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Low brain tissue oxygenation contributes to the development of delirium in critically ill patients: a prospective observational study

The Cerebral Oxygenation and Neurological Outcomes Following Critical Illness (CONFocal) Research Group, on behalf of the Canadian Critical Care Trials Group

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ABSTRACT

Purpose: To test the hypothesis that poor brain tissue oxygenation (BtO₂) during the first 24 hours of critical illness correlates with the proportion of time spent delirious. We also sought to define the physiological determinants of BtO₂.

Materials and Methods: Adult patients admitted to the ICU within the previous 24 hours were considered eligible for enrollment if they required mechanical ventilation, and/or vasopressor support. BtO₂ was measured using near-infrared spectroscopy, for 24 hours after enrollment. Hourly vital signs and clinically ordered arterial and central venous blood gases were collected throughout BtO₂ monitoring. Patients were screened daily for delirium with the confusion assessment method for the intensive care unit (CAM-ICU).

Results: BtO₂ and the proportion of time spent delirious did not result in significant correlation (p = .168). However, critically ill patients who spent the majority of their ICU stay delirious had significantly lower mean BtO₂ compared to non-delirious patients, (p=0.017). BtO₂ correlated positively with central venous pO₂ (p=0.0003) and haemoglobin concentration (p = 0.001). Logistic regression indicated that lower BtO₂, higher narcotic doses and a history of alcohol abuse were independent risk factors for delirium.

Conclusions: Poor cerebral oxygenation during the first 24 hours of critical illness contributes to the development of delirium.

Trial registration: This trial is registered on clinicaltrials.gov (Identifier: NCT02344043), retrospectively registered January 8, 2015.

Key Words: Near-infrared spectroscopy, Delirium, CAM-ICU, Critical Illness, Brain tissue oxygenation, Cerebral perfusion.
Introduction

Delirium is common during critical illness and manifests as an acute fluctuating change in mental status characterized by an altered level of consciousness or disorganized thinking [1]. Delirium has been associated with increased mortality, longer intensive care unit (ICU) length of stay and mechanical ventilation duration [2,3] and long-term cognitive impairment [4]. Although the underlying etiology of delirium is unknown, neuropathological studies suggest that diffuse neuronal ischemia is common in critically ill patients, primarily affecting brain areas susceptible to hypoxic-ischemic injury such as watershed areas in the frontal cortex [5]. Therefore, poor cerebral perfusion may contribute to delirium. Reliable cerebral perfusion measurements during critical illness have only recently become available.

Near infrared spectroscopy (NIRS) is a non-invasive strategy to measure regional brain tissue oxygenation (BtO$_2$)[6], and has been used as a surrogate marker for cerebral perfusion during cardiac surgery. In this clinical setting, low BtO$_2$ levels are associated with worse post-operative cognitive outcomes[7]. Low BtO$_2$ has also been associated with poor neurological outcomes in cardiac arrest survivors[8]. NIRS derived BtO$_2$ may serve as a marker and predictor of delirium. For example, in a small cohort of septic shock patients, lower BtO$_2$ was observed in delirious patients compared to non-delirious patients[9]. In another small sample of patients with septic shock, BtO$_2$ recordings over 72h were lower in patients who spent the majority of their ICU stay delirious, relative to non-delirious patients[10]. Although poor perfusion may contribute to delirium, the association between BtO$_2$ and delirium requires further study.

Our study tested the hypothesis that poor cerebral oxygenation during the resuscitative phase (i.e. first 24-48h) of critical illness is associated with the subsequent development of delirium throughout a patient’s ICU stay. Additionally, we aimed to identify the physiological determinants related to BtO$_2$ such as hemodynamics and clinical measures of tissue oxygenation.
Materials and Methods

Study design and participant recruitment:

The Cerebral Oxygenation and Neurological outcomes FFollowing CriticAL illness (CONFOCAL) study (NCT02344043 clinicaltrials.gov) is a single-centre prospective observational study. The full protocol has been previously published[11]; the acute neurological findings in this cohort are described herein. Adult patients (≥18 years) admitted to a 33-bed general medical/surgical and trauma ICU were eligible if they required mechanical ventilation with an expected duration >24 hours, and/or having shock of any etiology and were admitted to the ICU within the previous 24 hours. Shock was defined by vasopressor requirement with infusions of: dopamine ≥ 7.5 mcg/kg/min, dobutamine ≥ 5 mcg/kg/min, norepinephrine ≥ 5 mcg/min, phenylephrine ≥ 75 mcg/min, epinephrine at any dose, milrinone at any dose (only in conjunction with another agent), or vasopressin ≥ 0.03 u/min in conjunction with another agent)[4]. Participants were excluded if they had a life expectancy <24 hours, a pre-ICU diagnosis of cognitive dysfunction as indicated by their medical records on admission, or a primary central nervous system diagnosis (e.g. neurosurgical admission).

Data capture: Demographics, BtO₂, medications, and vital sign recording

At the time of enrollment, basic clinical and demographic information was collected. Thereafter, patients underwent BtO₂ monitoring with the FORESIGHT monitor (CASMED, Caster Medical, Canada). A single 5 cm sensor was placed in the centre of the patients’ forehead and BtO₂ data was captured every 2 seconds for 24 hours. The BtO₂ recordings were not revealed to the treating clinicians. Hourly physiological variables (e.g. blood pressure) were collected simultaneously. These BtO₂ and hourly physiological variables were then converted to
mean values for statistical analysis. Sedative/analgesic medications administered during the first 24 hours of critical illness either by continuous infusion or bolus doses were tallied and converted to “fentanyl equivalents” for narcotics, and “midazolam equivalents” for benzodiazepine medications[12].

*Delirium screening:*

Patients were assessed once daily for delirium throughout their ICU stay or (up to 30 days), the Confusion Assessment Method (CAM)-ICU[13], which was administered by trained researchers. Patients were assigned to one of 3 pre-defined subgroups: 1) comatose (Richmond Agitation Sedation Scale; (RASS) -4 or -5) and not assessable for the ICU stay, 2) delirious for the majority (≥50%) of the ICU stay, or 3) non-delirious for the majority of the ICU stay. As comatose patients cannot be screened for delirium, we used the number of non-comatose days as the denominator in calculating the proportion of ICU stay spent either delirious or non-delirious. We have chosen to consider coma as a distinct entity, rather than an extreme of cognitive dysfunction. For example, a patient may be admitted with respiratory failure due to pneumonia and is mechanically ventilated with pharmacological paralysis/heavy sedation, but would otherwise be neurologically intact if not for the iatrogenic coma. This contrasts significantly with the patient who has profound shock and remains comatose for the first 24 hours despite aggressive resuscitation and little or no sedation. We feel that including the number of days a patient spends in this highly heterogeneous state would dilute any putative relationship between BtO₂ and delirium. ICU discharge was documented as the day the discharge was ordered, as delayed discharges occur due to lack of ward beds.
Data analysis:

Sample size calculation and assessment of primary outcome:

Our primary hypothesis was that there is a negative association between BtO₂ recordings and the proportion of ICU time spent delirious (i.e. days CAM-ICU positive). Our primary analysis used Spearman’s correlation coefficient to test the correlation between the average BtO₂ during the first 24 hours in the ICU and the proportion of ICU days with delirium. We used Spearman’s rank correlation coefficient rather than Pearson’s correlation coefficient, because the scatterplot of BtO₂ versus proportion of ICU days with delirium clearly showed the data was not normal.

We enrolled 89 patients (i.e. at least 1 day of CAM-ICU screening) so that we would achieve approximately 80% power to detect a moderate correlation ($\rho=0.3$; [14]) using Spearman’s rank correlation coefficient at a 2-sided alpha=0.05. The actual power for a given correlation depends on the distribution of the two variables being correlated. For example, if the variables were distributed bivariate normally we would have about 78% power, while if the variables were distributed uniformly with BtO₂ ranging from 50 to 80 and proportion of delirium days ranging from 0 to 1, we would achieve 81% power (estimated using PASS software with 200,000 simulations[15]).

Secondary outcomes-physiological variables and medications:

A one-way between subjects analysis of variance (ANOVA) determined if mean BtO₂ measurements differed significantly between the three neurological states described above. Post hoc comparisons were performed using Tukey’s HSD test. Spearman’s rank correlation coefficients were conducted between mean BtO₂ recordings with mean hemodynamic/physiological parameters, that were collected during the 24 hours recording period, for all enrolled patients, as these parameters were not normally distributed. The Kruskal-
Wallis rank sum test was used to determine if there were significant differences in physiological variables, sedative medications, and narcotics, among delirious, non-delirious, and comatose patients. Dunn’s Multiple Comparisons Test was used, with Bonferroni adjustment, when the Kruskal-Wallis rank sum test was significant. Correlations and between group differences were considered significant if \( p<0.05 \). When the Bonferroni correction was applied, the corrected \( p \) value is stated.

**Logistic regression:**

To determine if \( \text{BtO}_2 \) is an independent predictor of delirium, logistic regression was used to estimate the unadjusted effect of each individual predictor on having a majority of ICU days delirious (after excluding comatose days). The models provide odds ratios of having a majority of ICU days delirious with 95% confidence intervals and corresponding \( p \)-values estimated by Wald’s method. We fitted a multivariable model adjusting for the following covariates specified a priori [11], as they were likely to be associated with delirium [16]: a history of hypertension, a history of alcohol abuse, total sedative dose (in midazolam equivalents), and total narcotic dose (in fentanyl equivalents). Due to the possibility of overfitting, we also provide a reduced model dropping covariates with \( p<0.15 \) by backward selection. Statistical analysis was performed using R Software version 3.3.2 [17] and SAS version 9.4 software (https://www.sas.com).
Results

Patient Characteristics:

From March 2014-September 2016, 1155 patients were assessed for eligibility, and 104 were enrolled (Figure 1). Patients were largely excluded because they were admitted with a primary neurological/neurosurgical diagnosis (n=272), were >24h post-ICU admission (n=211), had an expected duration of mechanical ventilation <24h (n=206), or had a history of cognitive impairment (n=106). One enrolled patient was identified as having a new ischemic stroke after inclusion and was therefore excluded. This sample had 19 patients (18%) that spent the majority (≥50%) of their ICU delirious, while 69 patients (67%) were non-delirious for the majority of their ICU stay. Fifteen patients (15%) remained comatose for their entire ICU stay (Table 1). Most patients were intubated at enrollment (95%), and most were being treated with vasoactive agents (69%). The median length of ICU stay was 7 days (IQR, 4 to 13) and median ICU mortality was 28 (27%) (Table 1).

Relationship between BtO₂ and the proportion of ICU stay spent delirious:

In order to quantify delirium, we used the proportion of time spent delirious as a continuous outcome variable, with mean BtO₂ during the 24 hours of recording as the predictor. The correlation between mean BtO₂ recording and the proportion of time spent delirious was non-significant (ρ = -0.148, 95% CI, -0.345 to 0.063; p = .168) (Figure 2A). As our pilot data demonstrated that septic shock patients spending the majority of their ICU stay delirious have lower values of BtO₂[10], we planned an a priori assessment of the following subgroups: based on whether or not patients spent the majority of their ICU stay delirious, non-delirious; or
comatose (i.e. RASS -4 or -5) for the entirety of their ICU stay. The mean (+/- SD) BtO$_2$ was significantly higher in patients who were non-delirious, compared to delirious patients (69.4 +/- 5.7 vs. 65.3 +/- 5.4; p=0.008). There was no significant difference in mean BtO$_2$ between comatose and delirious patients (p=0.784), nor comatose and non-delirious patients (p=0.199) (Figure 2B).

Clinical and demographic differences between delirious and non-delirious patients:

We compared the baseline demographics and clinical characteristics of the patients who were delirious or non-delirious during the majority of their ICU stay (Table 1). The groups were similar in terms of their baseline comorbidities, admitting diagnosis, and severity of illness on admission. Relative to non-delirious patients, the delirious group had a higher proportion of patients with a history of alcohol abuse (7/19 vs. 5/69, p=0.003) (Table 1).

Sedative and analgesic medications administered during the 24h period of BtO$_2$ recording:

The mean total doses of fentanyl equivalents were significantly different among the three groups (p=0.034). Delirious patients had significantly higher total doses of fentanyl equivalents, relative to non-delirious patients (p=0.014) (Figure 2C). There was no significant difference in total fentanyl doses between comatose and delirious patients (p=0.171), nor comatose and non-delirious patients (p=0.978) (Figure 2C). The total dose of midazolam equivalents was not significantly different among the three groups (p=0.24) (Figure 2D).

Hemodynamic parameters across all three neurological statuses:
We compared the differences between mean vital sign recordings among patients who were comatose, delirious, or non-delirious for the majority of their ICU stay. The median MAP was the only variable significantly different among the three groups (p=0.004). Comatose patients (69.6, IQR, 68.2 to 72.7) had significantly lower MAP relative to both non-delirious (75.1, IQR, 71.9 to 80.7, p=0.002) and delirious patients (74.9, IQR, 71.4 to 81.0; p = 0.030) (Supplemental Figure 1).

Physiological determinants of BtO₂:

All patients were pooled together to assess the relationship between BtO₂ and hourly vital sign recordings. The only traditional vital sign that was statistically significant was peripheral oxygen saturation, which displayed a significant negative association with BtO₂ (ρ=-0.341, 95% CI, -0.501 to -0.157; p=0.0004) (Supplemental Figure 2). Furthermore, we assessed the relationship between BtO₂ and other physiological determinants of oxygen delivery by correlating BtO₂ with arterial and central venous blood samples. This analysis indicated that BtO₂ had a significant positive association with central venous pO₂ (Figure 3A; 95% CI, 0.334 to 0.728; p=0.00003), but not arterial pO₂ (Figure 3B; 95% CI, -0.381 to 0.049, p=0.125). There was a significant positive association between BtO₂ and hemoglobin concentration (Figure 3C; 95% CI, 0.147 to 0.506; p=0.001).

BtO₂, history of alcohol abuse, and narcotic dose may predict the subsequent development of delirium:

To determine whether or not BtO₂ was an independent risk factor for spending the majority of a patients’ ICU stay delirious, logistic regression was performed (Table 2). The
univariate analysis demonstrated that increasing total dose of fentanyl equivalents and a history of alcohol abuse increased the odds of patients spending the majority of their ICU stay delirious, whereas increasing BtO₂ decreased these odds. Total midazolam dose and hypertension history did not significantly affect the odds of developing delirium. The full multivariable model estimate that after adjusting for fentanyl equivalents, midazolam equivalents, alcohol abuse and chronic hypertension, the odds of spending the majority of the ICU stay delirious is multiplied by 0.16 (i.e. decreasing the odds of being delirious) for each 10% increase in BtO₂ (95% CI, 0.05-0.56, p=0.004). Removal of the one outlying patient with a BtO₂ value below 55 and delirium throughout their entire ICU stay did not meaningfully change the estimates (data not shown).
DISCUSSION

The etiology of delirium appears to be multifactorial and prior studies have suggested that delirium is associated with the degree of multiorgan failure, inflammatory cytokines, microvascular damage, thrombosis, and impaired oxidative metabolism [18–20]. We propose that poor cerebral perfusion early in a patients’ ICU stay also contributes to the risk of developing delirium. Empirical evidence that cerebral hypoperfusion contributes to the development of delirium is limited. This may be related to the difficulties in measuring cerebral perfusion in this population. However, previous research has indicated that reduced regional cerebral blood flow during delirium resolved after recovery from delirium using xenon-enhanced CT[21]. Our findings further support their hypothesis that poor cerebral perfusion contributes to the development of delirium, suggesting that optimizing BtO2 may offer promising avenues of care during critical illness.

We looked specifically at differences in the administration of benzodiazepines and narcotics in our patient cohort, as these two medication classes may increase the risk of ICU delirium. Although there was no difference between the dose of midazolam equivalents administered to patients who spent the majority of their ICU stay delirious or non-delirious, delirious patients received a median narcotic dose that was almost 3-fold that of the non-delirious patients. Clinically, delirium may have been interpreted as pain, leading to the administration of higher doses. Conversely, the administration of narcotics may have led to deeper sedation, a potential confounder for positive CAM-ICU assessments. The underlying reason for administering higher narcotic doses will be pertinent metrics to analyze in future investigations.

Our data corroborates studies [3,22,23] describing alcohol abuse as an independent risk factor for the development of delirium. The reason for this association is unclear, but may extend beyond alcohol withdrawal. Alcohol abuse may place a patient at risk for nutritional
deficiencies, or be a surrogate marker for other unknown risk factors for the development of delirium. In our study, many patients were delirium-free for most of their ICU stay with BtO₂ levels below the median. Almost none of these non-delirious patients with low BtO₂ had a history of alcohol abuse. In contrast, nearly half of the delirious patients with BtO₂ below the median had a history of alcohol abuse. This finding raises the possibility that individuals with a history of alcohol abuse may not have enough cognitive reserve to tolerate poor BtO₂ during critical illness.

Our study also sought to characterize the underlying determinants of BtO₂ during critical illness. Recently, NIRS derived BtO₂ was demonstrated to be correlated with peripheral oxygen saturation, cardiac index, and MAP in a small cohort of patients with septic shock[24]. We found no consistent relationship between BtO₂ and either MAP or heart rate, possibly related to more heterogeneous groups of critically ill patients in our study. The weak negative correlation between peripheral oxygen saturation and BtO₂ may be related to the fact that peripheral oxygen saturation is derived from pulsatile (i.e. arterial) flow, whereas approximately 75% of the NIRS signal is derived from venous circulation [25,26]. This is further supported by our finding of a positive correlation between BtO₂ and central venous O₂ (see also ref. [24]).

The lack of correlation between BtO₂ and hemodynamic parameters (e.g. HR) could be related to the fact that the hourly vital sign recordings used for the correlations may not be representative of the overall signal [11,27]. Alternatively, there could be considerable inter-individual variability in the manner in which BtO₂ correlates with hemodynamics. For example, cerebral autoregulatory reflexes ensure constant cerebral perfusion across a range of hemodynamic states, such that BtO₂ should not correlate with hemodynamic variables. A loss of autoregulation results in cerebral perfusion being directly reliant on hemodynamic states, thus
leading to significant correlations between BtO$_2$ and hemodynamic parameters. Critically ill patients with severe sepsis have been shown to have impaired cerebral autoregulation during the first 24-48 h [28]. An assessment of cerebral autoregulation will be imperative in future studies designed to understand the relationship between BtO$_2$ and patient hemodynamics.

**Study limitations:**

Our study is limited by the single centre design and small sample of patients who spent the majority of their ICU stay delirious. Due to the fluctuating course of delirium, future analysis may need to incorporate multiple daily CAM-ICU assessments ($\geq$2). Furthermore, we were unable to fit a comprehensive model to explore the multifactorial nature of delirium, as well as adjust for relevant covariates. Furthermore, to further validate our logistic regression results, our models will need to be reconfirmed using a larger cohort of critically ill patients (e.g. multi-centre observational study) as this was strictly exploratory. In addition, the mean value of BtO$_2$ may not reflect individual variability. It is possible that a mean value (e.g. 70%) may be relatively ‘ischemic’ for one patient, while another patient may have adequate perfusion at the same mean. In addition, using data reduction techniques, such as mean/medians, may not be representative of the high-frequency BtO$_2$ signal. Despite these limitations however, we identified low BtO$_2$ as a novel marker associated with the development of delirium.

**Conclusions:**

This study demonstrates that low BtO$_2$ is an independent risk factor for the subsequent development of delirium. Although delirium in the ICU is a complex phenomenon, this finding raises the possibility that future studies may lead to targeted strategies to optimize cerebral oxygenation during critical illness to prevent delirium.
List of Abbreviations:

95% CI: 95% confidence interval

BtO₂: Brain tissue oxygenation

CAM-ICU: Confusion assessment method-intensive care unit

DBP: Diastolic blood pressure

HR: Heart rate

IQR: Interquartile Range

M: Mean

MAP: Mean arterial pressure

NIRS: Near-infrared spectroscopy

RASS: Richmond agitation sedation scale

ROC: Receiver operating characteristic

SD: Standard deviation

SpO₂: peripheral oxygen saturation

SBP: systolic blood pressure

DECLARATIONS:

Ethics approval and consent to participate:

The Queen’s University and Affiliated Hospitals Health Sciences Research Ethics Board has approved this study, which includes deferred consent for 24 hours. Informed consent was obtained from either the patient or their proxy.

Competing interests:

MDW has nothing to disclose.

DM has nothing to disclose.
JM is the scientific director of the Canadian Frailty Network

AD has nothing to disclose

JGB receives a stipend from the Trillium Gift of Life Network to support his role as the Hospital Donation Support Physician

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**Authors’ contributions:**

MDW participated in study design, data collection, data analysis and drafting of the manuscript.

DM participated in study design, data analysis and drafting of the manuscript.

JM participated in study design and drafting of the manuscript.

AD participated in sample size calculations, data analysis and the statistical plan.

JGB is the primary investigator. He participated in study design and drafting of the manuscript.

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References


[25] Scott JP, Hoffman GM. Near-infrared spectroscopy: exposing the dark (venous) side of


Figure Legends:

**Figure 1.** CONSORT diagram demonstrating patient inclusion and exclusion during patient recruitment. CAM-ICU; Confusion assessment method-intensive care unit.

**Figure 2 A.** The negative relationship between brain tissue oxygenation (BtO₂) and the proportion of the ICU stay that patients were delirious. The black line represents a linear model fit to the data, with the grey shaded region representing the 95% confidence interval. Each dot represents individual participants mean BtO₂. The ρ value represents the calculated Spearman’s rank correlation coefficient and the respective p value.

**Figure 2.B.** The association between brain tissue oxygenation (BtO₂) and neurological status during critical illness. The box represents the interquartile range (IQR), with the black line inside the box representing the median. The whiskers above and below represent the upper quartile +1.5 x IQR or the lower quartile -1.5x IQR, respectively. The black circles represent individual patient mean BtO₂ recordings. Note. The * value indicates a significant Tukey HSD value (p < 0.05).

**Figure 2C.** Fentanyl total doses across comatose, delirious, and intact patients. The box represents the interquartile range (IQR), with the black line inside the box representing the median. The whiskers above and below represent the upper quartile +1.5 x IQR or the lower quartile -1.5x IQR, respectively. The black circles represent individual patient mean total doses. Note. The * value indicates a significant Dunn’s Test (p < 0.05).
**Figure 2D.** Midazolam total doses across comatose, delirious, and intact patients. The black line represents the median, as the data was not dispersed enough to calculate an interquartile range. The black circles represent individual patient mean total doses.

**Figure 3.** Scatter plots illustrating the various relationships between mean brain tissue oxygenation (BtO$_2$) recordings and mean levels of various determinants of oxygen delivery among all patients during the 24 hours of recording. Black data points represent each individual patient. The blue line represents a linear model fit to the data, with the grey shaded region representing the 95% confidence interval. The ρ values represent calculated Spearman’s rank correlation coefficients and their respective p values.

*Note.* PaO$_2$ = Partial pressure of arterial oxygen, PvO$_2$ = Partial pressure of venous oxygen, Hb = Hemoglobin.
<table>
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<tr>
<td>Respiratory Failure</td>
<td>32 [31]</td>
<td>24 [34]</td>
<td>5 [26]</td>
</tr>
<tr>
<td>Severe sepsis/septic shock</td>
<td>34 [33]</td>
<td>22 [31]</td>
<td>6 [32]</td>
</tr>
<tr>
<td>Neurological</td>
<td>1 [1]</td>
<td>1 [1]</td>
<td>0 [0]</td>
</tr>
<tr>
<td>Median age (yrs, [IQR])</td>
<td>69 [61-77]</td>
<td>68 [54-77]</td>
<td>71 [67-76]</td>
</tr>
<tr>
<td>Male gender (No. [%])</td>
<td>66 [64]</td>
<td>41 [59]</td>
<td>15 [79]</td>
</tr>
<tr>
<td>Admitting diagnosis (No. [%]):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory Failure</td>
<td>32 [31]</td>
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</tr>
</tbody>
</table>

Table 1: Demographic and clinical characteristics of total CONFOCAL patient cohort, and divided as per the predominant neurological status observed during the ICU stay. Comatose patients had a RASS of -4 or -5 for the duration of their ICU stay, and could not be screened with the CAM-ICU. As the Bonferroni correction was used, differences were considered statistically significant if p<0.003.

*Fisher’s exact test was used to compare categorical data. The Wilcoxon rank-sum test was used for continuous data.

**Other (n=8) included: Drug overdose or withdrawal (3), renal failure (2), pancreatitis (1), acute myelocytic leukemia (1), pre-eclampsia (1).

***Cardiac includes: arrhythmia, prior myocardial infarction, prior cardiac arrest, known coronary artery disease, congestive heart failure.

****Respiratory includes a diagnosis of asthma or COPD.
Table 2: Logistic regression results.

<table>
<thead>
<tr>
<th>Predictors from patient history or first 24 hours in ICU</th>
<th>Single predictor models</th>
<th>Full Multivariable model</th>
<th>Selected Multivariable model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P-value</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Per 10 unit increase in mean BtO2 during first 24 hours</td>
<td>0.27 (0.10 - 0.74)</td>
<td>0.011</td>
<td>0.16 (0.05 - 0.56)</td>
</tr>
<tr>
<td>Per 1000 mcg increase in Fentanyl equivalent received during the period of BtO₂ recording</td>
<td>1.81 (1.17 - 2.82)</td>
<td>0.008</td>
<td>2.02 (1.15 - 3.55)</td>
</tr>
<tr>
<td>Per 100 mg increase in Midazolam equivalent received during the period of BtO₂ recording</td>
<td>1.07 (0.68 - 5.71)</td>
<td>0.21</td>
<td>0.96 (0.25 - 3.63)</td>
</tr>
<tr>
<td>Alcohol abuse (yes vs no)</td>
<td>7.47 (2.03 - 27.47)</td>
<td>0.003</td>
<td>6.83 (1.36 - 34.2)</td>
</tr>
<tr>
<td>Chronic hypertension (yes vs. no)</td>
<td>0.49 (0.17 - 1.37)</td>
<td>0.173</td>
<td>0.64 (0.17 - 2.34)</td>
</tr>
</tbody>
</table>

OR-odds ratio; CI-confidence interval

Model with BtO₂ as only predictor:
Hosmer-Lemeshow goodness of fit test of selected multivariable model = 0.64
C-index (a.k.a. area under the receiver operating characteristic curve) of single predictor model = 0.70

Full multivariable model based on covariates selected a-prior:
Hosmer-Lemeshow goodness of fit test of selected multivariable model = 0.11
C-index of selected model = 0.81

Selected multivariable model selected by backwards selection with retention criteria of p<0.15:
Hosmer-Lemeshow goodness of fit test of selected multivariable model = 0.87
C-index of selected model = 0.83
1155 patients screened in the ICU

1051 patients excluded:
- Primary neurological diagnosis (n=273)
- <24h post admission (n=211)
- Expected duration of MV <24h (n=206)
- History of cognitive impairment (n=109)
- Expected survival <24h (n=81)
- Cardiac arrest (n=68)
- Consent declined (n=9)
- Other (n=97)

104 patients enrolled

- Comatose (RAISS <4 or >5) for majority of ICU stay (n=15)
- Able to be evaluated with CAM-I CU for at least 1 day (n=89)

- Censored post-hoc for unrecognized stroke (n=1)

Eligible for CAM-I CU screening (n=88)

CAM-I CU negative for majority of ICU stay (n=69)

CAM-I CU positive for majority of ICU stay (n=19)

*Other reasons included unavailability of staff/equipment, family not approachable for research consent, and documented refusal to participate in research studies.
Highlights

- Low BtO$_2$ is an independent risk factor for the subsequent development of delirium.
- BtO$_2$ and the proportion of time spent delirious were not significantly correlated.
- BtO$_2$ was positively associated with central vpO$_2$ and haemoglobin concentration.
- Other delirium risk factors: higher narcotic doses and a history of alcohol abuse.