The Future of ICU Informatics

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Neuromonitoring in NICU

Monitoring of neurologic function in patients at high risk for

- **Primary brain injury** from procedure or condition
- **Secondary brain injury** after a prior neurologic insult

The primary focus of Neurocritical Care for CNS problems is the prevention, identification, and treatment of secondary brain injury.
## Scope of Problem

### Primary Brain Injury
- Ischemic stroke
- Trauma
- SAH
- ICH
- During and post-procedure
  - Endovascular
  - Surgical

### Secondary Brain Injury
- Ischemic stroke
- Trauma
- SAH
- ICH
- Status epilepticus?
- Meningitis, encephalitis?
Neuromonitoring in NICU

Ideal Neuromonitor

- Continuous
- Safe
- Easy to implement
- Accurate
- Reliable
- Gives quantitative, not just relative, information
- Identifies changes while patient/tissue still salvageable
- Provides therapeutic, not just prognostic, information
Categories of Neuromonitors

- **Clinical**
  - Neurologic examination

- **Physiologic**
  - Pressure - ICP, BP
  - Flow - CBF, TCD
  - Electrical - EEG, EP

- **Metabolic**
  - Oxygen – P_{bt}O_2, S_jVO_2
  - Metabolites - microdialysis
What Happens in the NeuroICU Today?

Physiology Matters
Secondary Brain Insults (SBIs)

- Exacerbate injury in vulnerable cells
- Decreased substrate delivery
  - Hypotension
  - Hypoxia
- Increased metabolism
  - Fever
  - Seizures
- Worsen hemorrhage or edema
  - Hypertension
- Cellular toxicity
  - Hyperglycemia
Does this Drive NeuroICU Care?

• **Ischemic stroke**
  – Hypotension – worsened ischemia
  – Hypertension – brain hemorrhage (esp after t-PA)
  – Fever
  – Hyperglycemia

• **Subarachnoid hemorrhage**
  – Hypertension – aneurysm re-rupture
  – Hypotension – ischemia from vasospasm

• **Intracerebral hemorrhage**
  – Hypertension – hematoma expansion

• **Traumatic brain injury**
  – Hypotension, hypoxia, elevated ICP, fever
This is a data intense environment
NeuroICU “Data Management”

- Large amounts of continuous complex data require robust tools for storage, reporting, and analysis (for any line of work)

- Routine problem now for corporate, industrial, financial world

- We’re dealing with the most important thing in the world
  - Human life
  - The brain

- So how are we doing?
What do we do with all this data?

- Monitoring has advanced tremendously since the origins of critical care in the 1960s

- We look at the data in basically the same way
• **Call HO if temp > 38.5°C**
• **Call HO if SBP > 180 mmHg**
• **Call HO if SBP < 90 mmHg**
• **Call HO if ICP > 20 mmHg**
• **Call HO if \( O_2 \) sat < 93%**
• **Call HO if glucose > 200 mg/dl**
• **Call HO if \( P_{bt}O_2 \) < 15 mmHg**
• **Call HO if \( S_jVO_2 \) < 50%**

Treating thresholds one at a time; Keeping it between the lines
Paper charts in most ICUs, electronic charts in some
Rounding in the NeuroICU Today
<table>
<thead>
<tr>
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<th>Comment</th>
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<td>PM 61</td>
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<td>8/8</td>
<td>COP 19</td>
<td>0.5</td>
</tr>
</tbody>
</table>
• Treat the moment
  – Order for intervention targeting single parameter
    » Tylenol for T > 38.5°C
    » Labetalol for SBP > 180 mmHg
    » Fluid bolus or pressors for SBP < 90 mmHg
    » Mannitol for ICP > 25 mmHg

• Review of nursing bedside chart for trends

• Usually no attention to relationship among parameters (ICP, MAP, P_{bt}O_{2}, temp, gluc)
  – Experience of practitioner
  – Data not manageable
This is good, right?

Pharmacokinetics & dose-response relationships

Multivariable regression models of disease prediction

Gene expression microarrays and bioinformatic analyses
So What’s the Problem?

- Some of what we don’t know

1) Do SBIs have a dose-response relationship with outcome?

2) We treat univariate in a multivariate world
   - Interaction and relationship between various physiologic parameters?
   - Event signatures?

3) How do we integrate new measures (e.g. $P_{btO_2}$)?

4) How often do we need to collect physiologic data to optimize patient care?

This is complicated
• Dose-response relationship between SBIs and outcome makes intuitive sense

• What’s a “dose” of … ?
  – Fever
  – Hypotension
  – Hypoxia
  – Elevated ICP
  – Hyperglycemia
Secondary Brain Insults and Outcome

- Any occurrence
  - TCDB: hypotension or hypoxia
  - Fever at hospital admission: ICH and ischemic stroke
  - Hyperglycemia at hospital admission: ischemic stroke
  - High BP at admission (in diabetics): ICH expansion

- Number of occurrences
  - Jugular venous oxygen desaturations (< 50% for > 10 min)

- Duration (or % time) above a threshold
  - TCDB: ICP
  - Fever: ICH

Robertson, *Neurotrauma*, 1996
<table>
<thead>
<tr>
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</table>

T_{max} 39.4

Fever Burden?
Borrowing from Pharmacokinetics

- “Dose” is area under the curve (AUC)

Graph showing body temperature over hours from hospital admission.
Does It Matter How we Define Dose?

Impact of ED episodes and dose of hypotension on risk of in-hospital death after severe TBI (n=107)

<table>
<thead>
<tr>
<th>SBI</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any hypotension (n=26)</td>
<td>3.39</td>
<td>1.34-8.56</td>
<td>.009</td>
</tr>
<tr>
<td>1 episode of hypotension</td>
<td>2.05</td>
<td>0.67-6.23</td>
<td>0.21</td>
</tr>
<tr>
<td>≥ 2 episodes of hypotension</td>
<td>8.07</td>
<td>1.63-39.9</td>
<td>0.01</td>
</tr>
</tbody>
</table>

* Manley, Arch Surg, 2001
* Barton, Acad Emerg Med, 2005
Mannitol Dose-Response

![Graph showing ICP (mm Hg) over time for different doses of mannitol. The x-axis represents time in minutes (0 to 100), and the y-axis represents ICP in mm Hg (10 to 25). Two lines represent different doses: 50g (solid line) and 100g (dashed line). The graph illustrates the decrease in ICP over time following the administration of mannitol.](image-url)
How Often Do We Need to Collect this Data?

- Current standard
  - Paper chart - Q 1 hour and as needed
  - CareVue (electronic medical record) – up to Q 15 min

- Study comparing Q 1 min vs. medical record (MR) for SBI identification and dose (n=16; 72 hours each)

<table>
<thead>
<tr>
<th>Subject</th>
<th># of Events</th>
<th>AUC in mmHg.min</th>
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<tbody>
<tr>
<td></td>
<td>Q 1 min</td>
<td>MR</td>
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<tr>
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<td>11</td>
</tr>
<tr>
<td>16</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>17</td>
<td>40</td>
<td>23</td>
</tr>
</tbody>
</table>

Hemphill, *Physiological Measurement*, 2005
NICU Data Acquisition 2003

- Independent CPU
- Multiple serial ports
  - Overhead monitor (Philips)
  - Ventilator (Draeger)
  - Brain O₂ (Licox)
  - CBF (Hemedex)
- Data time-synched
- Operator must initiate data acquisition
Physiology Cluster Analysis

Self-organizing map reduces high-dimensional information to a two-dimensional grid
Borrowing from Genomics

Self-organizing Map

Distance Map Projection

Cluster analysis of microdialysis data (26 patients) - Nelson, *Crit Care Med*, 2004
Pattern Recognition

PHYSIOLOGIC SIGNATURES
Some Obvious Problems

• If this were easy, it would have been done a long time ago.

• Data cleaning
  – Bedside charts are “cleaned” at the time of entry
  – Major problem for continuous physiological data
  – Need automatic cleaning algorithms

• Interoperability of systems
  – Devices (and their exported data) are often proprietary
  – Physiological, text, and other data in separate systems
  – Data not in common language across institutions or systems
To most people, hospital informatics means:
- Electronic Medical Records (EMR)
- Computerized Order Entry (CPOE)
- Billing software
- Records to satisfy regulatory requirements (e.g. JCAHO)

This is not what “informatics” meant in the Human Genome Project.

GE, Philips, Siemens
- Will try to sell you their off the shelf system and tell you its what you need
- Don’t believe them
Too Complicated... Who Cares?

• First report from INSTITUTE OF MEDICINE Committee on Quality of Health Care in America

• Future reports:
  – re-designing the health care delivery system for the 21st Century
  – aligning financial incentives to reward quality care
  – critical role of information technology as a tool for measuring and understanding quality
Learning Lessons from History - CT

• First CT machine
  – 9 days to scan an object
  – 21 hours to computer process information

• Sir Godfrey Hounsfield – Nobel prize speech 1979
  – “When I investigated the advantages (of CT scanning) over conventional x-ray techniques, it became apparent that the conventional methods were not making full use of all the information that x-rays could give.”

Evidence-based Neurocritical Care

• Expertise matters

• Pronovost, *JAMA*, 2002 – systematic review of 26 studies
  – Presence of intensivist ass. w/ better outcomes
  – Only 1 neuroICU studied

• Neurointensivists – improved outcome
  – Suarez, *Critical Care Medicine*, 2004
  – Varelas, *Critical Care Medicine*, 2004
    » Semi-closed unit; 30% TBI

• Understanding
  – Why expertise makes a difference even without a specific obvious treatment
  – How to harness and “export” expertise
Neurocritical Care Database/Informatics

GOALS

1) Identify physiological signatures to diagnose patients and predict outcomes

2) Use real-time data to rationally drive clinical decisions and treatment based on the specific physiologic abnormality

3) Determine dosage and delivery for commonly used NICU medications

4) Suggest new clinically-relevant experimental research models

5) Develop user-friendly “behind the scenes” data analysis that aids interpretability and clinical applicability
• **Collaborative Project**
  – Admit it: this is beyond bedside clinicians
  – Clinicians, computer scientists, informatics, industry

• **UC Discovery Grant**
  – Pilot project between UCSF, UC Berkeley, Intel
  – Two years: develop data warehouse methods, pilot data analysis
  – Expand to multi-center project (will require large numbers of patients with long-term outcome)

• **NIH/NINDS SBIR – Scott Winterstein, PhD**
  – Data acquisition methodology and device library
NICU Data Acquisition 2008

- The primary data are:
  1. Bedside physiological data (Aristein-"homemade")
  2. ICU Patient Care Chart (Carevue-Philips)
  3. Lifetime Clinical Record (Invision-Siemens)

- No kiosk – each bed with networked data acquisition
- Bedside physiological data collected continuously (Q1 minute) and automatically into Data Registry Server
- Must have contextual data (e.g. medications and timing) in order to make sense of physiological data
• NeuroICU monitoring tools have advanced beyond our current ability to understand how to use them
• This is due to the disconnect between data generation and data analysis
• Advances in real-time user-friendly data analysis must accompany advances in neuromonitoring techniques
• This will be a “long haul”
• This is a large-scale collaborative effort across institutions
• Avoid the temptations to
  – Be impatient and give up
  – Assume the data we want is easily obtained/acquired
  – Expect big answers right away
  – Read too much into early simple analyses
  – Assume large companies will provide us with the solutions
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Another case of too many scientists and not enough hunchbacks
Frequent monitoring of physiological vital signs is standard of care in the intensive care unit (ICU). Most patients admitted to an ICU are connected to at least one continuous monitor, such as an electrocardiogram or a pulse oximeter. Blood pressure and temperature may be measured intermittently or continuously. Depending on the patient’s specific diagnosis and severity of injury, additional monitors are placed (e.g., intracranial pressure (ICP) monitor, central venous pressure monitor, pulmonary artery catheter, jugular venous oxygen catheter, brain tissue oxygen probe, end-tidal carbon dioxide monitor). This process often results in continuous monitoring of a dozen or more.
clinical variables, with real-time values displayed on bedside or overhead computer monitors for visualization by nurses and physicians (1–3). However, the ability to acquire this data has outstripped the ability to record, process, and integrate this high volume of information into routine patient care.

**Monitoring Meets Informatics**

A fundamental purpose of neurocritical care monitoring is to prevent secondary brain injury by identifying and treating insults such as hypotension, hypoxia, fever, and elevated ICP. Unfortunately, current methods of evaluating the data acquired during monitoring rely on the relatively simplistic identification of events, often indicated by an alarm, when a predetermined threshold is crossed. This approach leaves open many questions. For example, what is hypotension? Is it a single event below some threshold (e.g., mean arterial pressure [MAP] < 90 mmHg)? How does one pick the threshold? Additionally, how do clinicians even know that these events have occurred? Even though continuous physiological data is often being generated, this information is almost always recorded intermittently, often hourly, in medical records with no data on duration of events. Typically, this is the only information available for physician review on rounds. Many reports have used relatively gross descriptors such as whether an event occurred, or, at most, how many times it occurred. In contrast, Struchen et al. studied the relationship between outcome and duration of adverse physiological events, defined as variables such as ICP, MAP, and cerebral perfusion pressure (CPP) exceeding certain thresholds, and found that duration of events accounted for a significant portion of the variance in Disability Rating Scale scores (4).

Despite the availability of multimodal monitoring, detection of potential insults is performed by asking separate, univariate questions rather than by integrating and interpreting the multivariate patient situation. Routine ICU orders often focus on individual physiological parameters. For example, “Call physician for ICP > 20 mmHg.” Although treatment thresholds, protocols, and management styles may vary among institutions, this general paradigm holds. Adequate management is assumed if individual parameters of interest are maintained between commonly accepted upper and lower thresholds. This univariate approach does not reflect the physiological complexity of the patient with severe injury. For example, alteration of respiratory rate may affect multiple parameters such as arterial blood gas values, ICP, and brain tissue oxygenation. Although clinicians are aware of these physiological complexities, which were the impetus for instituting multimodal monitoring, few tools have been developed to electronically store, integrate, and analyze this multidimensional information.

Advances in the use of biostatistics and informatics have fundamentally altered the way information is examined in many aspects of medical care and human biology. For example, the use of multivariable regression techniques to assess the impact of several factors that may jointly influence a parameter of interest such as patient outcome is now standard in epidemiology. The field of human genetics has also been revolutionized by advances in informatics. In fact, one of the necessary aspects of the Human Genome Project has been the development of new bioinformatics approaches that allow the study of the complex interactions of multiple genes. We can now analyze microarray data by using methods such as hierarchical clustering to identify patterns relevant to molecular biology. More broadly, however, bioinformatics (including buzzwords like pattern analysis and data mining) can be thought of as a set of computational and quantitative methods that are applicable not only to basic science but also to physiological data analysis and to clinical decision making. Significant amounts of multivariate data are now being generated in the ICU, and computer algorithms are increasingly being adapted to provide clinicians with capabilities to predict, diagnose, and treat (5,6). We expect that in neurocritical care, just as in epidemiology and human genetics, the interaction of multiple parameters is more relevant than any individual factor. We suspect that the reason this has not been explored more extensively is because the analytical tools for studying complex physiological interactions have not been available.

This manuscript develops the idea that advances in neurocritical care monitoring must be accompanied by advances in methods of analyzing the data being captured. Furthermore, these new methods must take into account the complex interaction of multiple processes occurring in the critically ill patient rather than viewing them as mutually exclusive. Our aims were (1) to present challenges and opportunities for high-frequency multimodal monitoring to quantitatively detect secondary brain insults, and (2) to develop clustering methodology to construct multivariate physiological data “profiles” to classify patients for diagnosis and treatment.

**A Multivariate Approach to Continuous Data Analysis**

San Francisco General Hospital (SFGH) is an acute care hospital operated by the City and County of San Francisco. The SFGH Neurotrauma and Critical Care Database contains physiological and nursing care data as well as demographic information. The main hardware components of the system are bedside monitors connected to a standard personal computer via serial cables. Such a system is not entirely unique. Goldstein et al. described a real-time, continuous physiological data acquisition system for a 16-bed ICU for the study of parametric and waveform data (7). We capture over 20 physiological variables (Table 1), plus date, time, and optional comments. Data is collected automatically at 1-minute intervals and is output into text files. In addition to reliable data capture, however, we also place an emphasis on multivariate data analysis. Quantitative analysis can be used to answer questions related to measurement, classification, or prediction for diagnosis and treatment. The choice of analytical methods depends on the type of question. For example, descriptive statistics can measure variables and help to frame biomedical questions, whereas clustering can be used for classification. During this study, caregivers did not have access to the analyses or the full data set we describe.

We performed exploratory analysis retrospectively on a sample high-frequency data set from patients with traumatic brain injury (TBI) to visualize and describe the large amounts of physiological data generated in the ICU. Data analysis was performed using SPSS v.13 (SPSS Inc., Chicago, IL). We used descriptive statistics to determine ranges and distributions of the physiological variables in Table 1. Data was collected from
23 patients every minute for a median of 7 days (mean ± s.d.: 5.7 ± 2.3). The median duration of observation per patient was 8453 minutes (8518 ± 7554). Collection was performed using Viridia bedside monitors (Philips), Licox tissue oxygen monitors (Integra NeuroSciences), and Draeger ventilators and required no intervention outside of standard clinical care. Monitoring data was integrated by a middleware software backbone (Aristein Bioinformatics). Not all patients admitted with TBI met our monitoring protocol. Those that did were continuously monitored only if a bed with the appropriate monitoring infrastructure was available. An additional design constraint that reduced our patient sample was the desire to continuously monitor patients for 1 week rather than to truncate their monitoring period simply to connect the next patient. Collected data included occasional spurious or missing values caused by system problems, cable disconnection, or other technical issues. To address this issue, we constructed 23 patient files with raw data and cleaned them according to simple rules: we did not delete outliers, but data such as heart rate equal to zero and unrealistically high ICP were ignored during analysis.

The concept of multivariate data classification involves using quantitative algorithms to separate subjects into two or more categories according to their features. Clustering can be used to divide data into a hierarchy. The traditional representation of this hierarchy is a tree, with a single cluster containing every subject at the beginning and individual subjects arranged in groups at the end (Figure 1). In contrast to a more knowledge-based approach like an expert system, hierarchical clustering is primarily data-driven. Advantages of knowledge-based approaches include the benefits of clinical intuition, whereas advantages of data-driven approaches include the unbiased discovery of unexpected relationships. The variables used in the cluster analysis were chosen based on the current monitoring capabilities in our ICU, the variables that we believed a priori might be important, and the variables for which sufficient data was captured. We used median values of physiological parameters for each patient from their entire ICU stay based on measures acquired every minute. Using Cluster v2.11, we log-transformed our physiological data, centered the data set around patient and variable medians, and normalized values. Data was then clustered using average linkage hierarchical clustering. The ICU physiological data was arranged into a two-dimensional grid with similar patients and correlated variables next to each other (8) by creating a “heat map” and cluster tree (Figure 2) using TreeView v1.6 (Cluster and TreeView can be found at http://rana.lbl.gov/EisenSoftware.htm). Such a heat map is more commonly used to display gene expression data. Whereas gene expression heat maps display up- or down-regulation of many genes across many samples (tissues, patients) or time periods, we are displaying high or low values of many physiological measures across many patients. The clusters represent correlations between subjects. Red areas indicate high values whereas green areas indicate low values. The heat map is a compact, intuitive way to visualize a moderately large data set (18 variables across, 23 patients down). We described the patient clusters according to clinical measures such as Glasgow Coma Score (GCS) and Injury Severity Score (ISS) which were recorded once per patient.

### Exploratory Analysis

We first performed exploratory analysis on the data set. We captured heart rate, CPP, arterial blood pressure (ABP) values, and ICP for all patients (Table 2). We also captured brain tissue oxygen tension ($P_{brO_2}$), brain temperature, and respiratory parameters (plateau pressure, tidal volume, minute ventilation, and respiratory rate) for nearly all (78–91%) patients.

<table>
<thead>
<tr>
<th>Source</th>
<th>Variable</th>
<th>Definition</th>
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<tr>
<td>Viridia bedside monitor</td>
<td>MAP</td>
<td>mean arterial blood pressure</td>
</tr>
<tr>
<td></td>
<td>ABP – systolic</td>
<td>systolic arterial blood pressure</td>
</tr>
<tr>
<td></td>
<td>ABP – diastolic</td>
<td>diastolic arterial blood pressure</td>
</tr>
<tr>
<td></td>
<td>ICP</td>
<td>intracranial pressure</td>
</tr>
<tr>
<td></td>
<td>ETCO₂</td>
<td>end tidal CO₂</td>
</tr>
<tr>
<td></td>
<td>SvO₂</td>
<td>oxygen saturation of venous blood from brain heart rate</td>
</tr>
<tr>
<td></td>
<td>HR</td>
<td>cerebral perfusion pressure</td>
</tr>
<tr>
<td></td>
<td>CPP</td>
<td>oxygen saturation in capillaries</td>
</tr>
<tr>
<td></td>
<td>Core Temp</td>
<td>body temperature</td>
</tr>
<tr>
<td>Licox tissue oxygen monitor</td>
<td>$P_{brO_2}$</td>
<td>brain tissue oxygen</td>
</tr>
<tr>
<td></td>
<td>Brain Temp</td>
<td>brain tissue temperature</td>
</tr>
<tr>
<td>Draeger ventilator</td>
<td>Plateau pressure</td>
<td>pressure applied to small airways and alveoli</td>
</tr>
<tr>
<td></td>
<td>PEEP breathing</td>
<td>positive pressure applied at the end of expiration</td>
</tr>
<tr>
<td></td>
<td>Peak breathing</td>
<td>pressure measured by ventilator in major airways lung volume during normal breath</td>
</tr>
<tr>
<td></td>
<td>Tidal volume</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Spontaneous minute volume</td>
<td>tidal volume x respiratory rate - (patient breathing)</td>
</tr>
<tr>
<td></td>
<td>Minute ventilation</td>
<td>tidal volume x respiratory rate - (ventilator)</td>
</tr>
<tr>
<td></td>
<td>Respiratory rate</td>
<td>respiratory rate</td>
</tr>
<tr>
<td></td>
<td>Inspired O₂</td>
<td>fraction of inspired oxygen</td>
</tr>
</tbody>
</table>
Median values within each patient time course were computed for all variables. Heart rate medians generally ranged between 60 and 110 beats per minute across patients, CPP ranged between 70 and 100 mmHg, MAP ranged between 80 and 110 mmHg, and ICP ranged between 5 and 15 mmHg with some high outliers (Figure 3). Of the variables with incomplete collection, \( P_{\text{O}_2} \) ranged between 10 and 60 mmHg with some high outliers, plateau pressure ranged between 10 and 30 mmHg, tidal volume ranged between 0.5 and 0.75 L, minute ventilation ranged between 7 and 15 L per minute with some high outliers, and respiratory rate ranged between 10 and 30 breaths per minute with some high outliers. We also computed means, standard deviations, and estimates of distribution symmetry such as skew and kurtosis. These physiological data ranges can be helpful in determining “typical” and “crisis” periods in the patient with severe injury. We found that other variables were not as informative for analysis because values were basically constant. For example, peak end expiratory pressure (PEEP) was typically 5 cm H\(_2\)O, fraction of inspired oxygen was typically 0.4, and SpO\(_2\) was almost always 100%. We also saw, as expected, that respiratory variables were correlated with each other as were hemodynamic variables (data not shown).

The potential benefits of applying informatics to exploratory analysis of continuous, high-frequency physiological ICU data are illustrated by two patient cases. Patient A was a 40-year-old man who suffered a head injury after a fall from a ladder. On arrival, his GCS was 7, and he had one nonreactive pupil. Visual inspection of the patient’s entire ICP time course (Figure 4A) indicates that ICP was usually less than 20 mmHg despite a...
period of raised ICP on day 4 (approximately 3500–4100 minutes) and increased ICP volatility on day 6 (beginning at approximately 6000 minutes; Figure 4B). Nursing documentation shows that on day 4 in the mid-morning, cerebrospinal fluid (CSF) was being drained at least four times per hour. Thus, nursing documentation in conjunction with high-resolution physiological data is critical to explain this patient’s physiological course. This patient’s ICP was greater than 20 mmHg for only 5.4% of the total monitoring time. Such measurement demonstrates how continuous data can be used beyond summary data to determine the dose (i.e., degree, duration, and frequency) of events likely to contribute to the severity of secondary brain injury. Patient A was in the ICU for 18 days and was discharged to a rehabilitation facility with a Glasgow Outcome Score Extended (GOS-E) of 4 (upper severe disability).

Patient B was a 47-year-old male injured in an industrial accident. His GCS was 9, and he was intubated on arrival. As seen by the total ICP time course for this patient (Figure 4C), ICP over the first 6000 minutes (100 hours) of observation was frequently near or greater than 20 mmHg (15.4 ± 7.2 mmHg). There followed a period (approximately 1500 minutes in duration) during which ICP fell to 11.5 ± 7.9 mmHg. This was followed by another period (approximately 200 minutes; Figure 4D) during which ICP rose to 23.0 ± 8.3 mmHg. During this period, even though the variance was “typical” for this patient, sharp ICP spikes could be observed, and ICP was generally greater than in the “volatile” period for Patient A (Figure 4B). It is noteworthy that hourly recording of ICP values in the bedside nursing chart (as is often done in routine care) would underestimate the true ICP during this time period. To illustrate, the ICP values for 3 consecutive hours during this period were 20, 17, and 17 mmHg, which would suggest to a physician reviewing this chart on rounds that the patient’s ICP was within an acceptable range. However, such hourly measurements do not reflect the many ICP readings greater than 20 mmHg and several readings greater than 30 mmHg. In the final period of observation of approximately 3000 minutes, ICP fell slightly—and this time showed far less variability—to 18.6 ± 3.7 mmHg. Ultimately, he required a hemicraniectomy and right frontal lobectomy. This patient’s ICP was greater than 20 mmHg for 24.7% of the monitoring time, nearly five times the amount for Patient A. This type of data integration over time indicates the severity of his patient’s injury and would suggest a commensurate treatment response. Patient B was in the ICU for 19 days, and his total hospital length of stay was 31 days. He was discharged to rehab with a GOS-E of 2 (vegetative).

Classification Analysis

Using hierarchical clustering, the 23 patients were assigned to three groups. The seven patients in Group A include those whose respiratory and blood pressure values were lowest (Figure 2) and those with the worst outcomes. Specifically, only three patients in the total sample of 23 died, but two of them were in Group A; two patients in the total sample were vegetarian, and both were in Group A. As such, our approach potentially appears to be predictive of outcome based on clustering of physiological data. Group A included the youngest patients (average age, 34.3 ± 14.4) with the lowest average arrival GCS motor score (3.6 ± 1.9) and average ISS (21.9 ± 6.6) (9). The 10 patients in Group B included those with...
higher blood pressure and CPP and were, on average, the oldest (44.3 ± 17.0) and had the highest ISS (30.3 ± 11.3). The six patients in Group C had the highest average arrival motor score (5.2 ± 1.3) and the highest values for respiratory rate, plateau pressure, and peak breathing pressure.

These patient profiles are complex, and to our knowledge, this is the first effort to fully integrate a multivariate data set to construct patient profiles that could ultimately be used in diagnosis and treatment. The division of patients into three groups is not definitive; with more physiological or demographic data, the patients could be divided into more, smaller, and perhaps even different groups. However, the three groups we describe are robust for this physiological data set insofar as they are quantitatively validated by independent, demographic and clinical data. Cluster analysis demonstrates that even patients that are similar in many respects (treatment protocols, etc.) are different in other ways, and it is this insight that we are looking for. By its nature, the execution of a clustering algorithm will always produce one or more clusters. However, from the tree of physiological variables, several clusters emerge as expected (based on known physiological relationships), and serve as internal controls: for example, systolic blood pressure, diastolic blood pressure, and MAP values cluster together (Figure 2). $P_{a}O_{2}$ and end-tidal $CO_{2}$ (ETCO$_2$) also cluster, consistent with the known relationship between $CO_{2}$, cerebral blood flow, and $P_{a}O_{2}$. Because clustering physiological data is a new approach, the high degree of correlation where it is expected represents validation of the methodology. Analysis of a more restricted set of noninterrelated variables would risk missing unexpected relationships. In fact, other clusters emerge that are unanticipated. For example, in this dataset, ICP clusters with inspired oxygen. Upon review of the physiological data and nursing documentation, we noticed instances in which ICP spiked when inspired oxygen was raised to 100% while the patient was being suctioned. This has led to modification of our clinical practice during suctioning. The clustering of core temperature with $SpO_{2}$ and heart rate with PEEP may not be informative, because $SpO_{2}$ and PEEP were both essentially constant.

Fig. 4. Multiple ICP time series scatterplots for two patients. (A) ICP time course over the entire monitoring period for Patient A indicates some high outliers, with a period of raised ICP on day 4 (at approximately 3500 minutes). ICP is usually below the 20 mmHg reference line. The narrow dashed line box from 6300 to 6500 minutes indicates the period expanded in panel B. (B) Slightly increased ICP volatility on day 6 (at approximately 6300 minutes). This graph depicts the potential effect on interpretation when continuous data is only recorded at hourly intervals. Increased ICP volatility might not have been noticed had ICP values only been recorded hourly. (C) ICP time course for Patient B. The dashed box from 8000 to 8200 minutes indicates the period expanded in panel D. (D) A period of 200 minutes during which ICP was 15 ± 6 mmHg. Even though the variance was “typical” for this patient, sharp ICP spikes could be observed, and ICP was generally greater than in Patient A’s “volatile.”
The heat map is a quantitative, high-throughput, and visually intuitive way to group patients and possibly associate them with diagnoses or treatment strategies. This approach has potential clinical significance in the possibility of identifying new patients who, based on multiple characteristics, are at risk to experience complications or worsened outcome. In this manner, ongoing refinement of physiological profiles could be used to target specific treatments. Future studies will be needed on larger patient samples to determine statistical significance and potential for translation to the bedside.

The State of the Art and Future Directions

Our aims were (1) to present challenges and opportunities for high-frequency multimodal monitoring to quantitatively detect secondary brain insults, and (2) to develop clustering methodology to construct multivariate physiological data “profiles” to classify patients for diagnosis and treatment. We first presented issues of continuous data summarization, visualization, and integration with nursing documentation. We then presented the first application of hierarchical clustering to construct physiological data profiles for patient classification, diagnosis, and treatment. These initial efforts are among the first to begin to integrate multivariate, continuous data analysis into acute care, and they elucidate the complexities of ICU informatics, from reliable data capture to useful interpretation. Future hypothesis-driven, prospective approaches must address quantitative and clinical issues together, not independently, to answer questions about clinical care that is optimized for individual patients.

Prior studies have employed exploratory data analysis in neurocritical care. Jones et al. examined time series MAP, ICP, and CPP data and related their variability to outcome. Their data were displayed on polygraphs, and patterns were described to help interpret the data produced at the bedside (10). In other studies, Cifu et al. have used various statistical methods to study post-acute functional outcome after brain injury (11–14). Worldwide, several groups have developed free, generalizable software resources to enable more powerful analysis specifically tailored to physiological data. These include PhysioToolkit from the National Institutes of Health (NIH) National Center for Research Resources, Scilab from the French Institut National de Recherche en Informatique et en Automatique, TISEAN from the Max Planck Institut in Germany, ICM+ from the University of Cambridge, and HRV Analysis from the University of Kuopio in Finland.

Classification methods have seen limited use in the ICU but could potentially be applied to a wide variety of problems. For example, Stuss et al. evaluated the ability of measures of initial injury severity, tests of attention, and demographic characteristics to predict recovery of memory in patients with TBI using classification and decision tree analysis. They identified four groups of patients and concluded that approaches that take into account multiple measures provide a more sensitive predictive index (15). Similarly, Andrews et al. compared results of logistic regression with those of tree analysis of a head-injury data set including a range of secondary insults and 12-month outcomes. They found, perhaps not surprisingly, that tree analysis confirmed some regression results and challenged others (16). Other groups have conducted similar studies (17–20).

Potential downsides exist to pursuing more complete data acquisition and processing; among them, the difficulty in interpreting the vast amount of data that is acquired. With all the parameters continuously collected and the issues that occur in an ICU that may corrupt information (e.g., transducers being zeroed, ventriculostomies being opened for drainage, patients being turned, monitor disconnections for transport to imaging studies and procedures), there is great potential for data overload and false information. Thus, fundamental goals of any physiological informatics approach must be to ensure reliability of the data, avoid collecting and processing large volumes of “meaningless” data, and establish relationships between physiological data and clinical events. All this must be done with output that is user-friendly and enhances the ability of the clinician to care for patients, rather than detracts from patient care. This is not a task for clinicians alone. At our institution, we have developed a collaboration between our clinicians, bioinformaticians, and computer scientists with the goal of addressing these complex and novel issues.

Neurotrauma physicians have been caring for critically injured patients for decades. We recognize the value of clinical expertise. Yet it is often difficult to formalize how this expertise is gained, other than through “experience.” As critical care informatics evolves, it is important to determine if it aids decision making regardless of the level of practitioner experience, standardizes care, serves as a training resource for junior clinicians, or provides better information access even without making specific recommendations. These are controversial areas. We have shown that Q1 minute data capture of many variables across many patients is feasible and can potentially lead to new clinical insights. Data visualization and use of descriptive statistics are good first steps in physiological data analysis. However, visualization of large time spans of data for even moderate numbers of concurrent variables often becomes overwhelming, even after normalization, so computational methods such as hierarchical clustering can be useful for patient classification.

The potential benefits of neurocritical care informatics are alluring because improvements to the nature and timing of interventions could reduce secondary injury, long-term disability, and death. The lessons of epidemiology and human genetics indicate that powerful statistical and informatics tools can significantly extend knowledge in those fields. We believe that the future of neurocritical care lies not just in developing new monitors, but in the ability to more fully understand the information that we already have.

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References


