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Original Article

New Approaches to Physiological Informatics in Neurocritical Care

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Abstract

Introduction: A fundamental purpose of neurocritical care is the management of secondary brain injury. This is often accomplished by monitoring and managing individual patient parameters including physiological vital signs. Yet, the ability to record physiological data exceeds our ability to fully integrate it into patient care. We propose that advances in monitoring must be accompanied by advances in methods of high-frequency, multivariate data analysis that integrate the multiple processes occurring in critically ill patients.

Methods: We describe initial work in the emerging field of physiological informatics in critical care medicine. We analyzed data on 23 patients with brain injury from our Neurotrauma and Critical Care Database, which contains more than 20 physiological parameters recorded automatically at one-minute intervals via bedside monitors connected to standard personal computers. We performed exploratory data analysis, studied two patient cases in detail, and implemented a data-driven classification approach using hierarchical clustering.

Results: In this study, we present challenges and opportunities for high-frequency multimodal monitoring to quantitatively detect secondary brain insults, and develop clustering methodology to construct multivariate physiological data "profiles" to classify patients for diagnosis and treatment.

Conclusions: Recording of many physiological variables across multiple patients is feasible and can lead to new clinical insights. Computational and analytical methods previously used primarily for basic science may have clinical relevance and can potentially be adapted to provide physicians with improved ability to integrate complex information for decision making in neurocritical care.

Key Words: Traumatic brain injury; intensive care; physiological monitoring; intracranial pressure; hierarchical clustering.

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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 v13 (SPSS Inc., Chicago, IL). We used descriptive statistics to determine ranges and distributions of the physiological variables in Table 1. Data was collected from

Table 1
Physiological Variables Included in the SFGH Neurotrauma and Critical Care Database
Monitored physiological parameters

Source	*Variable*	*Definition*
Viridia bedside monitor	MAP	mean arterial blood pressure
	ABP – systolic	systolic arterial blood pressure
	ABP – diastolic	diastolic arterial blood pressure
	ICP	intracranial pressure
	$ETCO_2$	end tidal CO_2
	SvO_2	oxygen saturation of venous blood from brain
	HR	heart rate
	CPP	cerebral perfusion pressure
	SpO_2	oxygen saturation in capillaries
	Core Temp	body temperature
Licox tissue oxygen monitor	$P_{Br}O_2$	brain tissue oxygen
	Brain Temp	brain tissue temperature
Draeger ventilator	Plateau pressure	pressure applied to small airways and alveoli
	PEEP breathing pressure	positive pressure applied at the end of expiration
	Peak breathing pressure	pressure measured by ventilator in major airways
	Tidal volume	lung volume during normal breath
	Spontaneous minute volume	tidal volume x respiratory rate - (patient breathing)
	Minute ventilation	tidal volume x respiratory rate - (ventilator)
	Respiratory rate	respiratory rate
	Inspired O_2	fraction of inspired oxygen

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 ($P_{br}O_2$), brain temperature, and respiratory parameters (plateau pressure, tidal volume, minute ventilation, and respiratory rate) for nearly all (78–91%) patients.

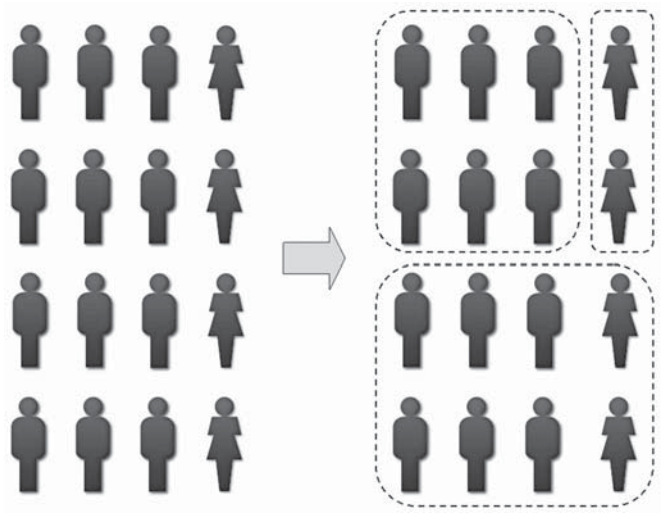

Fig. 1. A schematic example of classification, where an initial group of disparate subjects is divided into smaller groups of more similar subjects.

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, $P_{br}O2$ 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_2O, 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

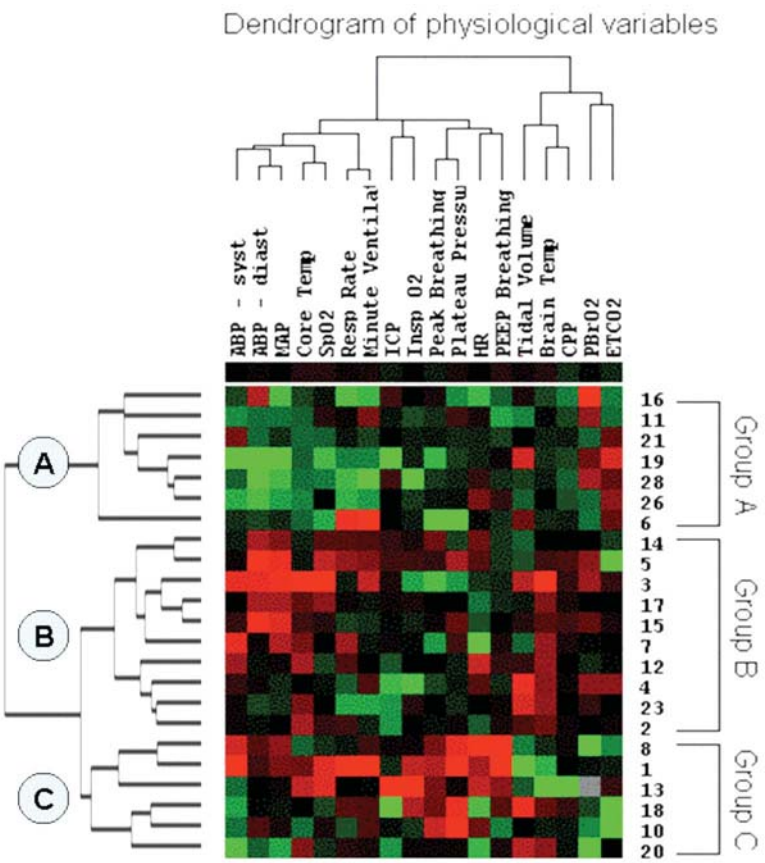

Fig. 2. Heat map of physiological variables. The heat map is labeled with the hierarchical cluster tree of variables and the three groups of patients, named A, B, and C.

Table 2
Table of Ranges in Values of 14 Variables of Interest for 23 Patients
Ranges of selected physiological parameters

	10th pctile	*10th pctile*	*Median*	*Median*	*90th pctile*	*90th pctile*
	Low	*High*	*Low*	*High*	*Low*	*High*
MAP (mmHg)	70	97	82	111	96	129
ABP – systolic (mmHg)	105	158	127	177	144	201
ABP – diastolic (mmHg)	53	76	64	86	75	104
ICP (mmHg)	1	11	4	17	9	24
Heart rate (beats/minute)	41	82	59	112	65	131
CPP (mmHg)	62	84	66	99	85	115
$P_{Br}O_2$ (mmHg)	6.7	35.1	8.8	59.45	23.4	100
Brain temp (°C)	31.2	38.2	31.8	38.6	32.5	39.4
Core temp (°C)	34.2	37.6	35.8	38.2	36.7	39.3
Plateau pressure (mmHg)	9	23	11	30	15	42
Peak breathing pressure (mmHg)	11	36	11	44	16	47
Tidal volume (L)	0.16	0.71	0.5	0.76	0.53	0.84
Minute ventilation (L/minute)	6.3	10.7	7.3	15.7	8.7	20.9
Respiratory rate (breaths/minute)	10	17	12	31	13	34

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).

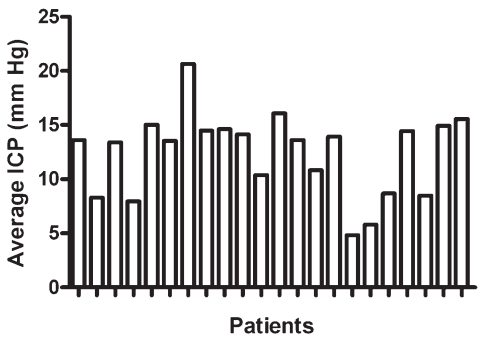

Fig. 3. The range of ICP values observed within and across 22 patients. Patient 13 is not included because of technical issues with ICP monitoring.

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 vegetative, 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

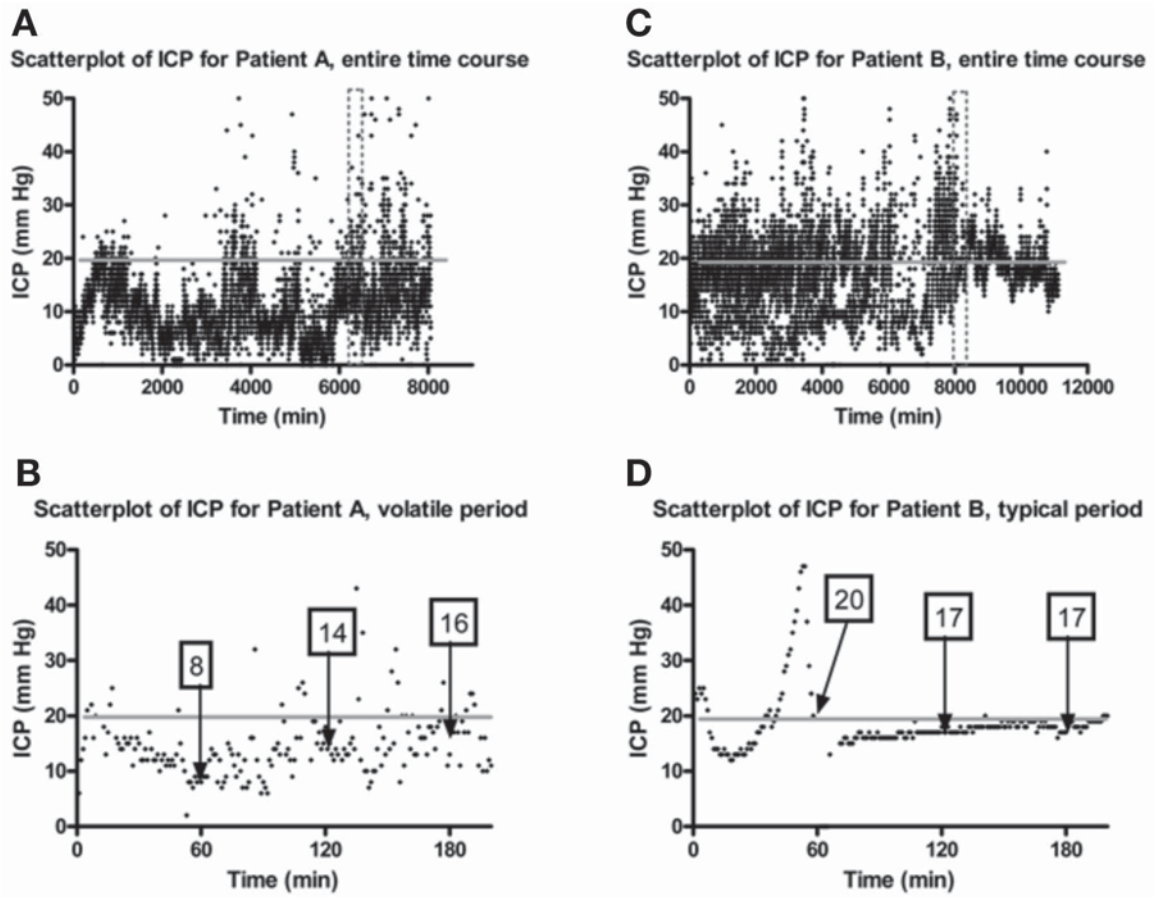

Fig. 4. Multiple ICP time series scatterplots for two patients. **(A)** ICP time course over the entire monitoring period for Patient A indicates some high outliers, with a period of raised ICP on day 4 (at approximately 3500 minutes). ICP is usually below the 20 mmHg reference line. The narrow dashed 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."

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). $P_{br}O_2$ and end-tidal CO_2 ($ETCO_2$) also cluster, consistent with the known relationship between CO_2, cerebral blood flow, and $P_{br}O_2$. 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.

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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