Non-neurological organ dysfunction in neurocritical care
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Citation

Abstract
Purpose:
To determine the incidence of non-neurological organ dysfunction in patients with severe neurological injury.

Materials and Methods:
Modified daily SOFA (mSOFA) scores were retrospectively calculated for 55 consecutive patients with severe head injury or subarachnoid hemorrhage. mSOFA was defined as the sum of the 5 non-neurological component SOFA scores, maximum mSOFA as the sum of the most abnormal non-neurological SOFA component scores and delta mSOFA as the difference between maximum mSOFA and admission mSOFA. Organ failure was defined as a SOFA component score ≥3.

Results:
Median (IQR) admission, maximum and delta mSOFA scores were 4 (3–6), 8 (6–9), and 2 (1–5), respectively. Respiratory and cardiac failure developed in 80% and 82% of patients, respectively. No patient developed renal or hepatic failure. Three patients developed hematological failure. There was no difference between survivors and nonsurvivors with respect to admission mSOFA (P = .45), maximum mSOFA (P = .54), or delta mSOFA (P = .19). There was no difference between those patients with favorable or unfavorable neurological outcome with respect to admission mSOFA (P = .24), maximum mSOFA (P = .84), or delta mSOFA (P = .20).

Conclusions:
Cardiopulmonary failure, as defined by SOFA, is common in intensive care unit patients with severe head injury and subarachnoid hemorrhage. In contrast to other intensive care unit patient populations, the mortality of patients with closed head injury or subarachnoid hemorrhage was not related to the severity of organ dysfunction on admission or its development during the intensive care unit stay.

INTRODUCTION
AFTER SEVERE traumatic brain injury (sTBI) and subarachnoid hemorrhage (SAH), cerebral blood flow is known to be reduced. A component of the neurocritical care management of these patients involves the support of cerebral perfusion pressure (CPP) with volume loading and inotropes. In addition, treatments commonly used for the management of intracranial hypertension, such as barbiturates and hypothermia, have known effects on the immune system and may lead to infection. Recently, there has been increasing concern that CPP-directed management of intracranial hypertension may lead to non-neurological organ dysfunction and worsen outcome. Robertson et al performed a randomized controlled trial of 2 head-injury management strategies [intracranial pressure (ICP)-targeted and cerebral blood flow (CBF)-targeted]. A fivefold increase in the incidence of adult respiratory distress syndrome (ARDS) was observed in the CBF-targeted group. There was no difference in neurological outcome at 6 months between those in the CBF-targeted protocol and those in the ICP-targeted protocol. In a secondary analysis, several factors were found to be significantly associated with an increased risk of ARDS: administration of epinephrine (5.7-fold increased risk), administration of dopamine in a larger than median dose (10.8-fold increased risk), and a history of drug abuse (3.1-fold increased risk). The etiology of ARDS was not described but volume overload was likely to be a contributing factor as fluid intake was greater and the intake/output balance was more positive in the patients who developed ARDS. In addition, the
pulmonary artery occlusion pressure and the central venous pressure were significantly higher in the patients with ARDS.

Although there have been several organ dysfunction scoring systems developed, the Sequential Organ Failure Assessment (SOFA) score is arguably the best validated for daily assessment. SOFA scores the cardiovascular, respiratory, hematological, renal, hepatic and neurological systems from 0 to 4 with 0 representing normal function and 4 representing the most abnormal function (Table 1). The scores are then added to create a daily measure of the burden of organ dysfunction (range, 0–24). This score has been validated in the general ICU patient and the trauma patient.[11, 12, 13]

**Figure 1**

Table 1: SOFA Score

<table>
<thead>
<tr>
<th>Organ Dysfunction</th>
<th>Score</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>≤20</td>
<td>0–100</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>≤30</td>
<td>0–100</td>
</tr>
<tr>
<td>Hematological</td>
<td>≤16</td>
<td>0–100</td>
</tr>
<tr>
<td>Hepatic</td>
<td>≤10</td>
<td>0–100</td>
</tr>
<tr>
<td>Neurological</td>
<td>≤12</td>
<td>0–100</td>
</tr>
<tr>
<td>Score</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The purpose of this study was to identify the incidence of non-neurological organ dysfunction as measured by SOFA and to determine the association of non-neurological organ dysfunction with outcome in those with SAH or sTBI admitted to the intensive care unit (ICU). We chose this population as it is at high risk for the development of organ dysfunction due to the frequent use of inotopes/pressors to maintain cerebral perfusion pressure and the use of hypothermia or barbiturates to treat intracranial hypertension.

**MATERIAL AND METHODS**

After approval from the local research ethics committee, we measured organ dysfunction for 55 consecutive patients with the diagnosis of severe traumatic brain injury (sTBI) or subarachnoid hemorrhage (SAH) admitted to the Neuroscience Critical Care Unit (NCCU) at Addenbrooke’s Hospital. The NCCU provides specialist neuro-intensive care facilities for the regional neuroscience services covering a population of 2.3 million. In our unit, an evidence based protocol[4] is used to manage severe traumatic brain injury. Cerebral perfusion pressure is maintained at 70 mm Hg. We aim for eucarbia, euthermia, euglycemia and PaO<sub>2</sub> > 80 mm Hg. All patients receive ICP and jugular venous saturation monitoring. Intracranial hypertension is managed with stepwise administration of sedation (propofol or midazolam and fentanyl), paralysis (atracurium), ventricular drainage, and mild hypothermia. Intracranial hypertension refractory to the aforementioned therapies is managed with moderate hypothermia, barbiturates, or surgical decompression where appropriate. Severe traumatic brain injury was defined as a postresuscitation GCS of ≤8 or the development of intracranial hypertension. In general, patients with good grade SAH [World Federation of Neurological Surgeons (WFNS) grade 1, 2, or 3] are managed on the ward or in the high dependency unit and are not included in this study unless they have developed complications requiring NCCU admission. All patients with poor grade subarachnoid hemorrhage (WFNS grade 4 or 5) are initially managed in the NCCU. Our treatment protocol for SAH includes early (prior to day 3 post-bleed) aneurysm clipping for those patients with a Glasgow Coma Score (GCS) motor component ≥4. Daily transcranial Doppler examinations are performed to screen for vasospasm. Vasospasm is treated with volume expansion and induced hypertension (clipped aneurysms) with invasive hemodynamic monitoring as appropriate.

Organ dysfunction was identified by retrospectively calculating daily modified SOFA (mSOFA) scores from prospectively collected physiological data. Each component SOFA score was calculated based on previously published recommendations.[12] The mSOFA score was defined as the sum of the 5 non-neurological component SOFA scores (range, 0–20). Maximum mSOFA was defined as the sum of the most abnormal non-neurological SOFA component scores during the patients stay. Delta mSOFA was defined as difference between the maximum SOFA and the admission mSOFA. An organ system failure was considered to be present if the SOFA component score was ≥3. Non-neurological multiple organ dysfunction (MOD) was identified if a patient developed failure of ≥2 non-neurological organ systems. Neurological outcome as measured by Glasgow Outcome Score (GOS) was determined at 6 month follow-up. GOS was dichotomized into favorable outcome (GOS 4, 5) and unfavorable outcome (GOS 1, 2, 3). Only the patient’s first admission with NCCU length of stay (LOS) ≥48 hours was considered. We did not include stay in the high dependency unit.

Data were managed using Excel 2002 (Microsoft Corp., Redmond, WA) and analyzed using Stata version 7.0 (Stata Corp, College Station, TX) computer programs. Normally or near-normally distributed variables were reported as means with standard deviations (SD) and non-normally distributed
variables as medians with inter-quartile ranges (IQR). Means were compared using the Student’s t test and medians using the Mann-Whitney U test. Differences in proportions among categorical data were assessed using the χ² statistic or Fisher’s exact test where appropriate. A P-value of <0.05 was considered significant.

RESULTS

PATIENT CHARACTERISTICS

The demographics of the patients are presented in Table 2. Thirty-two patients with sTBI and 23 patients with SAH were included in the study. Sixty-seven percent of patients were male and the mean age (±SD) was 41 ± 18 years. The mean APACHE II score was 13.6 ± 6.8. For those patients with severe traumatic brain injury, median post-resuscitation GCS was 7 (range 3–12) and 8 patients (25%) had pupillary abnormalities. Patients with SAH were graded according to the World Federation of Neurological Surgeons (WFNS) system. Thirteen patients had a clinical grade of 5, 7 patients had a clinical grade of 4, 1 patient had a clinical grade of 2, and 2 patients had a clinical grade of 1. Median ICU LOS was 11 days (range, 2–29) and median hospital LOS was 19.7 days (range, 2.5–62.5). Neurological outcome was available for 45 patients. Thirty-one percent of patients experienced favorable neurological outcome. ICU mortality was 20% and hospital mortality was 29%.

Figure 2
Table 2: Patient Characteristics

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>55</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observations</td>
<td>713</td>
</tr>
<tr>
<td>Number of patients by diagnosis (SAH/sTBI)</td>
<td>23/32</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>41 ± 18 years</td>
</tr>
<tr>
<td>Male/Female</td>
<td>37/18</td>
</tr>
<tr>
<td>APACHE II (admission, mean ± SD)</td>
<td>13.6 ± 6.8</td>
</tr>
<tr>
<td>Percentage of patients with intracranial hypertension</td>
<td>65%</td>
</tr>
<tr>
<td>Median ICU length of stay (range)</td>
<td>11 days (2–29)</td>
</tr>
<tr>
<td>Median hospital length of stay (range)</td>
<td>19.7 days (2.5–62.5)</td>
</tr>
<tr>
<td>ICU mortality</td>
<td>20%</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>29%</td>
</tr>
<tr>
<td>Number of patients with favorable/unfavorable neurological outcome</td>
<td>14/31</td>
</tr>
</tbody>
</table>

ORGAN DYSFUNCTION

Measures of organ dysfunction are summarized in Table 3 and Figure 1. Median (IQR) admission, maximum and delta mSOFA scores were 4 (3–6), 8 (6–9), and 2 (1–5), respectively. Cardiopulmonary insufficiency was common as 80% of patients developed respiratory failure and 82% of patients developed cardiovascular failure as defined by the SOFA score. In contrast, no patient developed renal or hepatic failure and only 3 patients (5.5%) developed hematological failure. Nine percent of patients did not develop any organ failure during their NCCU stay while 20%, 65%, and 5.5% of patients developed 1, 2, and 3 organ failure, respectively. The development of respiratory failure was significantly associated with the development of cardiovascular failure (P = .02).

Figure 3
Table 3: Organ Dysfunction

<table>
<thead>
<tr>
<th>Measure</th>
<th>Survivors</th>
<th>P-value</th>
<th>Neutropenic</th>
<th>Neurogenic</th>
<th>Hemorrhagic</th>
<th>Infective</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>mSOFA score</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Admission mSOFA median</td>
<td>6.0 (3.9)</td>
<td>6.0 (3.9)</td>
<td>6.0 (3.9)</td>
<td>6.0 (3.9)</td>
<td>6.0 (3.9)</td>
<td>6.0 (3.9)</td>
<td>6.0 (3.9)</td>
</tr>
<tr>
<td>Maximum mSOFA median</td>
<td>7.0 (4.1)</td>
<td>7.0 (4.1)</td>
<td>7.0 (4.1)</td>
<td>7.0 (4.1)</td>
<td>7.0 (4.1)</td>
<td>7.0 (4.1)</td>
<td>7.0 (4.1)</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, inter-quartile range.

Figure 4

Figure 1: mSOFA scores in survivors and nonsurvivors by day of ICU stay.

Although patients 45 years of age or older experienced significantly higher mortality (P = .04) and worse neurological outcome (P = .04), older patients did not have significantly different admission (P = .83), maximum (P = .17) or delta mSOFA scores (P = .11) compared to younger patients. There was no significant difference in admission mSOFA (P = .92) or maximum mSOFA (P = .16) between those with sTBI and SAH. However, those with sTBI developed more organ dysfunction during their ICU stay compared to those with SAH as measured by delta mSOFA.
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(median delta mSOFA 3 v 1, P = .03). For those with sTBI, there was no difference in admission mSOFA between those with poor post-resuscitation Glasgow Coma Score (GCS) (≤6) and those with a post-resuscitation GCS > 6 (P = .3). However, there were trends to higher maximum (P = .059) and delta mSOFA scores (P = .069) and worse neurological outcome in those with a lower post-resuscitation GCS. An association between severity of neurological injury and organ dysfunction could not be demonstrated for those with SAH, but numbers were small. Patients who developed intracranial hypertension had significantly higher maximum mSOFA scores (P = .004) and delta mSOFA scores (P = .001). This was related to significantly more cardiovascular and respiratory dysfunction in patients with intracranial hypertension. There was no significant difference in admission mSOFA between those who developed intracranial hypertension and those who did not (P = .35).

With the day of admission denoted as day 0, maximum cardiovascular organ dysfunction occurred on median day 1 (mean day 1.0, mode day 0). Maximum respiratory dysfunction occurred on median day 1 (mean day 1.9, mode day 0). In 38% of patients, maximum respiratory dysfunction occurred prior to maximum cardiovascular dysfunction. Thirty-one percent of patients had maximum cardiovascular dysfunction occur prior to maximum respiratory dysfunction. In the same proportion of patients maximum respiratory and cardiovascular dysfunction occurred on the same day.

MODIFIED SOFA SCORES AND OUTCOME

There was a significant association between the degree of organ dysfunction, as measured by the maximum mSOFA score, and length of stay. Median ICU length of stay was 17.9 days in those with a maximum mSOFA ≥8 compared with 5.8 days for those with a maximum mSOFA score <8 (P = .0001). Median hospital length of stay was 27.5 days in those with a maximum mSOFA ≥8 compared with 14.8 days for those with a maximum mSOFA score <8 (P = .007). There was no significant difference between survivors and nonsurvivors with respect to admission mSOFA (P = .45), maximum mSOFA (P = .54), or delta mSOFA (P = .19). Those with no organ failures, one organ failure, 2 organ failures, and three organ failures had mortality rates of 20%, 27%, 31% and 33%, respectively (P = .96). There was no significant relationship between the development of individual organ failure and mortality. There was no difference in mortality between those who developed multiple organ dysfunction (≥2 organ system dysfunctions) and those who did not. Neurological outcome was available for 45 patients (82%). mSOFA was not significantly different between those with favorable neurological outcome and those with unfavorable neurological outcome on any day of NCCU day except for day 1 (median mSOFA 5.5 v 6, P = .049). There was no significant difference in admission mSOFA between those patients with favorable or unfavorable neurological outcome (P = .24), maximum mSOFA (P = .84), or delta mSOFA (P = .20). No significant association could be demonstrated between the development of individual organ failure and neurological outcome. The development of multiple organ dysfunction was not associated with an increased incidence of unfavorable neurological outcome (P = .491).

DISCUSSION

The incidence of cardiovascular and respiratory failure, as measured by the relevant SOFA component score in those with SAH and sTBI, was found to be very high while the incidence of renal, hematological and hepatic failure was low. The high incidence of cardiovascular failure was expected as the calculation of the cardiovascular SOFA component score is dependent on the degree of inotropic support. The dose of sedation required in the patient with intracranial hypertension almost uniformly causes cardiovascular consequences requiring support. Further, artificial elevation of blood pressure through volume loading and/or inotropic support is frequently used to maintain cerebral perfusion pressure and to treat vasospasm. Thus, an inherent weakness of the SOFA cardiovascular component score in this subgroup of patients is the fact that it does not differentiate between true cardiovascular failure and physiological manipulation for cerebral perfusion maintenance. Given our management algorithm maintains a CPP of 70 mm Hg, a high SOFA cardiovascular component score may represent a state of shock or may be reflective of the difficulties in maintaining cerebral perfusion in those intracranial hypertension. Because severe neurological may itself result in cardiac dysfunction, it may indeed impossible to differentiate these two situations during CPP-targeted care.

To a certain extent, the high incidence of respiratory failure was also expected for a number of reasons. The use of hypothermia and barbiturates in treating intracranial hypertension may result in immune suppression and likely predisposes to pneumonia. In addition, pre-admission diminished level of consciousness may result in aspiration and impaired cough due to neurological injury.
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and sedation may result in atelectasis which impairs oxygenation and predisposes to pneumonia. Finally, volume overload may be a contributing factor as this is generally a first line intervention to maintain cerebral perfusion pressure or to treat vasospasm whether due to trauma or aneurysmal bleed. One could postulate the low incidence of renal failure was related to volume loading and the aggressive maintenance of mean arterial pressure. However, our patients were younger than in most general ICU studies meaning predisposing factors such as diabetes and vascular disease were likely to be less common in our patients. The low incidence of hematological failure was most probably due to the elevated platelet transfusion threshold applied by most physicians to the neurosurgical patient.

Similar to the results of Contant and colleagues,[19] we have identified an association between cardiovascular failure as measured by SOFA (increased inotrope dose) and respiratory failure. However, this association should not be interpreted to suggest respiratory dysfunction is caused by induced hypertension. A large proportion of our patients had their maximum respiratory dysfunction occur prior to their maximum cardiovascular failure. Further study is required to identify causality with specific attention to timing of organ dysfunction.

This is the first report of the use of the SOFA score in a neurocritical care population. We were unable to demonstrate an association between the amount of organ dysfunction and outcome in this sample of severely injured neurological patients. In a large cohort of patients with SAH, Gruber and colleagues calculated a modified MOD score as measure extracerebral organ dysfunction.[20] The authors found a significantly higher modified MOD score in those with poor outcome. The MOD score was first described by Marshall et al in a population of critically ill patients and is similar to the SOFA score. [21] The main difference between the two scores is the MOD score uses pressure-adjusted heart rate (PAR, the product of the heart rate and the ratio of central venous pressure to mean arterial pressure) as opposed to the SOFA score's use of the combination of mean arterial pressure and inotrope requirement to determine cardiovascular dysfunction. For the MOD score, the absence of a central venous monitor is assumed to represent normal cardiovascular function and therefore is scored as zero. This issue is crucial for the interpretation of Gruber's results since, if one examines mean physiological parameters of those with good and poor outcome, it is only the mean cardiovascular and respiratory values of those with poor outcome that represent abnormal function (MOD component score ≥1). If clinicians were more inclined to place invasive monitoring in sicker patients, then those with poor grade subarachnoid hemorrhage may have been at greater “risk” of identification of cardiovascular dysfunction. Further, the cardiovascular SOFA component score has recently been shown to have better discriminatory value than the cardiovascular MOD component score in determining outcome.[22] However, the MOD cardiovascular component score is therapy independent. This may be a more appropriate measure in a neurocritical care population who commonly undergo pharmacological support of blood pressure.

Of particular interest is the relatively low mortality rate found in those with multiple organ dysfunction. Although Gruber et al found a 30.7% mortality rate for single organ system failure, a 91% mortality rate for 2 organ system failures, and a 100% mortality rate of 3 or more organ system failures. Our corresponding rates were 27%, 31% and 33%, respectively. The general critical care literature also supports a strong association between multiple organ dysfunction. Part of the observed disparity is most certainly explained by differences in case mix. Our patients tended to be young with little comorbidity. In addition, our population also included traumatic brain injury while the study by Gruber only examined organ dysfunction in patients with SAH. Although we could not identify differences in organ dysfunction between those with SAH and traumatic brain injury, this may be related to our relatively small sample size and it is possible these populations of patients are indeed different with respect to organ dysfunction. Further, the incidence of non-neurological organ dysfunction in the Gruber study was significantly different compared to our study. Only 36.8% of patient's in met neurological organ system failure in the study by Gruber as compared to 95% in our study. In addition, 14% of patient's in Gruber's study developed renal failure (or would have if hemodialysis had not been initiated) compared to none in our study.

Although no association between non-neurological organ dysfunction and outcome and was found, we cannot exclude the possibility of a type II error due to the relatively small sample size. The small sample size also limited our ability to adjust for confounding variables. Therefore, this work must be confirmed in a larger prospective trial which is currently under way at the University of Calgary. This study has been designed to compare measures of organ dysfunction (MOD and SOFA) and assess their validity in this specific subgroup
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of critically ill patients.

In conclusion, we have identified a high incidence of cardiopulmonary dysfunction and a low incidence of renal, hematological or hepatic failure as measured by a modified SOFA score in those with severe traumatic brain injury or subarachnoid hemorrhage managed in a tertiary care neurocritical unit. Although we found no association between non-neurological organ dysfunction as measured by the SOFA score and outcome, this result needs to be confirmed in larger prospective trials.

References
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