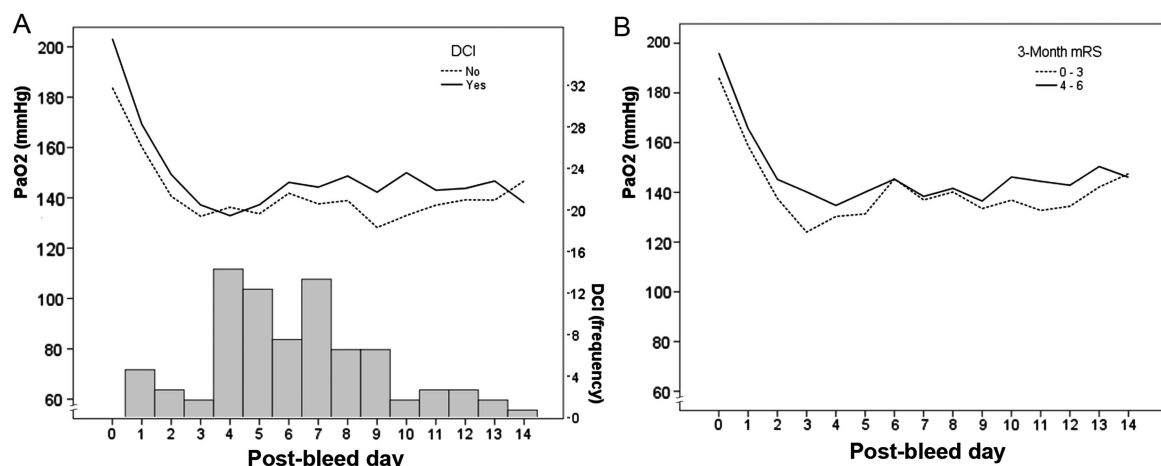
Figure 2 Average daily PaO_2 on each postbleed day. PaO_2 according to the development of (A) delayed cerebral ischaemia (DCI) and (B) poor outcome. Histogram shows the number of patients who developed DCI.

oedema (p=0.004), and sepsis (p=0.022). Exposure to hyperoxia was marginally associated with poor outcome (p=0.087). Increase in oxygen burden was related to high proportion of patients with poor outcome (figure 4). In multiple logistic regression analysis, older age (p=0.001), higher Hunt–Hess grade (p=0.012), aneurysm size (p=0.024), rebleeding (p=0.035) and hyperoxia (p=0.042) independently predicted poor outcome.

DISCUSSION

Our main finding is that exposure to hyperoxia was associated with an increased risk for DCI and poor outcome after SAH. As expected, given our selection of high-grade SAH patients, we had a high rate of DCI (38.5%) and poor functional outcome (53.5%). Exposure to hyperoxia was related to approximately three times the risk of DCI and twice the risk of poor 3-months outcome. This relationship was independent of the SAH severity and other comorbidities.

Currently, no guidelines for oxygen therapy in SAH exist. In this study, during the first week after SAH, three quarters of patients were exposed to an average $PaO_2 \geq 123$ mm Hg, and a quarter of patients were exposed to an average $PaO_2 \geq 173$ mm Hg. As seen in our cohort, a recent study has shown that the risk of being exposed to hyperoxia is common in critically ill patients, and such condition was not addressed with any adjustments in ventilator settings.[17]

Hyperoxia causes oxidative stress by generation of reactive oxygen species and is known to cause lung injury.[8] [18–20] Detrimental cerebral effects of hyperoxia have been reported. Oxidative stress may cause brain injury through unavailability of nitric oxide, inflammation and neuronal necrosis.[21] [22] Hyperoxia decreases the availability of nitric oxide through reduced basal production, oxidative quenching and decreased release from the S-nitrosohemoglobin binding.[21] This contributes to vasoconstriction and decrease in cerebral blood flow.[10] [23–25] Additionally, mitochondria-derived reactive oxygen species can cause neuronal inflammation.[26] [27] Hyperoxic reperfusion after global cerebral ischaemia has been reported to promote neuronal inflammation and long-term neuronal loss.[22] At high pressure, hyperoxia has caused paralysis due to neuronal necrosis in rats.[28] Furthermore, oxidative stress has a role in the formation and rupture of cerebral aneurysm through inflammation, activation of matrix metalloproteinases, and lipid peroxidation.[29]

Recently, hyperoxia has been shown to be associated with poor outcomes in other acute brain injury populations. A large
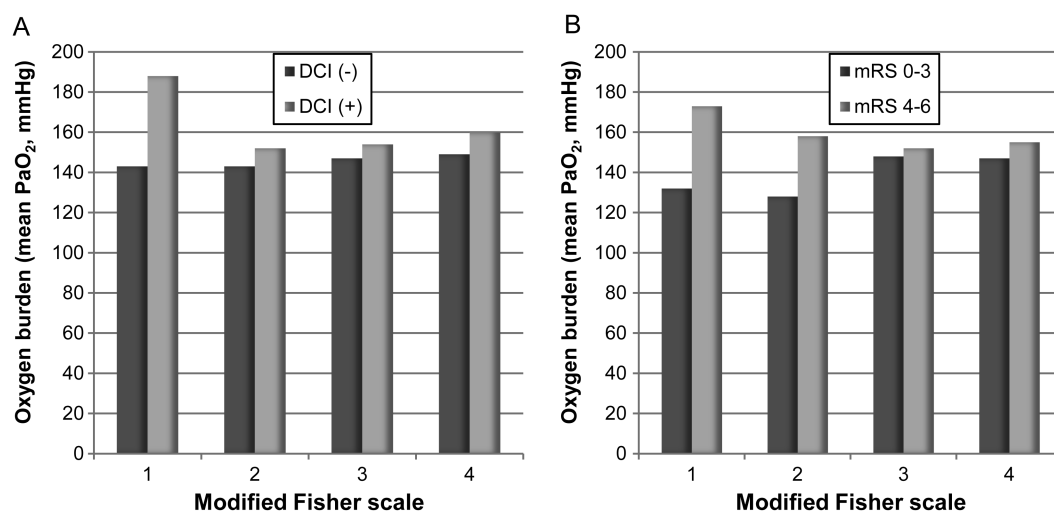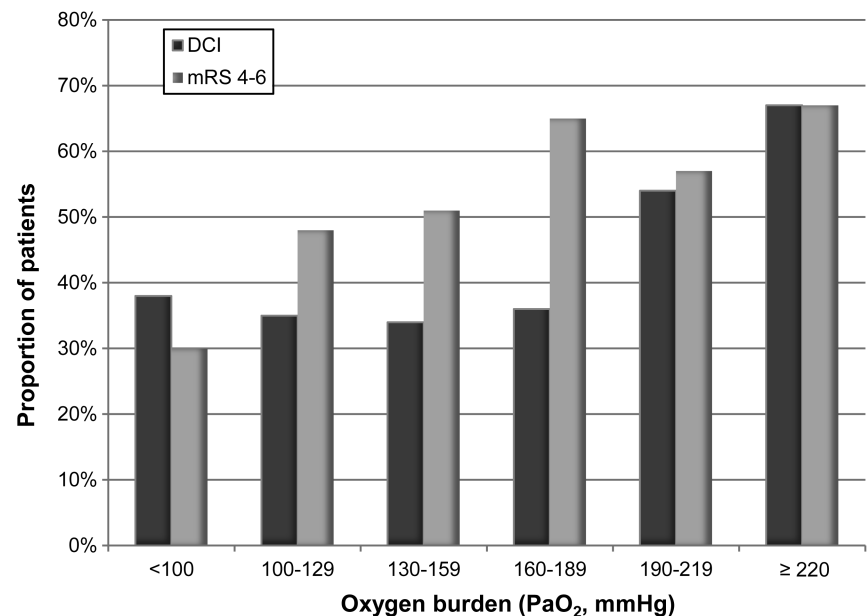

Figure 3 Oxygen burden according to severity of SAH. (A) In all grades of modified Fisher scale, oxygen burden was higher in patients with delayed cerebral ischaemia (DCI) than in those without DCI. (B) Oxygen burden was higher in patients with poor outcome than in those without poor outcome.

Table 2 Factors associated with the delayed cerebral ischaemia

	Univariable analysis OR (95% CI)	Multivariable analysis OR (95% CI)
Modified Fisher scale		
1–2	Reference	Reference
3	1.95 (0.93 to 4.10)	2.29 (1.04 to 5.04)
4	2.60 (1.24 to 5.48)	3.15 (1.42 to 6.98)
Rebleeding	1.87 (0.95 to 3.66)	
Global cerebral oedema, follow-up CT	2.81 (1.40 to 5.64)	2.95 (1.41 to 6.18)
Intracranial pressure crisis	2.15 (1.21 to 3.83)	
Pneumonia and/or pulmonary oedema	1.87 (1.06 to 3.29)	2.27 (1.22 to 4.22)
Sepsis	1.84 (1.01 to 3.36)	
Exposure to hyperoxia	2.68 (1.50 to 4.78)	3.16 (1.69 to 5.92)

Table 3 Factors associated with poor outcome

	Univariable analysis OR (95% CI)	Multivariable analysis OR (95% CI)
Age, years	1.04 (1.02 to 1.06)	1.05 (1.02 to 1.08)
Hunt–Hess grade	1.78 (1.31 to 2.43)	1.74 (1.13 to 2.68)
Aneurysm size, mm	1.08 (1.02 to 1.15)	1.08 (1.01 to 1.16)
APACHE II score	1.07 (1.03 to 1.12)	
Rebleeding	3.07 (1.31 to 7.22)	3.06 (1.09 to 8.64)
Global cerebral oedema, follow-up CT	3.26 (1.66 to 6.42)	
Pneumonia and/or pulmonary oedema	2.48 (1.35 to 4.58)	
Sepsis	2.39 (1.14 to 5.03)	
Exposure to hyperoxia	1.78 (0.92 to 3.44)	2.30 (1.03 to 5.12)

APACHE II, Acute Physiology and Chronic Health Evaluation II.

multicentre cohort study found that exposure to hyperoxia was common following resuscitation from cardiac arrest, and associated with increase in hospital mortality.[2] Retrospective studies in patients with traumatic brain injury have also found an association between worse functional outcomes and higher mortality in patients exposed to hyperoxia.[3][30] In both studies, oxidative stress due to reactive oxygen species has been postulated as the pathomechanism of the aggravation of initial brain injury.[22] Conversely, studies have found that hyperoxia may be of therapeutic benefit for patients with brain injury. A pilot study showed that high-flow oxygen therapy via facemask transiently improved neurological deficits and MRI abnormalities compared with room-air therapy in patients with acute ischaemic stroke.[6]

A magnetic resonance spectroscopy study also found that normobaric oxygen therapy decreased lactate level and preserved N-acetyl-aspartate peak in patients with acute ischaemic stroke.[7] Other studies showed that hyperoxia was related to improvement of cerebral metabolism and reduction of intracranial pressure in patients with traumatic brain injury.[4][5] At present, the role of hyperoxia remains controversial in patients with acute brain injury. Future clinical trials are warranted to address this issue.

DCI is an important complication after SAH, increasing the mortality and morbidity for survivors.[16][31] Complex pathophysiology is related to the development of DCI, including vasospasm, neurovascular inflammation and microcirculatory dysfunction.[32] Narrowing of the lumen of large or small vessels

Figure 4 Relationship of oxygen doses to delayed cerebral ischaemia (DCI) and poor outcome. The proportion of patients with DCI and poor outcome increased in high oxygen burden.

No. of patients

	<100	100-129	130-159	160-189	190-219	≥ 220
DCI (-)	8	44	55	32	12	4
DCI (+)	5	24	28	18	14	8
mRS 0-3	7	29	33	13	9	3
mRS 4-6	3	27	35	25	12	6

may cause ischaemia distal to the involved sites. Effects of hyperoxia on the vasoconstriction and reduction in cerebral blood flow may contribute to DCI.[10 23] Oxygen-free radicals may also be involved in neurovascular inflammation through activation of microglia and astrocytes.[22 26 27] Furthermore, hyperoxia can impair cerebral microcirculation by disturbing fibrinolysis and activation of the coagulation system.[33] Vasoconstriction, inflammation and impaired cerebral microcirculation have all been postulated to be important processes for the development of DCI.

Our study has limitations. First, this was an observational study, and findings should be interpreted cautiously. Despite our findings of hyperoxia's association with DCI, hyperoxia may be a surrogate marker rather than a cause in the development of DCI. In a retrospective study, potential interactions among variables may not be completely excluded by multivariate analysis. Second, we chose to include only patients who were intubated and had PaO_2 examined. Patients included in our study were older and had more severe symptoms than those who were excluded. This is a potential source of selection bias and it is unclear if our findings can be generalised to the low-grade SAH patient. Third, due to the design, we were also not able to obtain detailed information on ventilator settings, such as modes and fraction of inspired oxygen, shunting and metabolic status. However, regardless of the ventilator settings, we believe that the PaO_2 levels were the most critical values regarding the development of DCI because the effect of ventilator settings, shunting and metabolic status would most likely work through PaO_2 levels. Additionally, measurements of PaO_2 were inconsistent across patients in terms of time points and interval. These limitations, due to retrospective nature, should be addressed in future prospective studies. Fourth, a consensus on the definition of hyperoxia in SAH is not available in terms of a level and duration of PaO_2. A recently published large multicentre cohort study defined hyperoxia as PaO_2 of 300 mm Hg or greater in the first (within 24 h after admission) arterial blood-gas analysis.[2] However, their definition of hyperoxia was based on 'consensus of all authors', because the precise PaO_2 level associated with maximal risk is unknown.[2] Moreover, the previous study's population was cardiac arrest victims, whose secondary brain injury would occur mostly within 24 h. On the contrary, in patients with SAH, secondary brain injury in the form of DCI occurs typically between 3 and 14 days after SAH.[16] Another study of patients with traumatic brain injury averaged PaO_2 level during the first 24 h of hospital admission and defined hyperoxia as PaO_2 levels of 200 mm Hg or greater.[3] This definition of hyperoxia, however, was arbitrarily based on the authors' clinical experiences of rarely seeing PaO_2 values greater than 200 mm Hg. Moreover, to our best knowledge, there are no laboratory data to define hyperoxia in SAH population. Thus, we defined hyperoxia as the highest quartile of area under the curve of PaO_2 based on our patients' data. Although hyperoxic PaO_2 levels (≥ 173 mm Hg) of our patients were moderate compared with PaO_2 levels (≥ 300 and ≥ 200 mm Hg) of the previous studies, we believe that continuous exposure to excess oxygen could also be harmful. When our patients were exposed to higher oxygen doses, the risks of developing DCI and poor outcome further increased. We favour avoiding hyperoxia, but a cutoff value of 173 mm Hg based on our retrospective study cannot be recommended. Further studies remain to be published to address the cutoff value.

In conclusion, our study suggests that exposure to hyperoxia may be associated with DCI and poor 3- month outcome in SAH patients requiring mechanical ventilation. Exposure to excess oxygen after SAH may represent a modifiable factor for morbidity and mortality in this population. Further studies are necessary to validate our findings and explore its clinical implications.

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